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1 Title

Phase III Randomized, Parallel-Group, Single-Blind, Multicenter Clinical Investigation of the Inhalation App-Module Embedded in AsthmaTuner (version later than 5.4.13.5) to Improve Inhalation Technique Versus Standard (Non–App-Based) Education in Adolescents and Adults with Asthma and/or COPD Using DPI and/or MDI

Protocol Identifier

- Protocol ID: Rescript 555
- Short Title/Acronym: To be confirmed
- Device Name: Inhalation app-module embedded in AsthmaTuner (iOS/Android), version later than 5.4.13.5
- Device Manufacturer: MediTuner AB; SRN: SE-MF-000028534

Version and Dates

- Protocol Version: 01
- Protocol Date: 29 Oct 2026
- Initial Sponsor Approval Date: 29 Oct 2026
- Version History:

- Version 01 (29 Oct 2026): Initial version
- Future amendments: To be confirmed

Sponsor

- Legal Sponsor: Jitendrarescript
- Address: ABc, Mumbai, India
- Sponsor Representative: To be confirmed
- Sponsor 24/7 Medical Contact: To be confirmed
- Sponsor Email/Telephone: To be confirmed

Study Governance and Key Roles

- Coordinating Investigator: To be confirmed
- Medical Monitor: To be confirmed
- Data Safety Monitoring Board (DSMB): Established; charter and contact details to be confirmed
- Contract Research Organization (if applicable): Not applicable/To be confirmed
- Collaborators/Co-sponsors: None

Study Setting and Sites

- Scope: Single-country
- Country: To be confirmed
- Centers: Multicenter (list of participating hospitals/clinics to be appended upon approvals)
- Recruitment Settings: Outpatient respiratory/asthma/COPD clinics; details to be confirmed

Regulatory and Ethics Identifiers

- Regulatory Framework: EU MDR or applicable national authority oversight (reference identifiers to be confirmed)
- Competent Authority Submission/Approval: To be confirmed
- Ethics Committee/IRB Approval: To be confirmed
- Clinical Investigation Registration (e.g., Eudamed CIV-ID/CTIS/ClinicalTrials.gov/EU CTR): To be assigned
- UDI/Device Registration Status: To be confirmed for investigational configuration of the inhalation app-module

Study Design Summary

- Design: Two-armed, parallel-group, individual single-blind, stratified randomization by inhaler type (DPI/MDI/both), 1:1 allocation
- Control: Standard education of inhalation technique using a standardized criteria list; non–app-based education
- Intervention: Standard care plus app-based education and training of inhalation technique via the investigational inhalation app-module
- Population: Individuals aged ≥16 years with documented asthma and/or COPD using DPI and/or MDI
- Follow-up Duration: 6–12 weeks post-randomization

Official Correspondence

- Sponsor Correspondence Address: Jitendrarescript, ABc, Mumbai, India
- General Study Queries: To be confirmed
- Safety Reporting Contact (SAE/UADE): To be confirmed
- Device Manufacturer Contact: MediTuner AB, Sweden; SRN: SE-MF-000028534; Address and contact to be confirmed

Document Control

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- Supersession: This version supersedes all prior drafts. Future amendments will be version-controlled and dated.

2 STUDY DESIGN SCHEMATIC INPUTS

Study-flow narrative (operational sequence)

- Pre-enrollment screening and consent: Potential participants identified in outpatient or inpatient respiratory care are pre-screened for basic eligibility (age ≥16 years; asthma and/or COPD; current daily DPI and/or MDI use; smartphone iOS/Android; national electronic ID access). The PI or delegate obtains written informed consent prior to any study-specific procedures, consistent with ISO 14155 and ICH-GCP [1,2].

- Committee eligibility review and enrollment rule: Following site screening, the Site Enrollment Committee (SEC) conducts a rapid eligibility review. Enrollment is permitted only after SEC approval (quorum required) and PI attestation of eligibility. Randomization (1:1; stratified by inhaler type: DPI/MDI/both) occurs after approval [1,3].

- Procedure day with baseline assessments: At or shortly after enrollment, baseline assessments are completed, including medical history, concomitant medications, spirometry, inhaler technique evaluation, and required safety laboratories as specified for this protocol. Investigational device provisioning is performed for the intervention arm (app access activation; shipment/hand-over of spirometer and Airflow Trainer). Control arm receives standardized non–app-based technique education using a pre-defined checklist [1,4,5].

- Post-initiation/discharge tasks and scheduling: Participants receive training on device/app use (intervention arm), instructions for technique practice, AE/SAE/UADE reporting, and contact information. The site schedules the primary endpoint visit at Week 6–12 and the 30-day safety check, and provides the long-term follow-up calendar (6 months, 12 months, annually through Year 5), including remote options where permitted [1,3,6].

- 30-day safety visit: Focused safety assessment for AEs, UADEs, device deficiencies, and any early usability issues. Remote conduct is permitted with telemedicine and app/phone-based data capture when clinically appropriate and compliant with local regulations [1,3,6].

- 6–12 week primary endpoint visit: Primary efficacy assessment of correct inhalation technique success rate using standardized, pre-specified criteria with central review of technique artifacts (e.g., videos/flow curves), plus safety and usability evaluations [4,5].

- 6-month efficacy visit: Reassessment of inhalation technique success, spirometry, app engagement metrics (intervention arm), health status and rescue medication use, and continued safety monitoring [1,4,5].

- 12-month efficacy visit: Reassessment as at 6 months; evaluation of durability of effect, continued usability, and safety [1,4,5].

- Annual visits through Year 5 and study close-out: Annual safety and effectiveness follow-up through Year 5, emphasizing persistence of correct technique, sustained app use patterns (intervention), respiratory outcomes, and device/software safety signal surveillance. The close-out visit includes final safety assessment, inventory reconciliation, deactivation of investigational app access, and confirmation of care transition [1,3].

Visit schedule and timing windows

Visit	Nominal timing from randomization	Window (allowable)	Mode (onsite/remote)	Deviation handling
Screening and consent	Day −28 to 0	±7 days	Onsite or hybrid	Out-of-window requires PI justification; no study-specific procedures pre-consent [1,2]
SEC eligibility review and enrollment	Day 0 to +7	0 to +7 days	Central/site committee	Enrollment only after SEC approval; delays beyond +7 days require re-verification of key criteria
Procedure/baseline	Day 0	±7 days	Onsite preferred	If >7 days from SEC approval, repeat key eligibility and baseline technique
30-day safety	Day 30	±3 days	Onsite or remote	If missed, perform within 14 days; document reason and impact [1,3]
Primary endpoint (Week 6–12)	Day 42 to Day 84	Target at Day 56 ±14 days within the 6–12 week window	Onsite or hybrid with central review	If outside 6–12 weeks, primary endpoint is considered out-of-window; central adjudication may accept data within +14 days with pre-specified sensitivity analyses [1,4]
6-month visit	Month 6	±14 days	Onsite or remote	If missed, perform within 30 days; otherwise skip and document; no replacement of participant [1]

12-month visit	Month 12	±21 days	Onsite or remote	If missed, perform within 45 days; otherwise skip and document
Annual Year 2–5	Month 24/36/48/60	±30 days	Onsite or remote	If missed, perform within 60 days; otherwise skip and document
Study close-out	Within 30 days after final annual visit or early termination	±14 days	Onsite or remote	Complete final safety and accountability; document early exits

Allowable deviations: Visits within windows are protocol-compliant. Out-of-window assessments require PI documentation of reason, risk assessment, and impact on endpoints, consistent with ISO 14155 and ICH-GCP. Primary endpoint timing adheres to the 6–12 week window; acceptance of limited deviations for analysis must be pre-specified and approved by the Sponsor and DSMB [1–3].

Per-visit assessment checklists, endpoint mapping, and central review

Visit	Assessment item	Endpoint mapping	Central review required
Screening/consent	Informed consent; demographics; diagnosis verification; inhaler type (DPI/MDI/both); smartphone/eID check	Feasibility (screening yield)	No
Screening/consent	Inclusion/exclusion eligibility confirmation; pregnancy status if applicable	Safety/feasibility	No
Screening/consent	Concomitant medications; exacerbation history (past 12 months)	Exploratory efficacy (risk stratification)	No
Baseline/procedure	Physical exam; vitals; SpO2	Safety	No
Baseline/procedure	Safety laboratories (panel per protocol: to be confirmed)	Safety	No
Baseline/procedure	Spirometry per ATS/ERS standards (FEV1, FVC)	Exploratory efficacy	Yes (quality grading) [4]
Baseline/procedure	Inhaler technique assessment against standardized checklist (arm-agnostic)	Efficacy baseline	Yes (adjudication) [5]
Baseline/procedure	Device/app provisioning (intervention); control education delivery per checklist	Feasibility/usability process metrics	No
30-day safety	AE/SAE/UADE review; device deficiencies and malfunctions; concomitant meds	Safety	Yes (UADE classification) [1,3]
30-day safety	App usage metrics (intervention): logins, training sessions, completion	Usability/feasibility	Yes (automated central extract)
30-day safety	Inhaler technique spot-check (as feasible)	Exploratory efficacy	Yes (if video/flow upload)
Week 6–12 primary	Standardized inhaler technique performance (success/fail by pre-defined criteria)	Primary efficacy endpoint	Yes (dual adjudication) [5]
Week 6–12 primary	Spirometry; rescue medication use; patient-reported ease-of-use	Secondary efficacy/usability	Yes (spirometry QC)
Week 6–12 primary	AE/SAE/UADE review; device deficiency	Safety	Yes (UADE classification) [1,3]
6-month	Inhaler technique success; spirometry; exacerbations since last visit	Secondary efficacy	Yes

6-month	System usability scale or equivalent (intervention)	Usability	No
6-month	AE/SAE/UADE review; device deficiency	Safety	Yes
12-month	Inhaler technique success; spirometry; health status (e.g., CAT/ACT to be confirmed)	Secondary/exploratory efficacy	Yes (spirometry QC)
12-month	App engagement (intervention) and adherence to education	Usability/feasibility	Yes
12-month	AE/SAE/UADE review; device deficiency	Safety	Yes
Annual Y2–Y5	Inhaler technique success; respiratory outcomes; health care utilization	Long-term effectiveness	Yes (if submissions)
Annual Y2–Y5	AE/SAE/UADE review; device deficiency; software update exposure	Long-term safety	Yes
Close-out	Final AE/SAE/UADE status; device/app deactivation; accountability	Safety/feasibility	No

Notes:

- Standardized technique criteria and adjudication procedures will be finalized in the Adjudication Manual; central reviewers will be blinded to treatment allocation to reduce assessment bias [1,5].
- UADEs and device deficiencies are categorized and reported per ISO 14155 and applicable MDR requirements [1,3].
- Spirometry follows ATS/ERS standards; central quality control will grade acceptability and repeatability [4].

Handling missed visits, remote alternatives, and unscheduled safety checks

- Missed visits: If a visit cannot be completed within the window, perform it at the earliest opportunity within the permitted grace period. For the primary endpoint window (6–12 weeks), if missed, obtain technique assessment within +14 days and flag for sensitivity analysis; if unobtainable, do not replace the participant. Document all deviations, rationale, and potential impact per ICH-GCP and ISO 14155 [1,2].

- Remote alternatives: Telemedicine and remote data collection (e.g., app-based technique practice logs, patient-reported outcomes, video uploads, and shipped/at-home spirometry where permitted) are allowed when clinically appropriate and compliant with local regulations and data privacy laws. Identity verification uses eID processes where applicable. Remote assessments must follow validated procedures to ensure data integrity and participant safety [1,3,6].

- Unscheduled safety checks: At any time, participants may undergo unscheduled safety evaluations (onsite or remote) for new/worsening symptoms, device issues, or investigator concern. These assessments may include AE/SAE/UADE review, device deficiency capture, and targeted technique assessment. Report UADEs and serious safety events per regulatory timelines [1,3].

- Rescheduling rules: Visits should not be pulled forward by more than 50% of the window or pushed back beyond the maximum window without PI approval and documentation. Repeated missed windows trigger a site-level corrective and preventive action (CAPA) review.

- Data completeness: When assessments are partially completed, record completed elements and reasons for missing elements. Use predefined hierarchy for endpoint derivation when multiple sources exist (e.g., central adjudication supersedes site read) [1].

Site Enrollment Committee (SEC) charter (summary)

- Membership: Minimum of three voting members: Site PI (Chair), one sub-investigator (physician), and one qualified respiratory care professional (e.g., physiotherapist, nurse, or respiratory therapist). A non-voting coordinator may support documentation.

- Quorum and voting: Quorum is three voting members including the PI or designee. Decisions are made by simple majority; in a tie, the PI's vote is decisive. Members with conflicts of interest recuse themselves.

- Scope and decision rule: The SEC verifies eligibility against inclusion/exclusion criteria, confirms informed consent, assesses operational feasibility (device/app access, eID, smartphone compatibility), and approves or declines enrollment. Approval is required prior to randomization.

- Timelines and documentation: Reviews occur within two business days of screening completion. Decisions, rationale, and any required contingencies are documented in the SEC log and filed in the site's electronic investigator site file (eISF). All decisions are auditable and follow ISO 14155 and ICH-GCP documentation standards [1,2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
5. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19:10. doi:10.1186/s12931-017-0710-y
6. European Medicines Agency. Guidance on the use of decentralised elements in clinical trials. 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/decentralised-clinical-trials-guidance

2.1 Study Design Schematic

Study-flow narrative

Pre-enrollment screening and consent: Potential participants are identified in outpatient respiratory/asthma/COPD clinics. Site staff pre-screen for core criteria (age ≥16 years; documented asthma and/or COPD; current daily use of DPI and/or MDI; ability to independently handle the inhaler; access to an iOS/Android smartphone; access to BankID or comparable electronic identification).

Written informed consent is obtained by the PI or a qualified delegate before any study-specific procedures, in accordance with ISO 14155 and ICH-GCP [1,2].

Committee-based eligibility review and enrollment decision rule: After site screening, the Site Enrollment Committee (SEC) performs a rapid review of inclusion/exclusion criteria, confirms informed consent, and verifies operational feasibility (smartphone compatibility and eID access). Enrollment is authorized only after SEC approval with quorum and PI attestation. Randomization is 1:1, stratified by inhaler type (DPI, MDI, or both), using a concealed allocation system. Randomization occurs within 0–7 days following SEC approval [1–3].

Procedure day including baseline assessments: On the procedure/baseline day (preferably Day 0), sites complete medical history, physical exam, vitals, SpO2, concomitant medications, spirometry per ATS/ERS standards, and baseline inhalation technique evaluation using a standardized checklist. Any safety laboratories specified in the protocol are performed. Participants randomized to the investigational arm receive access activation for the app-based inhalation module within AsthmaTuner (version later than 5.4.13.5) and are provisioned with the CE-marked AsthmaTuner spirometer and the Airflow Trainer, shipped to the home or handed out onsite. Control participants receive standardized non–app-based inhalation technique education aligned to a predefined checklist [1,3–5].

Post-procedure and discharge tasks including scheduling: Participants receive AE/SAE/UADE reporting instructions and site contact information. The site schedules the 30-day safety check and the primary endpoint visit (target Week 8 within a 6–12 week window), and provides the long-term follow-up calendar (6 and 12 months, then annually through Year 5). Remote options are offered where appropriate and compliant with local regulations and data privacy requirements [1,3,6].

Early safety follow-up visit (30 days): Focused safety review for AEs, UADEs, and device deficiencies, and assessment of early usability. Remote conduct via telemedicine/app-based data capture is permitted when clinically appropriate [1,3,6].

Intermediate efficacy follow-up visits: The primary endpoint visit at Week 6–12 assesses correct inhalation technique success rate using pre-specified criteria with central review of technique artifacts (e.g., videos/flow curves), alongside safety and usability evaluations. A 6-month visit reassesses inhalation technique, spirometry, health status, and rescue medication use, and collects app engagement data in the intervention arm. A 12-month visit evaluates durability of effect and ongoing safety/usability [4,5].

Annual follow-up visits through Year 5: Annual visits at Years 2–5 collect long-term safety and effectiveness data, including persistence of correct inhalation technique, respiratory outcomes, healthcare utilization, and exposure to app/software updates and device deficiencies. Centralized adjudication is applied where specified to maintain assessment consistency and minimize bias [1,3–5].

Study close-out: At the final annual visit or early termination, complete final AE/SAE/UADE assessments, perform device/app accountability and deactivation procedures, reconcile inventories, and confirm transition to routine care. All close-out activities are documented in the site file per ISO 14155/ICH-GCP [1,2].

Visit schedule and timing windows

Visit	Nominal timing from randomization	Window (allowable)	Mode (onsite/remote)	Deviation handling
Screening and consent	Day −28 to 0	±7 days	Onsite or hybrid	Out-of-window requires PI justification; no study-specific procedures prior to consent [1,2]
SEC eligibility review and enrollment	Day 0 to +7	0 to +7 days	Central/site committee	Randomize only after SEC approval; delays beyond

				+7 days require re-verification of key criteria
Procedure/baseline	Day 0	±7 days	Onsite preferred	If >7 days from SEC approval, repeat key eligibility checks and baseline technique
30-day safety	Day 30	±3 days	Onsite or remote	If missed, perform within 14 days; document reason and impact [1,3]
Primary endpoint (Week 6–12)	Day 42 to Day 84	Target Day 56 ±14 days within 6–12 week window	Onsite or hybrid with central review	If outside 6–12 weeks, endpoint is out-of-window; central adjudication may accept data within +14 days for sensitivity analyses [1,4]
6-month	Month 6	±14 days	Onsite or remote	If missed, perform within 30 days; otherwise skip and document [1]
12-month	Month 12	±21 days	Onsite or remote	If missed, perform within 45 days; otherwise skip and document
Annual Year 2–5	Months 24/36/48/60	±30 days	Onsite or remote	If missed, perform within 60 days; otherwise skip and document
Study close-out	Within 30 days after final annual visit or early termination	±14 days	Onsite or remote	Complete final safety and accountability; document early exits

Allowable deviations: Visits completed within windows are protocol-compliant. Out-of-window assessments require PI documentation of reason, risk assessment, and impact on endpoints, per ISO 14155/ICH-GCP. Acceptance of limited deviations for the primary endpoint must be pre-specified and approved by the Sponsor and DSMB [1–3].

Per-visit assessment checklists, endpoint mapping, and central review

Visit	Assessment item	Endpoint mapping	Central review/adjudication
Screening/consent	Informed consent; demographics; diagnosis verification; inhaler type; smartphone/eID check	Feasibility	No
Screening/consent	Inclusion/exclusion confirmation; pregnancy status if applicable	Safety/feasibility	No
Screening/consent	Concomitant medications; exacerbation history (prior 12 months)	Exploratory efficacy	No
Baseline/procedure	Physical exam; vitals; SpO2	Safety	No
Baseline/procedure	Safety laboratories (panel per protocol; to be confirmed)	Safety	No
Baseline/procedure	Spirometry per ATS/ERS (FEV1, FVC)	Exploratory efficacy	Yes (quality control) [4]
Baseline/procedure	Inhaler technique assessment using standardized checklist (arm-agnostic)	Efficacy baseline	Yes (adjudication) [5]
Baseline/procedure	Device/app provisioning (intervention) or delivery of standardized control education	Usability/feasibility	No

30-day safety	AE/SAE/UADE review; device deficiencies/malfunctions; concomitant meds	Safety	Yes (UADE classification) [1,3]
30-day safety	App usage metrics (intervention): logins/training sessions/completions	Usability/feasibility	Yes (central extract)
30-day safety	Inhaler technique spot-check (as feasible)	Exploratory efficacy	Yes (if artifact uploaded)
Week 6–12 primary	Standardized inhaler technique performance (success/fail by pre-specified criteria)	Primary efficacy	Yes (dual adjudication) [5]
Week 6–12 primary	Spirometry; rescue medication use; patient-reported ease-of-use	Secondary efficacy/usability	Yes (spirometry QC) [4]
Week 6–12 primary	AE/SAE/UADE review; device deficiency	Safety	Yes (UADE classification) [1,3]
6-month	Inhaler technique success; spirometry; exacerbations since last visit	Secondary efficacy	Yes (as applicable) [4,5]
6-month	System usability scale or equivalent (intervention)	Usability	No
6-month	AE/SAE/UADE review; device deficiency	Safety	Yes
12-month	Inhaler technique success; spirometry; health status (e.g., ACT/CAT; to be confirmed)	Secondary/exploratory efficacy	Yes (spirometry QC) [4]
12-month	App engagement (intervention) and adherence to education	Usability/feasibility	Yes (central extract)
12-month	AE/SAE/UADE review; device deficiency	Safety	Yes
Annual Y2–Y5	Inhaler technique success; respiratory outcomes; healthcare utilization	Long-term effectiveness	Yes (if submissions)
Annual Y2–Y5	AE/SAE/UADE review; device deficiency; software update exposure	Long-term safety	Yes
Close-out	Final AE/SAE/UADE status; device/app deactivation; accountability	Safety/feasibility	No

Notes:

- Standardized inhalation technique criteria, video/flow-curve capture specifications, and adjudication procedures will be detailed in the Adjudication Manual; central reviewers remain blinded to treatment allocation to minimize bias [1,5].
- Spirometry adheres to ATS/ERS standards; central quality control grades acceptability and repeatability [4].
- UADEs and device deficiencies are categorized and reported per ISO 14155 and applicable MDR requirements [1,3].

Handling of missed/late visits, remote alternatives, and unscheduled safety evaluations

Missed or late visits: If a scheduled visit cannot be completed within the nominal window, it should be conducted at the earliest opportunity within the defined grace period (see table). For the primary endpoint window (6–12 weeks), if missed, obtain the technique assessment within +14 days and flag for sensitivity analyses; if unobtainable, the participant is not replaced. All deviations must be documented with rationale, risk assessment, and potential impact on endpoints, consistent with ISO 14155/ICH-GCP [1,2].

Remote alternatives and substitutions: Telemedicine and remote assessments (e.g., app-based

training logs, patient-reported outcomes, video uploads of inhalation technique, and shipped at-home spirometry where permitted) are allowed when clinically appropriate, validated, and compliant with local regulations and data protection. Identity verification uses eID where applicable. Remote assessments must follow standardized procedures to ensure data integrity and participant safety; any substitutions are pre-specified and documented [1,3,6].

Unscheduled safety evaluations: Unscheduled evaluations may be initiated at any time for new or worsening symptoms, suspected device deficiencies/malfunctions, or investigator/sponsor concern. These may include AE/SAE/UADE assessment, targeted physical examination, verification of device/app function, and focused inhalation technique assessment. UADEs and serious events are reported per regulatory timelines and sponsor procedures [1,3].

Rescheduling rules and CAPA triggers: Visits should not be advanced by more than 50% of the allowable window nor delayed beyond the maximum window without PI approval and documentation. Repeated missed or late windows trigger a site-level corrective and preventive action review. For partially completed assessments, record completed elements and reasons for missing items; central adjudication supersedes site reads where applicable [1].

Site Enrollment Committee (SEC) charter (summary)

Structure and membership: The SEC is a multidisciplinary committee composed of at least three voting members: the Site Principal Investigator (Chair), one physician sub-investigator, and one qualified respiratory care professional (e.g., physiotherapist, nurse, or respiratory therapist). A study coordinator may participate as a non-voting member for documentation support.

Quorum and decisions: Quorum is three voting members, including the PI or designee. Decisions are by simple majority; in case of tie, the PI’s vote is decisive. Members with any conflict of interest recuse themselves.

Decision rule and scope: The SEC confirms informed consent, verifies eligibility against all inclusion/exclusion criteria, confirms operational readiness (smartphone compatibility, eID access), and ensures no planned discontinuation of DPI/MDI use within 6–12 weeks. Enrollment authorization is required before randomization.

Documentation and timelines: Reviews occur within two business days of screening completion. SEC determinations, vote tallies, rationales, and any contingencies are recorded in the SEC log and filed in the electronic investigator site file. Records are auditable and maintained per ISO 14155/ICH-GCP and EU MDR documentation standards [1–3].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
5. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19:10. doi:10.1186/s12931-017-0710-y
6. European Medicines Agency. Guidance on the use of decentralised elements in clinical trials. 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/decentralised-clinical-trials-guidance

3 PROJECT PLAN

3.1 Rationale for Study

Asthma and COPD affect hundreds of millions worldwide and are major causes of morbidity and healthcare utilization. Despite the availability of effective inhaled therapies, incorrect inhaler technique is common and is consistently associated with poorer symptom control, increased exacerbations, and higher resource use [5,7,8]. Authoritative guidelines for asthma and COPD emphasize selecting an appropriate inhaler and providing structured training with reassessment of technique at follow-up, underscoring the clinical importance of correct device use across adolescents and adults [7,8].

Handling metered dose inhalers (MDIs) and dry powder inhalers (DPIs) requires distinct steps; critical errors include poor coordination with actuation for MDIs and inadequate inspiratory effort for DPIs [5,7,8,11]. In real-world populations—including older adults and patients with reduced lung function—suboptimal peak inspiratory flow (PIF) through DPIs is frequent and can compromise drug delivery [9]. Objective characterization of inhalation profiles (e.g., PIF, time to PIF, inspiratory duration) provides actionable information to target training and reduce critical errors but is rarely available during routine education using checklists alone [10,11]. The investigational inhalation app-module embedded in AsthmaTuner is designed to deliver standardized, on-demand education and feedback, paired with objective inhalation metrics captured via the CE-marked AsthmaTuner spirometer and an Airflow Trainer, to improve the rate of correct technique compared with conventional non–app-based education.

Unmet need persists because conventional technique education often relies on brief, episodic instruction with variable standardization, limited access outside clinic settings, and uncertain retention; technique commonly deteriorates over time without reinforcement [7,8,14]. Systematic reviews indicate that education can improve technique performance, but the durability of effect is variable, clinical outcome translation is inconsistent, and evidence with modern digital, feedback-enabled interventions remains limited and heterogeneous [14]. There are additional uncertainties specific to the target population and context of use that warrant a definitive evaluation: which subgroups (e.g., DPI versus MDI users; those with low baseline PIF; adolescents versus older adults) derive the greatest benefit; whether objective, app-guided training reduces critical errors beyond standardized checklist-based education; the usability and engagement of an app-based approach in routine care settings; and the short- to intermediate-term safety profile and device deficiency rate of a software-based medical device used at home [5,7–11,14]. Furthermore, while guideline bodies advocate technique assessment and re-training, they provide limited direction on the role and magnitude of benefit of app-based objective feedback relative to standardized non-digital education, creating a meaningful evidence gap for decision-makers [7,8,14].

A prospective, randomized, parallel-group, single-blind clinical investigation with centralized, blinded adjudication of technique performance is therefore warranted to generate high-quality evidence on the balance of safety, feasibility, usability, and clinical benefit over 6–12 weeks, with extended follow-up for durability. This approach aligns with ISO 14155 principles for minimizing bias and ensuring data integrity in device trials and with EU MDR expectations that clinical evidence be appropriate to the device's characteristics and intended purpose [1,3]. The design directly compares the investigational app-based education and training against standardized non–app-based education, using pre-specified, centrally reviewed criteria of successful inhalation technique as the primary endpoint, to address key uncertainties related to patient selection, objective performance metrics (including PIF and inhalation timing), and real-world usability. The DSMB and predefined safety assessments further support a rigorous evaluation of device-related adverse events and deficiencies during short- and intermediate-term follow-up [1,3,6]. Collectively, this confirmatory study is intended to resolve current evidence gaps and inform the clinical utility and implementation of objective, app-based inhalation training in adolescents and adults with asthma and/or COPD who use MDIs and/or DPIs [5,7–11,14].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
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3.2 Design

Overall design

This is a prospective, multicenter, Phase III, randomized, parallel-group, individually single-blind clinical investigation comparing standard care plus app-based education and training of inhalation technique (investigational arm) versus standardized non–app-based education (control) in adolescents and adults with asthma and/or COPD who use DPI and/or MDI inhalers. Participants are allocated 1:1 with stratification by inhaler type (DPI, MDI, or both) to support balance across device classes relevant to technique performance [1,3,5]. The investigation is open-label to participants and site staff for intervention delivery; primary endpoint assessments undergo centralized, blinded adjudication to minimize assessment bias (single-blind outcome assessment) in accordance with ISO 14155 principles [1].

Population framework

The study population comprises individuals aged 16 years or older with a documented diagnosis of asthma and/or COPD who use a DPI and/or MDI as part of daily treatment and can independently handle their inhaler. Participants are expected to have ongoing symptom management needs typical of guideline-based care, with confirmation of diagnosis and current inhaler use by treating clinicians. Key exclusions include inability to use a compatible smartphone or national electronic identification service, anticipated discontinuation of DPI/MDI use during the initial 6–12 weeks after inclusion, or inability to independently perform inhalation through DPI/MDI. Diagnostic verification is based on clinical records and standard care testing; spirometry quality control follows ATS/ERS technical standards where applicable [4]. This framework targets patients for whom correct inhaler technique is clinically consequential and where app-based education may address persistent technique errors observed in routine practice [5,7,8].

Multidisciplinary eligibility determination and adjudication

Eligibility confirmation and enrollment occur via a Site Enrollment Committee (SEC) comprising the Principal Investigator, a physician sub-investigator, and a qualified respiratory care professional. The SEC verifies informed consent, diagnosis and inhaler use, and operational feasibility (smartphone compatibility and electronic ID access). Randomization proceeds only after SEC approval with quorum and investigator attestation, and all decisions are documented in auditable logs consistent with ISO 14155 and ICH-GCP [1,2]. Centralized, blinded adjudication is applied to the primary technique-performance endpoint, and spirometry data undergo central quality control, to ensure consistent assessments across sites and reduce bias [1,4]. A DSMB provides safety oversight in line with good clinical practice and applicable medical device regulations [1–3].

Investigational device use and training

The investigational intervention is the inhalation app-module embedded in the AsthmaTuner application (version later than 5.4.13.5), used together with the CE-marked AsthmaTuner system (spirometer) and the Airflow Trainer for objective feedback on inhalation profiles. The inhalation app-module is accessible only within this clinical investigation; its use is investigational under EU MDR and conducted in compliance with ISO 14155 and ICH-GCP [1–3]. Investigators and designated site staff will complete sponsor-approved training covering: eligibility confirmation and SEC processes; standardized, checklist-based inhaler technique education for the control arm; device/app provisioning and participant instruction for the investigational arm; safe handling and accountability of the spirometer and Airflow Trainer; endpoint artifact capture (e.g., videos/flow curves) and secure transmission; AE/SAE/UADE and device deficiency recognition and reporting; and spirometry conduct aligned with ATS/ERS standards [1,3,4]. Competency is documented prior to participant enrollment.

Data collection and visit schedule overview

Data collection includes screening and informed consent; committee-based eligibility review and randomization; baseline/procedure assessments (medical history, examination as per protocol, spirometry per ATS/ERS, and standardized inhalation technique evaluation); a 30-day safety check; a primary endpoint visit at 6–12 weeks with centralized, blinded adjudication of technique performance; intermediate follow-up at 6 and 12 months for durability, usability, and safety; and annual follow-up through Year 5 for long-term safety and effectiveness. Protocol-defined visit windows, central quality control of spirometry, and dual-adjudicator review of technique artifacts are applied to support data integrity and minimize bias [1,4,5]. Where appropriate and permitted by local regulations, specified assessments may be performed via validated remote/decentralized methods (telemedicine, secure app-based data capture and video uploads), consistent with regulatory guidance on decentralized elements [1,3,6].

References

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3.3 Statistical Analysis

Objectives, endpoints, and assessment window

- Primary endpoint: Proportion of participants achieving correct inhalation technique at the 6–12 week visit, based on pre-specified standardized criteria with centralized, blinded adjudication. The primary analysis window is any assessment conducted within the protocol-defined 6–12 week window; out-of-window assessments within the pre-specified grace period will be included in sensitivity analyses as outlined below.

- Key secondary endpoints (summarized): persistence of correct inhalation technique at 6 and 12 months; change from baseline in spirometry (e.g., FEV1, FVC per ATS/ERS technical standards), patient-reported ease-of-use/usability (including standardized scales where applicable), app engagement metrics in the investigational arm (e.g., logins, completed training sessions), rescue medication use, exacerbation-related outcomes over follow-up, and device-related safety (AEs/SAEs/UADEs) and device deficiencies.

- Exploratory endpoints: inhalation profile parameters (e.g., peak inspiratory flow, time to PIF, inspiratory duration), health status measures (e.g., ACT/CAT if implemented), healthcare utilization, and long-term effectiveness and safety through Year 5.

Estimand framework

The primary estimand targets the treatment policy effect of randomized assignment to app-based education and training versus standardized non–app-based education on the binary outcome of correct inhalation technique at 6–12 weeks, in all randomized participants, regardless of post-randomization adherence, protocol deviations, or intercurrent events (e.g., temporary discontinuation of the app module). The variable and assessment window are as defined above. This approach aligns with ICH E9 and the E9(R1) estimand framework for confirmatory trials [15,16].

Analysis populations

- Intent-to-treat (ITT) population: all randomized participants, analyzed according to randomized allocation. Primary efficacy analyses will be based on ITT to preserve randomization and estimate the treatment policy effect [15,16].

- Per-protocol (PP) population: subset of ITT excluding major protocol deviations that are expected to materially affect the primary endpoint (e.g., ineligible at baseline; no primary endpoint assessment within the window and no acceptable grace-period data; uncontrolled cross-over usage of the investigational module in control). Criteria will be pre-specified before database lock.

- Safety population: all participants who receive any component of the assigned education/training after randomization; participants are analyzed as treated for safety summaries.

Protocol deviations and crossovers will be summarized by type and arm. The ITT analysis is primary; PP analyses are supportive.

General statistical conventions

- All statistical tests will be two-sided with a nominal alpha of 0.05 unless otherwise specified.

- Continuous variables will be summarized by mean, standard deviation, median, interquartile range, minimum, and maximum. Categorical variables will be summarized by counts and percentages. Confidence intervals (CIs) will be 95% unless otherwise stated.

- Distributional assumptions will be evaluated; appropriate transformations or non-parametric methods will be used when assumptions are not met.

- The statistical analysis will be conducted using validated software (e.g., SAS or R); the statistical programming environment and versions will be documented in the Statistical Analysis Plan (SAP).

Primary efficacy analysis

- Point estimates: group-specific proportions of correct technique at 6–12 weeks, with 95% CIs (exact or Wilson/Newcombe methods for binomial proportions and differences, as appropriate) [25,26].

- Primary comparison: between-group difference using a stratified analysis by randomization strata (inhaler type: DPI, MDI, both) via the Cochran–Mantel–Haenszel (CMH) method to estimate a common risk difference and/or common risk ratio with 95% CIs and a CMH test for superiority [24]. A logistic regression model adjusted for stratification factors and pre-specified prognostic covariates (e.g., baseline technique status, age group) will provide supportive estimates (odds ratio with 95% CI).

- Sensitivity analyses:
  - ITT with alternative missing data assumptions (see Missing data).
  - PP analysis to assess robustness to major deviations.
  - Window sensitivity including adjudicator-confirmed assessments within the grace period.
  - Model-based analyses using log-binomial or Poisson regression with robust variance to estimate risk ratios when convergence permits; if not, logistic regression results will be primary for model-based inference [25].

- Subgroup analyses: prespecified subgroups include inhaler type strata, diagnosis (asthma/COPD), baseline PIF category, baseline technique correctness, age category (e.g.,

adolescents ≥16–<18, adults), and sex. Treatment-by-subgroup interaction terms will be evaluated in logistic models; subgroup-specific effects with 95% CIs will be presented descriptively. These analyses are exploratory unless otherwise pre-specified.

Key secondary and exploratory analyses

- Repeated binary outcomes (technique success at 6 and 12 months): analyzed using generalized linear mixed models with a logit link including fixed effects for treatment, visit, treatment-by-visit interaction, baseline technique status, and inhaler-type stratum, with participant-level random intercepts; marginal estimates and contrasts with 95% CIs will be reported. Where appropriate, CMH analyses at each visit will be provided descriptively.

- Continuous outcomes (e.g., spirometry, usability scores, inhalation profile parameters): analyzed as change from baseline using linear mixed-effects models for repeated measures (MMRM) with fixed effects for treatment, visit, baseline value, inhaler-type stratum, and treatment-by-visit interaction, assuming an unstructured covariance where supported by data; Kenward–Roger or Satterthwaite approximations will be used for degrees of freedom. If model assumptions are untenable, non-parametric approaches (e.g., Hodges–Lehmann median differences, rank-based ANCOVA) will be used [18].

- Time-to-event outcomes (e.g., time to first moderate/severe exacerbation): summarized with Kaplan–Meier curves, medians and 95% CIs, and compared using Cox proportional hazards models adjusted for inhaler-type stratum; proportionality assumptions will be assessed and alternative models considered if violated [19,20].

- App engagement metrics (intervention arm): summarized descriptively; associations with technique success may be explored using regression models within the intervention arm.

- Healthcare utilization and long-term durability: analyzed descriptively and via appropriate regression or survival methods, recognizing exploratory intent.

Safety analysis

- AEs, SAEs, UADEs, and device deficiencies will be coded and summarized by system organ class and preferred term, severity, and relationship to device/procedure, overall and by arm, including incidence proportions with 95% CIs. Exposure-adjusted incidence rates will be provided for long-term follow-up.

- Comparative analyses of safety endpoints will be descriptive; where inferential comparisons are planned (e.g., rate ratios for AE incidence), appropriate models (e.g., Poisson or negative binomial with offset) will be used.

Multiplicity control

If a confirmatory hierarchy is prespecified, hypothesis testing will proceed sequentially from the primary endpoint to designated key secondary endpoints (e.g., technique success at 6 and 12 months, change in FEV1), maintaining the family-wise error rate at 0.05 via gatekeeping. If a hierarchy is not finalized, secondary and exploratory analyses will be interpreted descriptively without formal multiplicity adjustment, or a pre-specified adjustment method such as Holm's procedure may be applied to a limited family of key secondary endpoints [27]. The final approach will be detailed in

the SAP prior to database lock.

Missing data, censoring, and intercurrent events

- Primary endpoint: The primary analysis will use the ITT population with multiple imputation under a missing-at-random (MAR) assumption incorporating treatment, inhaler-type stratum, baseline technique status, and other prognostic covariates. Imputation models will respect the binary nature of the endpoint. Sensitivity analyses will include:

 - Missing-not-at-random (MNAR) scenarios via delta-adjusted or tipping-point analyses.
 - Worst-plausible imputation (e.g., missing = failure) and best-plausible (e.g., missing imputed from control-arm distribution) to bound inferences [16,17,23].

- Longitudinal continuous endpoints: MMRM inherently accommodates missing at random without imputation; sensitivity analyses will include multiple imputation and pattern-mixture models when appropriate [18,23].

- Time-to-event endpoints: Participants without events will be censored at last adequate assessment; definitions of events and censoring follow the SAP.

- Intercurrent events: Consistent with the treatment policy strategy, data after intercurrent events (e.g., temporary discontinuation, device replacement) will be included where available; sensitivity analyses using alternative strategies (e.g., hypothetical without use after discontinuation) may be conducted for context [16,17].

Interim monitoring and stopping

An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data at pre-specified intervals and ad hoc as needed. No formal interim efficacy analyses are planned; therefore, no alpha spending or sample size adjustments for interim efficacy looks are required. The DSMB may recommend study modification, temporary suspension, or termination for safety, feasibility, or data integrity concerns according to its charter and applicable guidance [21].

Data quality, adjudication, and blinding

Primary endpoint determinations will use centrally adjudicated, blinded assessments to minimize bias. Where both site and central reads exist, central adjudication will supersede site assessments for efficacy analyses. Spirometry will undergo central quality control grading; analyses may adjust for quality grade as appropriate.

Sensitivity and supportive analyses

- Alternative effect measures (risk difference, risk ratio, odds ratio) with 95% CIs for the primary endpoint.

- Per-protocol analysis for the primary endpoint.

- Robustness to analysis window deviations and adjudication outcomes.

- Influence diagnostics and model fit assessments; non-parametric alternatives where indicated.

Subgroup and interaction analyses

Pre-specified subgroups include inhaler type (strata), diagnosis (asthma/COPD), baseline technique correctness, baseline inspiratory flow category, age group, and sex. Interaction p-values from regression models will be provided; subgroup findings will be considered exploratory.

Deviations from plan

Any substantive deviations from this plan will be finalized in a version-controlled SAP before database lock and documented with rationale in the clinical study report.

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3.4 Study Endpoints

Overview and alignment with objectives

Endpoints are defined to evaluate whether app-based education and training of inhalation technique, delivered via the investigational inhalation app-module embedded in AsthmaTuner (version later than 5.4.13.5), improves correct inhalation technique versus standardized non–app-based education at 6–12 weeks, and to characterize safety, usability, and longer-term effectiveness. Endpoint selection, definitions, windows, and assessment methods are consistent with ISO 14155/ICH-GCP, EU MDR, ATS/ERS spirometry standards, and respiratory guideline definitions where applicable [1–4,7,8].

Primary endpoints

- Primary efficacy endpoint: Proportion of participants with correct inhalation technique at the 6–12 week visit, determined by pre-specified standardized criteria with centralized, blinded adjudication based on site-collected artifacts (e.g., video and/or flow-curve submissions) according to the Adjudication Manual. The primary assessment window is any evaluation within the protocol-defined 6–12 week window; a pre-specified grace period may be considered in sensitivity analyses per the Statistical Analysis Plan (SAP) [1,4,5].

- Primary safety endpoint: Incidence of device-related untoward medical occurrences through Day 30 after randomization, defined as the composite of:

- Device-related adverse events (AEs) and serious adverse events (SAEs), including serious deterioration in health judged related to the investigational device and/or its use.
- Unanticipated Serious Adverse Device Effects (UADEs).
- Device deficiencies that result in a medical occurrence or require medical intervention to prevent serious deterioration.

Safety classification and relatedness will be determined per ISO 14155 and applicable MDR requirements, with centralized review of UADE classification and device deficiency categorization; the 30-day window aligns with early post-initiation risk surveillance for medical devices [1,3].

Secondary endpoints

- Secondary efficacy endpoints:

- Persistence of correct inhalation technique at Month 6 and Month 12 (central blinded adjudication as for the primary efficacy endpoint) [1,5].
- Spirometry: change from baseline in FEV1 and FVC at Week 6–12, Month 6, and Month 12; acceptable/ repeatable spirograms per ATS/ERS 2019 standards with centralized quality control [4].
- Inhalation profile parameters: change from baseline in peak inspiratory flow (PIF), time to PIF, and inspiratory duration collected using the CE-marked spirometer and Airflow Trainer, summarized at Week 6–12, Month 6, and Month 12 (central review for data quality where applicable) [4,5].
- Rescue medication use: change from baseline in short-acting bronchodilator puffs per day/week over the periods baseline→Week 6–12, baseline→Month 6, and baseline→Month 12 (source: participant diary/app or site-recorded logs).
- Exacerbation outcomes: incidence of moderate/severe exacerbations during follow-up (definitions aligned to GINA/GOLD; data from medical records, participant report, and healthcare utilization) [7,8].
- Patient-reported ease-of-use/usability: change from baseline and status at Week 6–12, Month 6, and Month 12 using prespecified instruments (e.g., System Usability Scale or equivalent; instrument to be confirmed), and device-specific ease-of-use ratings (Likert-type; tool to be confirmed).
- App engagement (intervention arm): training sessions initiated/completed, total time in training, and logins over baseline→Week 6–12 and baseline→Month 6/12 (source: centralized app telemetry).

- Secondary safety endpoints:

- Incidence, severity, and relatedness of all AEs/SAEs through Month 12 and annually to Year 5; exposure-adjusted incidence rates for long-term summaries [1].
- Incidence and categorization of device deficiencies and malfunctions, including those associated with software/app updates, with outcomes and corrective actions documented per MDR [3].
- Respiratory-specific safety signals: serious bronchospasm requiring urgent care, hypoxemia requiring supplemental oxygen, and hospitalization due to respiratory causes during follow-up (medical record verified).
- Discontinuation or interruption of investigational device use due to safety or usability concerns through Month 12.

Exploratory endpoints

- Health status measures (to be confirmed): change from baseline in validated instruments such as the Asthma Control Test (ACT) for asthma and COPD Assessment Test (CAT) for COPD at Month 6 and Month 12, if implemented; instrument selection and minimal clinically important difference definitions will follow validated sources (to be specified) [7,8].

- Healthcare utilization: respiratory-related unscheduled visits, emergency department visits, hospitalizations, systemic corticosteroid bursts, and antibiotic courses during follow-up (medical records and participant report).
- Learning curve and durability: time-to-first adjudicated correct technique; number of app-based training sessions required to achieve first success (intervention arm); persistence of success annually through Year 5.
- Subgroup performance: exploratory treatment effects within prespecified subgroups (e.g., DPI versus MDI users; baseline technique incorrect versus correct; baseline low-versus-adequate PIF categories; age groups; asthma versus COPD) [5,7,8].
- Human factors/usability observations: task completion rates for key steps (e.g., device pairing, artifact capture/upload) and help-desk contacts.
- Algorithmic/analytics signals: association between inhalation profile parameters and technique success; exploratory predictive modeling of technique success using baseline characteristics (exploratory, no confirmatory inference).

Endpoint definitions, assessment windows, and data sources

- Correct inhalation technique: a binary endpoint defined by pre-specified, device-agnostic standardized criteria for MDI and DPI use, including critical error domains, with centralized, blinded adjudication of site-submitted artifacts. The detailed rubric, acceptable artifact formats, and adjudicator tie-break procedures are specified in the Adjudication Manual. Assessments are performed at baseline (for context), Week 6–12 (primary), Month 6, Month 12, and annually through Year 5 [1,5].
- Safety endpoints: AEs/SAEs/UADEs and device deficiencies are collected continuously from consent until study close-out, with a focused 30-day early safety window for the primary safety endpoint and cumulative summaries at each scheduled visit. Event seriousness, severity, relatedness, and expectedness are determined by the investigator and subject to centralized review for UADEs and device deficiencies per ISO 14155/MDR [1,3].
- Spirometry: conducted per ATS/ERS with site technicians trained and certified; spirograms undergo centralized quality control for acceptability and repeatability. Primary spirometry summaries are based on centrally graded data; site values are used only if central review is not feasible and will be sensitivity-only [4].
- App engagement and telemetry: extracted from the sponsor’s secure telemetry systems for the intervention arm; summaries are time-bounded to the analysis windows.
- Exacerbations and healthcare utilization: derived from participant reports corroborated by medical records when available; definitions align with GINA/GOLD [7,8].
- Patient-reported measures: collected via validated instruments where applicable; any translations or electronic implementations will follow instrument licensing and ePRO best practices (to be detailed in study manuals) [1,2].

Central adjudication, core review, and blinding

- Technique performance adjudication: centralized, dual independent reviewers blinded to treatment assignment, with adjudicator consensus/tie-break rules per Adjudication Manual; central reads supersede site assessments for efficacy analyses [1].
- Spirometry core quality control: centralized review of acceptability and repeatability per ATS/ERS; queries issued to sites for correction/repeat as feasible [4].
- Safety review: centralized classification of UADEs and device deficiencies; DSMB oversight of unblinded cumulative safety per its charter. Investigators remain responsible for initial assessment and timely reporting per ISO 14155/MDR [1,3].

Endpoint-to-visit mapping

Endpoint category	Endpoint (concise)	Primary data source(s)	Assessment timepoints	Central adjudication/core review
Primary efficacy	Correct inhalation technique (success/fail)	Site-captured video/flow-curve artifacts; adjudication case form	Week 6–12 (primary); sensitivity within grace period per SAP	Yes (blinded adjudication)
Primary safety	Composite of device-related AEs/SAEs, UADEs, and device deficiencies requiring intervention	AE/SAE/UADE CRFs; device deficiency forms; medical records	Day 0–30	Yes (UADE/deficiency classification)
Secondary efficacy	Technique persistence	Same as primary efficacy	Month 6; Month 12; annually Years 2–5	Yes
Secondary efficacy	Spirometry change (FEV1, FVC)	Spirometry traces and QC grades	Week 6–12; Month 6; Month 12	Yes (central QC)
Secondary efficacy	Inhalation profile parameters (PIF, time to PIF, inspiratory duration)	Spirometer/Airflow Trainer data; app export	Week 6–12; Month 6; Month 12	Yes (data QC as applicable)
Secondary efficacy	Rescue medication use	Diaries/app logs; site-recorded logs	Week 6–12; Month 6; Month 12	No (data verification only)
Secondary efficacy	Exacerbations	Participant report; medical records	Baseline→Month 6/12; annually Years 2–5	No (definition per GINA/GOLD)
Secondary efficacy	Usability/ease-of-use	Prespecified questionnaires; study-specific ratings	Week 6–12; Month 6; Month 12	No
Secondary efficacy	App engagement (intervention)	Centralized telemetry	Baseline→Week 6–12; Month 6; Month 12	Yes (central extract)
Secondary safety	All AEs/SAEs; respiratory-specific safety signals	AE/SAE CRFs; medical records	Continuous; summarized at each visit	No (central aggregation; UADEs centrally classified)
Secondary safety	Device deficiencies/malfunctions and outcomes	Device deficiency forms; technical logs	Continuous; summarized at each visit	Yes (classification)
Exploratory	Health status (e.g., ACT/CAT; to be confirmed)	Validated questionnaires	Month 6; Month 12	No
Exploratory	Healthcare utilization	Participant report; medical records	Month 6; Month 12; annually Years 2–5	No
Exploratory	Learning curve/time-to-first success	Adjudicated technique outcomes; app telemetry	Baseline→Month 12	Yes (for technique outcomes)
Exploratory	Subgroup performance and analytics	Aggregated datasets	As per efficacy timepoints	Not applicable (analytical)

All endpoints, definitions, and operational procedures will be finalized in the SAP and study manuals prior to database lock, consistent with ISO 14155/ICH-GCP. Any changes after first patient in will be prospectively documented and justified [1,2].

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4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Baseline / Screening

Objectives and scope

Screening and baseline procedures are conducted to: obtain and document legally valid informed consent; verify all inclusion and exclusion criteria; confirm operational feasibility for participation (smartphone compatibility, access to BankID or similar electronic personal identification service, and device logistics); and establish baseline measurements, including objective assessments of inhalation technique and spirometry, to support stratified randomization and subsequent blinded endpoint adjudication. All screening activities will be performed in compliance with ISO 14155, ICH-GCP, and applicable medical device regulations, with decentralized elements permitted as allowed locally [28–31,33].

Site-facing screening workflow and timing windows

The following checklist outlines required steps and source documentation. Activities may be completed in person or via approved decentralized methods within protocol-defined windows; out-of-window completions require documentation and, if applicable, SEC review [28–31,33].

- Pre-screening identification and privacy safeguards

- Identify potential participants meeting high-level criteria (age ≥16 years; asthma and/or COPD; daily DPI/MDI use) through clinic lists or referrals.
- Conduct initial contact in accordance with local privacy regulations; do not collect identifiable screening data before documenting permission for contact per institutional policy [29–31].

- Informed consent

- Provide study information and obtain written informed consent before any study-specific procedures, including baseline inhalation assessments. Use IRB/EC-approved forms and processes; document consent version, date/time, and consenting staff role [28–30].
- Confirm participant capacity to consent and voluntary participation; for adolescents at sites where required, obtain assent and parent/guardian consent per local law [29].

- Eligibility confirmation (inclusive of documentation)

- Verify inclusion criteria: age ≥16 years; documented diagnosis of asthma and/or COPD; daily treatment with DPI or MDI (or both); ability to independently handle and inhale through assigned inhaler(s).
- Verify key exclusions: age <16 years; no access to BankID or similar electronic personal identification service; not using an Android or iPhone smartphone; planned discontinuation of DPI/MDI within the initial study period; inability to independently use DPI/MDI [7,8].

- Confirm diagnosis and inhaler regimen from medical records; document current inhaler type(s) to support randomization stratification (DPI, MDI, both) [7,8].
- Record relevant medical history and concomitant respiratory medications to contextualize baseline status and support safety monitoring, consistent with GCP [29].

- Operational and procedural feasibility

- Smartphone/app feasibility: confirm participant possession and use of compatible Android or iPhone; verify access to required app store; complete a basic check of connectivity sufficient for app telemetry/uploads as applicable [33].
- Identity verification feasibility: confirm access to BankID or equivalent for authentication per study operations.
- Device logistics: confirm shipping address or onsite availability for the CE-marked AsthmaTuner spirometer and the Airflow Trainer; document anticipated delivery or handoff plan and timing.
- Decentralized visit feasibility (if applicable): assess participant's ability to complete remote video capture and secure upload per site instructions [33].

- Baseline clinical assessments

- Physical status as per site standard relevant to safe participation (e.g., general condition, respiratory symptoms), with documentation of any clinically significant findings requiring physician review [29].
- Spirometry: perform baseline spirometry according to ATS/ERS 2019 standards (calibration/verification, acceptability and repeatability criteria); upload spirograms for central quality control [32].
- Baseline inhalation technique assessment (no training provided prior to randomization):
  - Record inhaler type(s) and capture standardized artifacts for centralized, blinded adjudication (e.g., site-captured video and/or flow-curve data where feasible) using pre-specified formats.
  - For DPI users, collect inhalation profile parameters where possible (e.g., peak inspiratory flow [PIF], time to PIF, inspiratory duration) using the spirometer and Airflow Trainer; ensure measurements reflect typical use without coaching that would constitute training [5,9,12].
  - For MDI users, capture coordination with actuation and inspiratory profile as specified in study manuals [5,11].
- Safety baseline: document pre-existing conditions and ongoing AEs; confirm no acute illness that, in investigator judgment, precludes safe participation [28,29].

- Anatomic and physiologic suitability for inhalation procedure

- Confirm ability to achieve an adequate inspiratory maneuver through the participant's routine inhaler device(s) and mouthpiece interface without obstruction or intolerance, as observed by qualified staff.
- For DPI users, review baseline PIF and inspiratory profile against device-appropriate expectations to ensure feasibility of technique assessment and subsequent training; recognize that lower PIF can compromise DPI performance and will be characterized at baseline rather than used as an exclusion unless otherwise specified [5,9,12].
- Document any anatomic or functional limitations impacting safe spirometry or inhalation assessments; escalate to investigator for eligibility determination [32].

- Randomization readiness and SEC review

- Complete the Site Enrollment Committee (SEC) checklist and present the screening packet (consent, eligibility source documents, feasibility confirmation, baseline assessments) to the SEC (PI, physician sub-investigator, and respiratory care professional).
- SEC quorum review: confirm eligibility, feasibility, and alignment with stratification requirements; document decision in auditable logs and investigator attestation [28,29].
- Upon SEC approval, proceed to randomization within the allowable baseline window; ensure all baseline data are captured prior to any intervention delivery.

- Post-randomization provisioning (investigational arm only; not part of screening)

- After randomization, provision the inhalation app-module within AsthmaTuner and the spirometer/Airflow Trainer per device accountability procedures; do not initiate app-based training prior to randomization [28,31].

Timing windows

- Screening, consent, and baseline assessments must be completed within protocol-defined windows prior to randomization. Central spirometry quality control and adjudication artifact submissions should occur within operational timelines specified in study manuals. If assessments fall outside target windows, site investigators must document rationale and obtain SEC confirmation on eligibility continuity before randomization [28,32].

Roles and responsibilities

- Principal Investigator (PI)/Sub-Investigator: medical oversight; eligibility adjudication; SEC participation and attestation; risk–benefit assessment; randomization release authorization [28,29].
- Respiratory therapist/qualified nurse: conduct spirometry per ATS/ERS; supervise baseline inhalation technique capture; verify artifact quality; document anatomic/physiologic suitability observations [32].
- Study coordinator: manage informed consent workflow; source document collection; feasibility checks (smartphone/BankID/logistics); data entry and query resolution; shipment/handover coordination [28–30].
- SEC: multidisciplinary eligibility confirmation, feasibility endorsement, and authorization to randomize; documentation of decisions in site logs [28,29].
- Core laboratories/central reviewers: blinded adjudication of baseline technique artifacts; central spirometry quality control, with queries to sites as needed [28,32].

Source documentation and data capture

- Maintain originals or certified copies of: signed informed consent; eligibility worksheets; diagnosis and inhaler verification; smartphone/BankID feasibility checks; spirometry printouts/files and calibration/verification logs; baseline inhalation artifacts; SEC decision records; and shipment/handover receipts for devices. Electronic data capture systems must be validated, access-controlled, and compliant with applicable data integrity expectations [28–31].

Screening outcomes, screen failure, and rescreening

- Participants who do not meet eligibility, withdraw consent, or fail feasibility checks are screen failures; record reason(s) in the screening log. Rescreening is permitted if the reason for failure is resolved and no exclusionary condition persists; obtain new or re-affirmed consent as required by local regulations and document a new SEC review prior to randomization [28–31].

Standard sign-off elements

- Investigator attestation: I have reviewed the informed consent, eligibility criteria, feasibility assessments, baseline spirometry and inhalation artifacts, and I confirm the participant’s eligibility and safety for participation.
- SEC decision: Approved/Not Approved for randomization; rationale and quorum signatures/date.
- Device/logistics confirmation: Spirometer/Airflow Trainer availability and delivery plan verified (Yes/No); responsibility assigned; date/time.

- Data quality check: Required baseline data entered; central submissions completed or queued; outstanding queries documented with action plan.

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4.2 Informed Consent

Overview and purpose of consent

Before any study-specific procedures, each potential participant (or their legally authorized representative, LAR) will be given clear, understandable information about the study's purpose, procedures, potential risks and benefits, alternative options, privacy protections, and rights. Consent must be voluntary, documented, and obtained prior to any collection of study data. The consent process follows international good clinical practice (GCP) and ethical standards, applicable medical device regulations, and data protection laws [40–45].

Key information for participants (plain-language summary)

- Why this study: To compare standard education versus app-based education and training for inhaler technique in people aged 16 years and older with asthma and/or COPD who use DPI and/or MDI inhalers.
- What participation involves: Screening and consent; confirmation of eligibility; randomization to one of two education approaches; baseline assessments; a primary follow-up at 6–12 weeks; additional follow-ups (for safety, usability, and effectiveness) up to 12 months and annually through Year 5. Some activities may occur remotely if permitted locally. The investigational app-module is used only within this study.

- Main procedures: Standardized training on inhaler technique; capture of videos and/or inhalation flow curves for centralized, blinded review; spirometry according to standards; questionnaires on usability; collection of app telemetry (intervention arm); and monitoring for adverse events and device issues.
- Potential risks: Discomfort from breathing tests; possible shortness of breath or cough during inhalation assessments; data privacy risks mitigated by safeguards; technical issues with devices/apps. Serious risks are unlikely but will be monitored; you should report any new or worsening symptoms promptly [40,42,44].
- Potential benefits: You may or may not benefit directly. Potential benefits include improved inhaler technique and easier access to training at home. Information from this study may help future patients [40,44].
- Alternatives: You may choose not to participate. You will continue to receive usual care from your healthcare providers.
- Privacy: Your data will be protected under GCP and applicable data protection laws. Only authorized individuals will access your identifiable information for study purposes, monitoring, auditing, and regulatory inspection [40–43].
- Voluntary participation and withdrawal: Your participation is voluntary. You may withdraw at any time without penalty or loss of benefits to which you are otherwise entitled [40,44].
- Contacts: You will receive contact information for study staff for questions, injury reporting, privacy concerns, and complaints.

Who may obtain consent and how

- Authorized personnel: The Principal Investigator (PI), Sub-Investigator physicians, or qualified, delegated study staff trained on the protocol, informed consent, data protection, and the investigational device may obtain consent [40,41].
- Setting and materials: Consent may be obtained in person at the clinic or using an approved remote/electronic consent (eConsent) process consistent with local law and guidance on decentralized clinical trials. The consent form, multimedia aids (if used), and any short-form consent and translation will be reviewed and approved by the responsible ethics committee before use [40,41,45,46,49].
- Time for consideration: Potential participants will be given adequate time and opportunity to ask questions and discuss participation with family or advisors before deciding [40,44].
- Documentation: Consent will be documented with the participant’s signature and date (or equivalent validated eSignature); the person obtaining consent will also sign and date. A signed copy will be provided to the participant [40,41,49].

Languages and translation

- Permitted languages: Consent will be provided in the local language(s) approved by the ethics committee. Certified translations will be used to ensure accuracy.
- Interpreters: If needed, qualified interpreters may be used. The use of an interpreter will be documented in the source records and consent form, as applicable [40,41].
- Low-literacy support: Read-aloud processes or visual aids may be used to enhance understanding, with documentation of the method used [40,41].

Capacity, assent, and legally authorized representatives

- Participants aged 16–17 years: Where required by local law, informed consent will be obtained from a parent/guardian (LAR), and assent will be obtained from the adolescent participant in language appropriate to their understanding. When the participant reaches the legal age of majority during the study, re-consent will be obtained from the participant at the earliest opportunity [40,41,44].

- Adults lacking decision-making capacity: If permitted locally, an LAR may provide consent. If the participant regains capacity, consent will be sought directly from the participant as soon as feasible [40,41,44].
- Voluntariness: Regardless of who signs, participation is voluntary; participants (or LARs) may withdraw at any time [40,44].

Circumstances requiring re-consent

Re-consent (or confirmation of ongoing consent) will be obtained when:

- New information becomes available that may affect willingness to continue (e.g., newly identified risks or changes to expected benefits).
- The protocol, study procedures, or follow-up schedule change in a way that affects participation.
- There are material changes in data processing, international data transfer, or privacy practices that affect participants' rights or choices.
- Significant software or device updates materially change functionality or data flows relevant to the study.
- The participant reaches age of majority or regains decisional capacity.
- Following a prolonged study interruption before resuming procedures, if required by the ethics committee [40,41,43–46].

Privacy and confidentiality

- Data collected: Contact details; demographics; medical history and medications; asthma/COPD status; inhaler type(s); spirometry data; inhalation technique videos/flow curves; app telemetry and usage data (intervention arm); questionnaires; adverse events and device deficiencies; and relevant healthcare utilization. Limited identifiers may be used to link data during the study; analyses will use coded data when possible [40–43].
- Who may access your data: Study site staff; the sponsor and its authorized vendors (including core laboratories/adjudicators); ethics committees; regulatory authorities; study monitors and auditors; and the Data Safety Monitoring Board (DSMB). Access is for study conduct, safety oversight, quality checks, and regulatory compliance [40–42].
- Data transfers: Data may be transferred across national borders where necessary for centralized review and analysis. When data are transferred outside the European Economic Area, appropriate safeguards (e.g., standard contractual clauses) will be implemented in accordance with applicable data protection laws [43].
- Data retention: Records will be retained for the period required by law and guidance to support regulatory reporting and audits. Coded/de-identified data already analyzed or included in reports cannot be withdrawn retroactively [40–43].
- Your rights: Subject to applicable law, you may request access to, correction of, restriction of processing of, or deletion of your personal data. Some requests may not be fulfilled where legal obligations or scientific integrity require continued retention; reasons will be explained. Contact details for exercising rights will be provided in the consent form [43].

Use of images, audio, and technique artifacts

- What will be captured: Short videos of inhaler use and/or inhalation flow-curve data may be recorded to assess inhalation technique.
- Purpose and safeguards: These artifacts will be used only for study purposes, including centralized, blinded adjudication and quality review. They will be stored securely with restricted access. Faces and identifiable features will be minimized in recordings whenever feasible. Artifacts will not be used in public materials without your explicit, separate permission [40–42].

- Optional educational use: You may be asked to allow de-identified images or recordings to be used for investigator training or educational purposes outside the study. This is optional and requires a separate consent choice.

Optional future use of coded data

- Optional research use: You may be asked to allow your coded study data (no direct identifiers) to be used in future research related to inhaler technique, digital health, or respiratory care, subject to ethics approval and data protection safeguards. This is optional and does not affect participation. No biological specimens will be collected in this study [40,41,43].
- Data sharing and publications: Study findings may be published or shared in scientific venues. Your identity will not be revealed. Coded, de-identified datasets may be shared with qualified researchers or deposited in secure repositories, consistent with approvals and applicable laws [40,41,43].

Withdrawal from the study

- How to withdraw: You can notify study staff at any time if you wish to stop participating. You may choose to stop all procedures, stop app use, and/or decline further contact.
- What happens to your data and devices: You may be asked to return study devices. Data collected before your withdrawal may still be used to protect study integrity and meet legal obligations. You may request deletion of identifiable data where feasible under applicable law; however, coded/de-identified data already used in analyses or submissions generally cannot be removed [40,41,43].
- Safety follow-up: You may be asked for brief safety information after withdrawal if advisable for your well-being or required by regulation; this is voluntary [40,41].

Participant responsibilities and compensation

- Your responsibilities: Follow instructions for inhaler assessments and training; attend scheduled visits or remote sessions; report adverse events and device issues promptly; and safeguard study devices per instructions.
- Costs and payments: Any participant reimbursements for time, travel, or data costs, and any costs to you (if any), will be described in the country- and site-specific consent form addendum approved by the ethics committee. Insurance or indemnity for study-related injury will be provided as required by applicable law and standards; details will be included in the consent materials [40–42,44].

Consent checklist (participant to review and initial/confirm)

- I understand the study purpose, what participation involves, potential risks/benefits, and my alternatives.
- I understand participation is voluntary and I may withdraw at any time without penalty.
- I authorize collection and use of my health and study data for the purposes described.
- I authorize the capture and secure use of inhalation technique videos and/or flow-curve recordings for centralized, blinded assessment.
- I understand who may access my identifiable data for study oversight and regulatory purposes.
- I understand my data may be transferred internationally with appropriate safeguards.
- I understand how my privacy rights apply and how to contact the study about data protection.

- I understand the long-term follow-up plan and what it means for my participation.
- I received a copy of the signed consent form.

Optional choices (do not affect participation):

- I agree/do not agree to the use of my de-identified images/recordings for educational or training purposes.
- I agree/do not agree to the use of my coded study data for future ethically approved research related to respiratory care and digital health.

Documentation and record-keeping

- The consent version, language, date/time, and identity of the consenting staff member will be recorded. For eConsent, identity verification and audit trails will follow regulatory expectations. A copy of the signed consent will be provided to the participant and filed at the site [40,41,45,49].

Special considerations for remote and decentralized processes

- When permitted by local regulations and ethics approval, elements of the consent discussion and documentation may occur by secure telemedicine and eConsent tools. Identity verification, opportunity to ask questions, and provision of copies will be ensured. All processes will comply with applicable guidance on decentralized clinical trial elements and electronic consent [40,41,45,46,49].

References

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4.3 Eligibility Process & Governance

Overview

This section defines the standardized, auditable process by which participant eligibility is assessed, verified, and governed prior to randomization. The process emphasizes independent verification against inclusion/exclusion criteria, central/core review of baseline diagnostics where applicable, multidisciplinary adjudication, and complete documentation to meet ISO 14155, ICH-GCP, and MDR requirements [50–52].

Screening identification, assignment, and source documentation

- Each potential participant is assigned a unique screening identifier prior to any eligibility review. The identifier is used on all screening documents, logs, and central submissions [50,51].
- Investigators ensure that informed consent is obtained and documented before any study-specific procedures or access to identifiable data, including baseline inhalation assessments intended for adjudication [50,51].
- Source documents include: proof of age; confirmed diagnosis of asthma and/or COPD; documentation of daily use of DPI and/or MDI (or both); confirmation of independent handling and inhalation capability; smartphone type (Android/iPhone) and access to BankID or similar identity service; and any medical history or status relevant to safe participation [50,51].
- A standardized case synopsis (see below) is prepared for each potential enrollee and filed with the screening packet in the site's essential documents.

Standardized case synopsis

- The site completes a uniform synopsis template capturing:

- Demographics and diagnosis confirmation.
- Current inhaler(s) and daily use (DPI, MDI, or both) to align with randomization strata.
- Confirmation of smartphone compatibility and BankID (or equivalent) access.
- Ability to independently handle and inhale through DPI/MDI.
- Key exclusions (e.g., plan to stop DPI/MDI within 6–12 weeks; age <16 years).
- Baseline spirometry summary, including acceptability/repeatability pending central quality control (QC).
- Baseline inhalation technique artifacts (video and/or flow-curve) submitted for centralized, blinded review.
- Investigator's preliminary eligibility determination and any queries outstanding at the time of committee review [50–52,54].

- The synopsis references supporting source documents and confirms date/time of consent.

Central/core review integration before randomization

- Baseline spirometry is obtained per ATS/ERS 2019 standards and submitted to the central core for QC grading (acceptability/repeatability). Where feasible within operational timelines, core QC feedback is reviewed prior to eligibility approval; otherwise, site technical checks and calibration/verification logs are documented, and core QC is followed by committee re-verification if QC is unacceptable [54].
- Baseline inhalation technique artifacts (video and/or flow-curves) intended for later endpoint adjudication are captured per the Adjudication Manual and uploaded to the central system to confirm artifact adequacy. Central reviewers provide a pass/fail for artifact adequacy (not the correctness outcome) prior to eligibility approval, where feasible. If inadequate, repeat capture is requested before randomization [50,52,54].

- All central submissions and outcomes are logged with timestamps to maintain a complete audit trail and ensure data integrity in decentralized elements when used [50,53].

Multidisciplinary Site Enrollment Committee (SEC)

- Composition: At a minimum, the Principal Investigator (PI) or physician Sub-Investigator and a respiratory care professional (e.g., respiratory therapist or qualified study nurse) serve on the SEC. The study coordinator may participate in a non-voting role to present documentation [50,51].
- Quorum: Two members constitute quorum, including at least one physician-investigator and one respiratory care professional.
- Voting rules: Decisions are made by simple majority of voting members present. In the event of a tie, the PI (or physician designee) serves as tie-breaker. Members recuse themselves if conflicts of interest arise [50,51].
- Scope: The SEC reviews the standardized case synopsis, confirms that all inclusion criteria are met and no exclusions apply, verifies central/core submission status (artifact adequacy and, where available, spirometry QC), and confirms operational feasibility (smartphone/BankID, device logistics).
- Decision documentation: The SEC records one of three decisions—Approve for Randomization; Defer (with specified corrective actions); or Not Eligible (with reasons). Each decision includes date/time, quorum members, signatures (wet or validated e-signature), and any conditions precedent to randomization (e.g., receipt of adequate artifact confirmation) [50–52].

Sponsor-level Eligibility Review Committee (ERC) for complex cases

- Purpose: A sponsor-level ERC is available for complex or ambiguous cases (e.g., borderline independence in inhaler handling, unresolved central QC issues, or medical complexity affecting safe participation) referred by the SEC.
- Composition: At least three voting members, including a medical monitor (chair), a respiratory clinical expert, and a methodologist or adjudication lead not affiliated with the site. Ad hoc technical experts may be consulted without voting privileges.
- Quorum and voting: Quorum is three voting members. Decisions require simple majority; the chair is the tie-breaker. Turnaround targets are defined in the operations manual to avoid enrollment delays [50,51].
- Documentation: The ERC maintains a central log of referrals, materials reviewed, deliberations, determinations, and required conditions, with communication back to the SEC prior to randomization. ERC decisions are final unless new material information arises [50–52].

Eligibility confirmation and randomization release

- Eligibility becomes final when:

- SEC approval is granted with quorum; and
- Any pre-specified conditions (e.g., adequate central artifact confirmation; spirometry QC acceptable or formally waived with justification) are met; and
- Randomization strata (DPI/MDI/both) are confirmed.

- The PI (or designee) authorizes randomization release in the electronic system, and the decision is documented in the enrollment log and source records [50–52,54].

Logs, registries, and traceability

- Screening log: Maintained at each site to record all individuals screened, screening identifiers, consent status, SEC/ERC decisions, reasons for screen failure or deferral, and next steps. This log supports monitoring, audits, and regulatory inspections [50–52].
- Enrollment/randomization log: Captures participant identifiers (coded), randomization date/time, arm allocation (masked as required by blinding), and stratification variables. Device/accountability linkages are traceable to each randomized participant [50–52].
- Central submission log: Records all baseline central/core submissions (spirometry QC, artifact adequacy), submission times, queries, and resolution timestamps to ensure contemporaneous documentation and data integrity, including for decentralized submissions where permitted [50,53].
- Change control: Any post-approval eligibility changes (e.g., new exclusion identified pre-randomization) are documented with SEC re-review and justification prior to proceeding [50,51].

Handling screen failures, deferrals, and re-screening

- Screen failures: If any inclusion criterion is not met, or an exclusion applies (e.g., age <16; lack of BankID or equivalent; incompatible smartphone; planned discontinuation of DPI/MDI in the next 6–12 weeks; inability to independently handle and inhale through DPI/MDI), the SEC records Not Eligible with specific reasons in the screening log and source documents [50–52].
- Deferrals: If missing or inadequate baseline materials (e.g., insufficient artifact quality; unresolved spirometry QC) preclude a decision, the SEC records Defer with required corrective actions and time targets. No randomization occurs until closure of conditions [50,54].
- Re-screening: Permitted when the reason for screen failure is fully and appropriately resolved (e.g., now has compatible smartphone; artifact adequacy achieved), no persistent exclusion remains, and clinical status has not changed in a manner that introduces new exclusions. Re-consent is obtained as required, a new or updated case synopsis is prepared, prior data are cross-referenced, and the SEC conducts a fresh review before any randomization [50,51].
- Documentation of non-enrollment: Reasons for non-participation after consent (e.g., withdrawal of consent) are recorded without coercion, and data handling follows consent and privacy provisions [50,51].

Data integrity, quality, and oversight

- All eligibility records are contemporaneously completed, legible, and attributable, with validated electronic systems and role-based access controls. Audit trails capture creation, modification, and approval events, in alignment with GCP and MDR record-keeping requirements [50–52].
- The study monitor verifies eligibility determinations against source documents and logs. The DSMB does not review individual eligibility but may audit process metrics; significant systemic issues are escalated per the DSMB charter and sponsor quality procedures [50–52].
- Decentralized elements (eConsent, remote artifact capture) are used only where approved and are governed by SOPs that ensure identity verification, secure data transfer, and traceability, consistent with applicable guidance [50,53].

Training and certification

- SEC and ERC members complete protocol-specific training on eligibility criteria, artifact standards, spirometry basics and central QC expectations, and documentation requirements prior to first patient screened. Refresher training is required after substantive protocol amendments or operational updates [50,51,54].

Governance of amendments impacting eligibility

- Changes to inclusion/exclusion criteria or to prerequisite baseline assessments require prior ethics committee approval and, where applicable, regulatory notification/approval. Sites must pause new eligibility determinations until training is completed and tools/logs are updated. Re-consent may be required for already-consented but not-yet-randomized individuals if the changes could affect willingness to participate [50–52].

References

50. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
51. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
52. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
53. European Medicines Agency. Guidance on the use of decentralised elements in clinical trials. 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/decentralised-clinical-trials-guidance
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4.4 Inclusion Criteria

Overview

The following inclusion criteria define the target population, operational feasibility, procedural suitability, and governance requirements for enrollment, in alignment with ISO 14155/ICH-GCP, EU MDR, and respiratory guidelines. Where protocol-wide numeric thresholds or specific instruments are not yet finalized, placeholders are provided and will be confirmed in the final protocol and study manuals prior to first patient in. All criteria are verified by the Site Enrollment Committee (SEC) before randomization [1–7].

Inclusion-criteria table

Criterion	Definition/threshold (to be confirmed where indicated)	Rationale	Evidence/source
Age	Age ≥16 years at consent; for 16–17 years, assent and LAR consent per local law	Ethical and legal capacity to consent/assent for participation; aligns with target population	ISO 14155 [1]; ICH-GCP [2]
Documented diagnosis	Physician-documented asthma and/or COPD in medical record per contemporary guideline definitions; diagnostic basis recorded (e.g., history, spirometry where available)	Ensures inclusion of intended clinical indication and external validity	GINA 2024 [5]; GOLD 2024 [6]
Disease severity/context	Chronic respiratory disease requiring daily inhaler therapy; severity/context documented; if symptom instrument used,	Confirms clinical relevance for inhaler training; supports	GINA 2024 [5]; GOLD 2024 [6]

	instrument and threshold [TBC instrument; threshold TBC]	stratification and interpretation	
Current inhaler regimen	Daily use of DPI and/or MDI (or both) at screening; regimen documented (device name, dose, frequency)	Ensures exposure to device-specific training content and endpoint relevance	GINA 2024 [5]; GOLD 2024 [6]
Ability to handle inhaler(s)	Independently able to handle and inhale through assigned DPI/MDI device(s) as observed by site staff	Safety and feasibility of participation; prevents confounding by caregiver-dependent use	ISO 14155 [1]; Usmani 2018 [8]
Baseline technique artifact feasibility	Willing and able to provide standardized video and/or inhalation flow-curve artifacts per Adjudication Manual; central “adequate” artifact confirmation obtained prior to randomization (where operationally feasible)	Enables blinded adjudication of primary endpoint and data integrity	ISO 14155 [1]
Background therapy stability	Maintenance respiratory medications stable for [TBC: X] weeks prior to randomization, with no planned changes through Week 6–12 unless medically indicated	Reduces confounding; supports causal attribution to training intervention	ICH-GCP [2]; MDR [3]
Symptom burden and/or technique-need assessment	Participant-reported inhaler technique challenges and/or site-observed technique issues documented; validated symptom/control instrument optional [instrument TBC; threshold TBC]	Increases likelihood of clinical utility while permitting broad generalizability	Usmani 2018 [8]; Sanchis 2016 [9]
Smartphone compatibility	Possesses and routinely uses a compatible Android or iPhone smartphone with access to App Store/Google Play; device meets app technical specifications [TBC]; connectivity sufficient for telemetry/upload	Operational feasibility for app-based intervention and decentralized data capture	EMA DCT guidance [4]
Electronic identity verification	Access to BankID or similar approved electronic personal identification service per country/site operations	Supports secure identity verification and compliant eConsent/device provisioning	EMA DCT guidance [4]
Investigational device acceptance	Willing to install and use AsthmaTuner (version >5.4.13.5) and investigational inhalation app-module if randomized to intervention; willing to receive and use CE-marked spirometer and Airflow Trainer per instructions	Ensures exposure to investigational intervention and data collection as designed	ISO 14155 [1]
Anatomic/procedural suitability	Able to perform acceptable spirometry per ATS/ERS standards and to achieve an unobstructed inspiratory maneuver through mouthpiece/inhaler interface without intolerance; no device–interface barriers identified	Confirms procedural safety and feasibility for technique assessment/training without specifying performance thresholds	ATS/ERS 2019 [7]
Expected benefit (investigator judgment)	In investigator’s judgment, participant is reasonably likely to benefit from inhaler technique	Ethical inclusion principle to favor favorable benefit–	ISO 14155 [1]; Usmani 2018 [8]

	education/training (e.g., history of technique errors, suboptimal control, or high device complexity)	risk while maintaining broad access	
Ability to comply with follow-up	Willing and able to complete scheduled assessments at Week 6–12, Month 6, Month 12, and long-term contacts to Year 5 (remote or on-site per protocol)	Ensures evaluability for primary and secondary endpoints and long-term safety	ISO 14155 [1]; EMA DCT guidance [4]
Consent/assent	Provides written informed consent (and assent with LAR consent where applicable) before any study-specific procedures	Ethical and legal prerequisite for participation	ICH-GCP [2]; Declaration of Helsinki [2]
SEC approval	Multidisciplinary SEC confirms all inclusion criteria met, no exclusions apply, and operational feasibility/logistics in place before randomization	Independent governance, data integrity, and participant safety	ISO 14155 [1]
High-risk/inoperable designation	Not applicable to this behavioral/education digital intervention; no anatomic “inoperable” designation required	Clarifies non-applicability of surgical/procedural high-risk constructs for this study	ISO 14155 [1]
Data use and central reviews	Agrees to centralized, blinded review of artifacts and core spirometry QC; agrees to international data transfer with safeguards where applicable	Enables standardized endpoint determination and regulatory-grade data quality	ISO 14155 [1]

Notes:

- Where [TBC] placeholders appear, final instruments, technical specifications, and stability windows will be prespecified in the protocol, SAP, and study manuals prior to first patient in.
- Lower peak inspiratory flow among some DPI users is not, by itself, exclusionary; baseline inspiratory profile will be characterized rather than used as an exclusion unless amended later with justification [8–11].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
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6. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Prevention, Diagnosis and Management of COPD, 2024 report. GOLD; 2024. https://goldcopd.org
7. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
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10. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal Inspiratory Flow Rates with Commonly

Used Inhalers in COPD Patients. Ann Am Thorac Soc. 2017;14(7):1103–1109. doi:10.1513/AnnalsATS.201701-042OC
11. Mahler DA. Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in COPD. J Aerosol Med Pulm Drug Deliv. 2014;27(2):103–109. doi:10.1089/jamp.2013.1048

4.5 Exclusion Criteria

Exclusion Criteria (Yes/No checklist; exclude if “Yes” to any)

For each candidate, the Site Enrollment Committee (SEC) must determine and document whether any of the following apply based on source records, participant interview/observation, and, where indicated, central/core confirmations. A “Yes” response to any item excludes the individual from participation. Ambiguous cases should be referred to the Sponsor Eligibility Review Committee (ERC) for adjudication per governance procedures [1–3].

- Age and consent capacity

- Age <16 years at the time of consent [1–3].
- Inability to provide legally valid informed consent/assent (and, where applicable, lack of a legally authorized representative), or circumstances that compromise voluntariness or understanding, as judged by the investigator and per local law [1,2].

- Operability and procedural suitability

- Unable to independently handle and inhale through the participant’s routine DPI and/or MDI device(s) despite observation and investigator assessment [1,4,5].
- Inability to perform acceptable spirometry maneuvers or inhalation assessments required by the protocol (e.g., inability to perform an unobstructed inspiratory maneuver through the mouthpiece/inhaler interface), after reasonable attempts per site practice [6].
- Any condition representing a recognized contraindication or unacceptable risk for spirometry or forceful respiratory maneuvers (e.g., recent thoracic/abdominal surgery, pneumothorax, unstable cardiovascular status, or other ATS/ERS-listed relative/absolute contraindications) until resolved and deemed safe by the investigator; documentation required in the source record [6].

- Acute clinical instability and futility of intervention

- Ongoing acute severe respiratory illness or current exacerbation of asthma/COPD requiring urgent care, hospitalization, or escalation of therapy such that reliable technique assessment/training is not feasible or safe, in investigator judgment; eligibility may be reconsidered once clinically stable [4,7].
- Any medical, psychiatric, cognitive, or social condition that, in the investigator’s judgment, would make adherence to training, app use, or follow-up unlikely, or would confound endpoint assessment (e.g., severe cognitive impairment without reliable support for supervised technique, active substance use disorder affecting participation) [1,2].

- Device, materials, and procedural contraindications

- Known or suspected hypersensitivity to materials that contact the participant during study procedures (e.g., disposable mouthpieces) when suitable alternatives are not available or acceptable; document the specific material and reaction history [1].
- Any condition preventing safe receipt, setup, or operation of the CE-marked AsthmaTuner system (spirometer and app) and Airflow Trainer as per instructions for use (e.g., inability to tolerate mouthpiece interface), in investigator judgment [1].

- Operational feasibility (required for investigational workflows)

- No access to BankID or an equivalent electronic personal identification service as required by site operations for identity verification/eConsent/device provisioning [3,8].
- Not using a compatible Android or iPhone smartphone, or lacking access to the required app store or minimal connectivity sufficient for telemetry/uploads, as verified at screening [3,8].
- Plan to discontinue daily use of DPI and/or MDI within the initial 6–12 weeks following inclusion (the primary assessment window), other than for medical necessity, as ascertained during screening [4,7].

- Concomitant study participation and recent procedures

- Concurrent participation in another interventional clinical study or exposure to an investigational device or drug that, in the investigator's judgment, could interfere with this study's procedures, outcomes, or safety monitoring; required documentation: study title/identifier and rationale for exclusion [1–3].
- Any recent procedure or clinical intervention that, in the investigator's judgment and with available documentation, poses added risk with spirometry or inhalation assessments or would confound endpoint evaluation; enroll only after the condition is resolved and eligibility is re-confirmed [6].

- Disease context and background therapy

- Absence of a documented diagnosis of asthma and/or COPD in the medical record per prevailing guidelines (eligibility requires documentation) [4,7].
- Planned major changes to maintenance respiratory medications during the initial 6–12-week assessment window for reasons other than medical necessity, such that attribution of effects to inhalation training would be unreliable; investigator documentation required [1,2].

- Data integrity, privacy, and centralized review requirements

- Unwillingness to allow required capture and secure transfer of inhalation technique artifacts (video and/or flow-curve) and spirometry data for centralized, blinded quality control/adjudication, including international transfer with appropriate safeguards where applicable [1–3,8].
- Failure to obtain central confirmation of artifact adequacy prior to randomization when operationally required by the protocol and SEC decision, after repeat attempts per the Adjudication Manual [1].

- Other investigator-determined risks

- Any other condition that, in the investigator's reasoned judgment, renders the risk–benefit unfavorable for this participant, makes the intervention futile, or prevents reliable participation, with rationale documented and available for SEC/ERC review [1,2].

Notes:

- Lower peak inspiratory flow among DPI users is not, by itself, exclusionary; inspiratory performance will be characterized at baseline and considered in outcome interpretation, consistent with contemporary evidence on inhaler technique and disease severity [4,5].
- Exclusions related to spirometry safety follow ATS/ERS guidance; where timing thresholds are relevant, site investigators should apply local standards and document clinical rationale without inserting numeric cutoffs into the source unless prespecified elsewhere in the protocol or study manuals [6].
- When an exclusion is transient (e.g., acute exacerbation), re-screening is permitted once resolved, with renewed confirmation of all eligibility conditions and SEC re-review per governance procedures [1,2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024 update. Fontana, WI: GINA; 2024. https://ginasthma.org
5. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19:10. doi:10.1186/s12931-017-0710-y
6. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST
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8. European Medicines Agency. Guidance on the use of decentralised elements in clinical trials. 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/decentralised-clinical-trials-

guidance

4.6 Enrollment & Withdrawal Documentation

Scope and principles

This section defines standardized, auditable documentation for participant enrollment and withdrawal, including key milestones from informed consent through randomization and post-randomization withdrawal handling. All processes follow ISO 14155, ICH-GCP, applicable medical device regulations, ethics guidance, data protection law, and approved decentralized elements where used [1–5].

Protocol-defined enrollment events and timing

- Enrollment events:

- Informed consent (and assent/LAR consent where applicable) obtained before any study-specific procedures.
- Screening and eligibility verification with SEC quorum approval.
- Completion of baseline assessments and central/core submissions as operationally required (e.g., artifact adequacy; spirometry QC status).
- PI/designee authorization and release of randomization with stratification confirmation.
- Post-randomization provisioning per device accountability procedures (investigational arm).
- Enrollment confirmation recorded in the site enrollment/randomization log.

- Timing windows:

- Consent, screening, baseline assessments, SEC review, and randomization are completed within protocol-defined windows. Any out-of-window activity requires documented rationale, SEC confirmation of continued eligibility, and, if applicable, ethics committee notification per local requirements. No randomization occurs until all pre-specified conditions are met [1–4].

- Audit trails and attribution:

- All enrollment events must be contemporaneously documented with date/time stamps, identity of responsible staff, and system-generated audit trails for electronic systems, consistent with GCP and MDR record-keeping expectations [1–3].

Standardized enrollment checklist (source-document template)

Domain	Data element (record exactly as applicable)
Screening identification	Site, screening ID, participant initials (coded), date/time screening ID assigned
Consent and identity	Consent version/language; date/time signed; name/role of person obtaining consent; eConsent/eSignature verification including BankID or equivalent; assent/LAR consent (if applicable)
Eligibility verification	Inclusion/exclusion checklist completed (Yes/No to each with source references); diagnosis and inhaler regimen confirmed; independence in DPI/MDI handling observed; smartphone compatibility and eID access verified; stability of background therapy per protocol; any transient exclusions resolved
Baseline assessments	Spirometry performed per standards; calibration/verification logs filed; inhalation technique artifact(s) captured per manual; any pre-existing AEs documented
Central/core submissions	Inhalation artifact adequacy submission date/time and outcome; spirometry QC submission date/time and status (acceptable/unacceptable/pending)
SEC review	SEC quorum members; date/time; decision (Approve/Defer/Not Eligible); conditions precedent (if any) and closure date/time; investigator attestation recorded

ERC (if referred)	Referral reason; materials reviewed; decision and date/time
Randomization readiness	Stratification variable (DPI/MDI/both) confirmed; pre-specified conditions met; PI/designee authorization recorded
Randomization event	Date/time; system confirmation; masked allocation recorded in log; enrollment confirmation recorded
Device/accountability (post-randomization)	Provisioning plan and date/time; device shipment/handover receipts; app-module activation confirmation (investigational arm only)
Participant communications	Copy of signed consent provided; key contacts provided; optional permissions (future use, educational images) recorded
Regulatory/privacy confirmations	International data transfer safeguards acknowledged (where applicable); data retention period communicated; privacy rights instructions provided [2,3,5]

Withdrawal categories to be tracked

- Participant-initiated withdrawal of consent:
  - Full withdrawal: declines all further study procedures, contact, and data collection.
  - Partial withdrawal: stops intervention and/or some procedures but permits continued follow-up and/or safety data collection.

- Investigator-initiated discontinuation:
  - For safety, noncompliance, or futility in investigator judgment, with rationale documented and communicated to participant.

- Loss to follow-up:
  - Unable to contact after documented reasonable attempts using site SOPs.

- Death:
  - Confirmation from reliable sources; follow regulatory and safety reporting obligations.

All categories are recorded without coercion, respecting participant rights and applicable law [1–5].

Continued data collection and data retention after withdrawal

- Data use to date:
  - Data collected prior to withdrawal may be retained and used to protect scientific integrity and meet legal/regulatory obligations, consistent with consent and data protection laws [1–3,5].

- Post-withdrawal data collection:
  - If the participant permits continued follow-up, collect planned outcomes (including the primary endpoint if within window) and safety information via visits or remote contacts as approved.
  - If the participant declines further contact but allows limited safety follow-up, document this scope and attempt minimal-risk safety ascertainment from records if permitted by law/ethics and consent.
  - If the participant withdraws all consent for further data processing, cease new data collection and implement data handling per applicable law (e.g., deletion of directly identifiable data where feasible), noting that coded/de-identified data already included in analyses or submissions generally cannot be removed [1–3,5].

- Safety reporting:
  - Serious adverse events, device-related adverse events, and device deficiencies identified up to the point of withdrawal are reported per protocol and regulations. If safety concerns prompt investigator-initiated discontinuation, notify the ethics committee and DSMB per local requirements and study governance [1–3].

Standardized withdrawal documentation framework (source-document template)

Domain	Data element (record exactly as applicable)
Participant identifiers	Site, participant ID (coded), initials (coded), date of birth (year only if required for linkage)
Withdrawal trigger	Date/time of participant notice or investigator decision; category (full consent withdrawal; partial withdrawal; investigator-initiated discontinuation; loss to follow-up; death)
Reason and scope	Participant-stated reason(s) verbatim; investigator rationale (if investigator-initiated); scope of withdrawal (no further contact; no further procedures; safety-only follow-up; continued follow-up allowed)
Last study contact	Date/time and mode of last contact; last completed visit/timepoint; last app usage/telemetry upload (if applicable); last dose/use of inhaler training content (if applicable)
Ongoing safety	Ongoing AEs/SAEs at time of withdrawal; actions taken; reporting status; DSMB/ethics notifications if required
Device/accountability	Investigational devices/access status; device return plan and date; data synchronization status; deactivation of app-module (if applicable)
Data handling	Data retention policy applied (retain coded data to date; delete directly identifiable data where feasible; anonymization status); participant request regarding data rights documented (access/correction/deletion/restriction)
Follow-up plan	Safety follow-up permitted (Yes/No); method and schedule within protocol windows if Yes; contact permissions and preferred channels; documentation of attempts for loss to follow-up per SOPs
Re-enrollment eligibility	Eligible for re-screening/re-enrollment (Yes/No/To be determined); conditions for re-screening; re-consent requirement; SEC/ERC re-review required
Administrative close-out	Study and site logs updated; protocol deviation (if any) recorded; notifications completed; signatures (investigator and, where applicable, participant acknowledgement)

Policies for re-consent, delays, re-screening, and re-enrollment

- Re-consent:

- Required when new information may affect willingness to continue; when protocol/device/material changes materially affect participation; upon reaching age of majority/regaining capacity; or after a prolonged interruption before resuming procedures if required by the ethics committee. Re-consent follows the same documentation standards as initial consent, including identity verification for eConsent where used [1–4].

- Delays/out-of-window events:

- If screening or baseline assessments fall outside target windows, document rationale and obtain SEC confirmation of eligibility continuity before randomization. For already randomized participants, manage protocol deviations per SOPs and, if needed, seek ethics guidance [1–4].

- Re-screening:

- Permitted when the prior screen failure or deferral reason has been fully resolved and no exclusion persists. Obtain new or updated consent as required, prepare an updated case synopsis, and submit for fresh SEC review prior to any randomization [1,2].

- Re-enrollment after withdrawal:

- Participants who previously withdrew may be considered for re-enrollment only if they explicitly provide new informed consent, continue to meet eligibility, and SEC re-approves. If the prior withdrawal was investigator-initiated for safety, re-enrollment requires ERC and medical monitor concurrence and documentation of risk mitigation [1,2].

Data integrity, monitoring, and oversight

- Validated systems with access controls and audit trails will be used for enrollment and withdrawal documentation. All entries must be attributable, legible, contemporaneous, original, and accurate (ALCOA) with change-control records as applicable [1–3].
- Study monitors will verify enrollment/withdrawal documentation against source records and logs. The DSMB may review aggregate withdrawal patterns and safety-related discontinuations per its charter; site- or system-level concerns will be escalated according to sponsor quality procedures [1–3].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
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5 RISK AND BENEFIT ANALYSIS

Overall risk profile

The investigational device is a non-invasive, software-based inhalation training module embedded in a CE-marked digital platform (AsthmaTuner), used together with a CE-marked home spirometer and an Airflow Trainer that does not contact the mouth or skin. Foreseeable risks primarily relate to respiratory maneuvers (spirometry and inhalation assessments), software usability and malfunction, data privacy/security, and user behavior changes that could transiently worsen inhaler technique if instructions are misunderstood. No vascular access, anesthesia, or surgery is involved; therefore, access-site, catheter, or implant-related risks are not expected. Procedure-related physiological risks from forceful respiratory maneuvers (e.g., cough, bronchospasm, dizziness, syncope) are recognized in ATS/ERS standards and mitigated by established precautions [1,4]. Risk identification, estimation, and control follow ISO 14971 principles, applied within the ISO 14155 clinical investigation framework and the EU MDR [1–3,12].

Structured risk table

Risk category	Risk definition	Likely timing	Early signs/symptoms	Prevention/mitigation	Immediate management	Escalation endpoint/criteria	Frequency
Procedure-related (respiratory maneuvers)	Cough, throat irritation, transient dyspnea during spirometry or inhalation assessments [4]	During testing/training sessions	Coughing, chest/throat discomfort, shortness of breath	Pre-assessment screening for contraindications; coaching; allow rest between maneuvers;	Stop maneuver; seated rest; fluids as needed	Persistent/worsening symptoms despite rest; need for medical evaluation	[To be completed]

				stop if symptomatic [4]			
Procedure-related (bronchospasm)	Triggering of bronchospasm by forced maneuvers [4]	During/soon after testing	Wheeze, chest tightness, drop in peak flow/FEV1	Avoid testing during exacerbations; preload rescue inhaler availability; minimize repetitions [4–6]	Administer short-acting bronchodilator per local practice; monitor	No improvement within 15–30 minutes; oxygen saturation decline; ED referral	[To be completed]
Procedure-related (dizziness/syncope)	Vagal response or hyperventilation with forced maneuvers [4]	During/within minutes of testing	Lightheadedness, pallor, nausea	Seated testing when indicated; avoid prolonged breath-holds; coach paced breathing [4]	Stop test; supine positioning; vitals	Loss of consciousness; injury; persistent hypotension	[To be completed]
Procedure-related (musculoskeletal strain)	Chest wall/abdominal discomfort from forceful efforts [4]	During/after testing	Muscle soreness, chest/abdominal discomfort	Screen for recent surgery or high-risk states; limit repeat efforts [4]	Rest; analgesics per site practice	Severe or focal pain; concern for surgical complication	[To be completed]
Procedure-related (infection control)	Cross-contamination via reusable components	During testing sessions	None early; later URI symptoms	Single-use mouthpieces; device cleaning per IFU; user hygiene	Stop use; medical evaluation if symptomatic	Confirmed transmission clusters or device contamination	[To be completed]
Device-specific (software malfunction)	App crash, incorrect prompts, inaccurate feedback	Any time during use	Error messages, inconsistent guidance	Validated builds; user training; helpdesk; fail-safes; IEC 62304-aligned lifecycle controls [11]	Stop session; re-initiate after update; report device deficiency	Recurrent malfunction affecting safety; UADE reporting [1–3,9,10,13,16]	[To be completed]
Device-specific (algorithmic misclassification)	Misinterpretation of inhalation quality metrics leading to incorrect feedback	During training sessions	Feedback conflicting with clinician advice	Blinded core processes for endpoints; human factors validation; conservative thresholds [1–3,12,14]	Defer to clinician judgment; retraining	Systematic error signal; DSMB/CEC review and corrective action	[To be completed]
Device-specific (usability/human factors)	User confusion leading to incorrect inhaler steps	Early use phases	Repeated errors, frustration	Onboarding; clear UI; usability-tested instructions; helpline [14]	Pause app; provide clinician support	Safety-impacting pattern persists; consider discontinuation	[To be completed]
Data privacy/security	Unauthorized access to personal data/recordings	Any time	Alerts of access anomalies	GDPR-compliant safeguards; access controls; encryption; minimization [10]	Contain breach; notify per law; mitigation	Personal data breach meeting legal thresholds	[To be completed]

Respiratory (exacerbation context)	Participation during unstable disease could worsen symptoms	During acute illness	Increased rescue use, reduced PEF/FEV1	Exclude unstable patients; reschedule after recovery [5,6]	Clinical management per guideline	Hospitalization; severe exacerbation	[To be completed]
Cardiovascular	Strain-induced arrhythmia/chest pain in susceptible individuals [4]	During maneuvers	Palpitations, chest pain	Screen for contraindications; seated testing	Stop; ECG if indicated; medical care	Ongoing chest pain/arrhythmia	[To be completed]
Neurologic	Headache; rare syncope due to hyperventilation [4]	During/after testing	Headache, lightheadedness	Breathing coaching; rest	Stop test; symptomatic care	Persistent deficits; injury	[To be completed]
Dermatologic	Local irritation from device handling/hypersensitivity to materials	During device handling	Skin irritation on hands	Avoid prolonged contact; IFU-compliant cleaning	Discontinue contact; topical care	Spreading reaction; allergy work-up	[To be completed]
Renal/hepatic	Organ injury related to study activities	Not expected	Not expected	No nephrotoxic/hepatotoxic exposures in protocol	N/A	N/A	Not applicable
Vascular/bleeding	Access-site injury, hematoma, thrombosis/embolism	Not expected (no invasive access)	Not expected	Not applicable	N/A	N/A	Not applicable
Pleural/pericardial effusion	Effusion related to study activities	Not expected	Not expected	Not applicable	N/A	N/A	Not applicable

Notes:

- Frequency: site investigators will record observed frequencies; no assumed rates are prespecified in this protocol.
- Events that meet ISO 14155/MDR definitions for AE/SAE, UADE, or device deficiency will be reported per the Safety Reporting section and MDCG 2020-10 guidance [1–3,16].

Risk mitigation

Pre-procedure (prior to baseline and training sessions)

- Eligibility screening for spirometry/inhalation maneuver contraindications and clinical stability per ATS/ERS and clinician judgment; defer during acute exacerbations or recent high-risk events [4–6].
- Participant orientation to app use, home spirometry technique, and safety stop rules; confirm availability of prescribed rescue medication and emergency contacts [1,4–6].
- Device setup verification: correct app version, successful pairing with spirometer, test data upload, privacy settings confirmed; document in source and device accountability logs [1–3,10–12,14].

Intra-procedure (during spirometry and inhalation assessments/training)

- Seated position when indicated; continuous observation; minimize maneuver repetitions to those needed for quality; allow recovery time; abort session for any concerning symptoms [4].
- Use single-use mouthpieces and IFU-compliant cleaning of non-contact components; maintain hygiene and ventilation in testing areas [1,4].

- Technical safeguards: real-time quality checks, error handling, and fallback to clinician guidance if app prompts conflict with safe practice [11,14].

Post-procedure (after each session)

- Brief symptom check; document adverse events or device deficiencies; reinforce inhaler steps and app instructions; provide support contact information [1–3].

Post-procedure Monitoring & Prophylaxis Checklist

- Vitals/symptom checks: assess for dizziness, wheeze, chest tightness immediately post-session; instruct on delayed symptom reporting.
- Imaging schedule: not routinely required; obtain only if clinically indicated.
- Lab monitoring: not routinely required; obtain only if clinically indicated.
- Anticoagulation/antiplatelet plan: not applicable to this protocol.
- DVT/PE prevention: not applicable (no immobilization/procedure risk).
- Pain control: over-the-counter analgesia per local practice if muscle soreness occurs; document advice.
- Organ-protection measures: avoid excessive testing in those with recent surgery; reinforce hydration and rest if prolonged sessions occurred.
- Follow-up: ensure access to urgent clinical assessment if respiratory symptoms worsen; schedule next session per protocol.

Complication management algorithms

The following flow-style sequences define triggers, diagnostics, actions, and escalation. For this non-invasive study, some events are not anticipated; however, if suspected, clinical care takes precedence and study procedures are stopped immediately.

1. Suspected device migration/malposition (not applicable to non-implanted software; interpret as “incorrect device/app setup or sensor misalignment”)

- Trigger: Inconsistent flow readings; app indicates sensor misplacement; repeated calibration failure.
- Diagnostics: Verify device pairing; inspect hardware connections; perform test maneuver; compare with clinician-observed effort.
- Treatment: Recalibrate; re-install app if needed; replace spirometer if hardware fault suspected; document device deficiency.
- Escalation: Persisting measurement error impacting safety or data integrity; PI leads escalation to sponsor helpdesk; report device deficiency and consider pausing participant use pending resolution [1–3,11,14,16].

2. Suspected thrombosis/embolism (not expected)

- Trigger: New chest pain, dyspnea, hemoptysis, unilateral leg swelling during participation.
- Diagnostics: Stop study activities; activate site emergency response; clinical evaluation per standard care.
- Treatment: As per institutional protocols; study team does not delay urgent care.
- Escalation: Hospitalization or confirmed thromboembolic event; PI reports SAE/UADE as applicable; DSMB review per charter [1–3,8,16].

3. Bleeding/hematoma (not expected)

- Trigger: Participant reports acute bleeding or hematoma unrelated to study procedures.
- Diagnostics: Stop study activities; assess severity; refer for medical care.
- Treatment: Local pressure if minor; emergency care if major.
- Escalation: Any moderate/major bleed or hospitalization; SAE reporting and DSMB review [1–3,8,16].

4. Acute kidney injury (not expected)

- Trigger: Participant reports decreased urine output, edema, or abnormal labs from external care.
- Diagnostics: Stop study activities; encourage medical evaluation.
- Treatment: Managed by treating clinician; study imposes no nephrotoxic exposures.
- Escalation: Confirmed AKI meeting SAE criteria; report and present to DSMB [1–3,8,16].

5. Pleural/pericardial effusion (not expected)

- Trigger: New chest pain, dyspnea, orthopnea.
- Diagnostics: Stop study activities; urgent clinical assessment; imaging as per standard care.
- Treatment: Managed by treating clinician.
- Escalation: Clinically significant effusion or hospitalization; SAE reporting and DSMB review [1–3,8,16].

Escalation leadership: The Principal Investigator (PI) leads medical escalation; thresholds for SAE classification and UADE/device deficiency follow ISO 14155 and MDR. Escalation endpoints and documentation requirements are defined in the Safety Reporting and DSMB Charter subsections [1–3,8,16].

Governance and oversight

- Pre-enrollment multidisciplinary review: The Site Enrollment Committee (SEC) ensures spirometry suitability, app feasibility, and operational readiness before randomization, with quorum, voting, and documentation rules applied consistently across sites [1].
- Independent DSMB: An independent Data Safety Monitoring Board provides ongoing safety surveillance, reviews unblinded aggregate safety/deficiency trends, protocol adherence impacting safety, and recommends continue/modify/pause actions. Meeting cadence: initial meeting pre–first patient in; reviews after the first 25–50 participants complete the 6–12-week assessment and at predefined intervals thereafter, or ad hoc upon safety signal [1–3,8].
- Clinical Events Committee (CEC): If used, an independent, blinded CEC adjudicates prespecified categories: respiratory exacerbations requiring systemic therapy or hospitalization, syncope, algorithm-related misuse leading to AE, deaths from any cause, unanticipated serious adverse device effects (USADEs/UADEs), and device deficiencies with potential to cause harm, applying ISO 14155/MDR definitions and an Adjudication Manual [1–3,16].

DSMB charter (templated)

- Purpose: Independent oversight of participant safety, study conduct affecting safety, and overall benefit–risk.
- Membership criteria: At least three members including a pulmonologist/respiratory physiologist, a biostatistician experienced in device trials, and a clinician with digital health/software risk expertise. Members must be independent of the sponsor and study sites, disclose conflicts, and sign confidentiality agreements [8].
- Meeting cadence: Pre-study organizational meeting; scheduled data reviews at predefined enrollment/time milestones; ad hoc meetings for safety signals.
- Data package: Enrollment and exposure; protocol deviations with safety relevance; AE/SAE/UADE summaries and narratives; device deficiency logs; unblinded arm-specific safety if needed; withdrawal patterns; data quality indicators.
- Stopping/pausing authority: Recommend to the sponsor to continue, modify, pause, or terminate for safety concerns, unreasonable risks, or futility related to safety; the sponsor documents decisions and notifications to regulators/ethics as applicable [1–3,8,16].
- Confidentiality: DSMB deliberations and unblinded data remain confidential; only recommendations and minimal supporting rationale are shared with sponsor and, as needed, regulators/ethics [8].
- Conflict-of-interest handling: Members with any financial or professional conflicts recuse; replacement members appointed as needed with documentation.

- Reporting lines: DSMB Chair communicates recommendations to the sponsor's Medical Monitor; the sponsor informs investigators, CEC, and regulators/ethics as applicable.

Stopping rules and monitoring

- Interim safety monitoring: The DSMB will perform scheduled reviews as above. Predefined primary pause conditions include any emerging safety pattern reasonably attributable to the investigational module or associated devices that materially worsens the risk–benefit (e.g., clusters of bronchospasm during training, syncope related to maneuvers, systematic algorithm error causing misuse). Thresholds and boundaries for action will be prespecified in the DSMB Operating Guidelines; where numeric cutoffs are required, they will be finalized prior to first patient in and referenced in the DSMB manual without being reproduced here [1–3,8].
- Secondary pause conditions: Significant device deficiency trends affecting safety (e.g., repeated measurement failures leading to unsafe guidance), material privacy/security incidents involving participant data, or CEC-identified unexpected serious events potentially linked to the device/workflow. Any secondary trigger prompts an ad hoc DSMB review [1–3,10,16].

SAE/UADE reporting flow (textual one-page)

- Site detects or is informed of an AE/SAE/UADE or device deficiency.
- Immediate actions: Ensure participant safety; stop study activities if needed; arrange clinical care.
- Site reporting to sponsor: Notify sponsor Medical Monitor within [to be confirmed: e.g., 24 hours] for SAEs/UADEs; submit initial report with available details (event description, onset, severity, outcome, relatedness, device status, concomitants, actions taken); follow with updates and final report per timelines [1–3,16].
- Sponsor actions: Determine reportability; submit required safety reports to ethics committee(s) and competent authorities per MDR and national requirements within mandated timelines; inform DSMB and CEC (blinded/unblinded packages per charters) [2,3,16].
- Documentation: Record in eCRF and source; retain device for analysis when safe; complete device deficiency form; preserve audit trails for any software updates applied after the event [1–3,11,16].

Benefits

Potential near-term benefits include improved inhaler technique via structured, accessible training and feedback, potentially reducing critical errors known to be associated with worse outcomes in asthma/COPD [5,6]. Intermediate-term benefits may include improved symptom control, fewer technique-related exacerbations, and greater self-efficacy and adherence due to on-demand training access. Long-term benefits may include sustained technique proficiency supporting better disease control.

Objective measures collected to evidence benefit include:

- Primary endpoint: Rate of successful inhalation technique at 6–12 weeks via centralized, blinded review of standardized artifacts.
- Technique physiology: Inspiratory flow parameters (e.g., peak inspiratory flow, time to PIF, inspiratory time) generated by the CE-marked spirometer and analyzed within the app-module workflow.
- Pulmonary function: Spirometry per ATS/ERS standards with centralized QC [4].
- Usability/feasibility: Predefined usability and feasibility metrics and participant-reported usability questionnaires (instrument(s) to be confirmed).
- Safety: AE/SAE/UADE and device deficiency rates and narratives [1–3].

Patient communication

During informed consent, the study team presents key information in plain language:

- The investigational app-module is available only within this study; standard inhaler technique education is available outside the study.
- Expected risks are generally mild and transient (cough, dizziness, bronchospasm) related to breathing tests; serious complications are unlikely but will be monitored; privacy safeguards are in place [1–6,10].
- Benefits are not guaranteed; technique may improve with app-based training, but results vary; long-term durability is uncertain.
- Alternatives include receiving standard education alone or not participating, with no penalty to usual care.
- Participants are instructed to stop any session if unwell and to contact the study team or seek urgent care for concerning symptoms. Any new information affecting willingness to continue will be promptly communicated and may require re-consent [1,2].

Site readiness

Site Readiness Checklist

- Training and credentialing

- Investigators and designated staff trained on protocol, ISO 14155/ICH-GCP, safety reporting, spirometry per ATS/ERS, device IFUs, data privacy, and the adjudication workflow [1,2,4,10,16].
- Documentation of competency for spirometry coaching and app onboarding; refresher training plan in place.

- Equipment and inventory

- Sufficient CE-marked spirometers and Airflow Trainers available; single-use mouthpieces stocked; spare devices and charging cables available.
- App version verification and controlled distribution process; helpdesk contact sheet posted.

- Procedures and safeguards

- Local procedures for screening spirometry contraindications; seated testing option available; rescue medication accessible.
- Cleaning/disinfection SOPs available and implemented per IFU; waste disposal aligned with site policy.
- Privacy/security: role-based access, encryption enabled, data transfer SOPs aligned with GDPR [10–12,14].

- Emergency preparedness

- On-site response plan for acute respiratory symptoms, syncope, or other urgent events; clear handoff to usual care/emergency services; PI-led escalation lines defined [1–3].

- Oversight and documentation

- DSMB/CEC contact and reporting pathways posted; SAE/UADE timelines and templates accessible [1–3,8,16].
- Logs for device accountability, deficiencies, software updates, and training records current and auditable.

- Post-discharge/remote support

- 24/7 or site-specified urgent contact route communicated to participants; rapid appointment pathway for urgent evaluation.
- Scheduled follow-up and remote data checks configured; process for pausing app use if safety concerns arise.

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6 STUDY PROCEDURES AND SCHEDULE

Overview

This section specifies all participant-facing and site-facing procedures, their timing, mode (on-site versus decentralized/remote), source documentation, and central processes required to achieve valid, reliable assessment of the primary and secondary endpoints in a late-phase device investigation. Procedures adhere to ISO 14155/ICH-GCP, EU MDR, ATS/ERS spirometry standards, and SPIRIT-aligned scheduling guidance, with decentralized elements implemented per competent authority guidance and site SOPs [1–5].

Visit structure, timing windows, and modes

- Population: Individuals aged ≥16 years with asthma and/or COPD using a DPI and/or MDI daily, randomized 1:1 within inhaler strata (DPI/MDI/both) to intervention (standard education plus app-based module) or control (standard education alone).
- Primary endpoint timepoint: Centralized, blinded adjudication of standardized inhalation technique artifacts captured at the 6–12-week follow-up visit.
- Modes of conduct:

- On-site visits: Screening/Baseline, Randomization/Onboarding, and the 6–12-week primary endpoint visit are preferably conducted on-site to ensure artifact quality and safety oversight during respiratory maneuvers [1,2,4].
- Remote contacts: Interim checks (e.g., Weeks 2 and 4) and long-term contacts (Months 6 and 12; Years 2–5) may be remote per approved decentralized procedures and participant preference, with identity verification, secure data transfer, and audit trails [3,5].

Visit timeline and allowable windows

Visit ID	Timepoint (target)	Window	Mode (preferred)
V0	Screening/Baseline Day −28 to 0	±0 within Day −28 to 0	On-site
V1	Randomization/Onboarding Day 0	0 to +7 days after V0 completion	On-site
V2	Interim check Week 2	±7 days	Remote or on-site
V3	Interim check Week 4	±7 days	Remote or on-site
V4	Primary endpoint visit Week 8	Window: Week 6 to Week 12	On-site
V5	Month 6	±4 weeks	Remote or on-site
V6	Month 12	±6 weeks	Remote or on-site
V7–V10	Annual contact Years 2–5	±8 weeks	Remote or on-site

Notes:

- When V0 and V1 occur the same day, activities must follow informed consent and eligibility verification before any randomization [1–3].
- The primary analysis defines V4 within the Week 6–12 window; if multiple artifacts are available within the window, the prespecified hierarchy in the Adjudication Manual applies (e.g., latest acceptable artifact within window) [1,2].

Procedures by visit

- V0 Screening/Baseline:

- Informed consent (and assent/LAR where applicable), identity verification.
- Inclusion/exclusion verification; standardized case synopsis completion; SEC approval.
- Baseline spirometry per ATS/ERS 2019 standards with site QC and central core QC submission; calibration/verification logs filed [1].
- Baseline inhalation technique artifact capture (video and/or inhalation flow-curves) per Adjudication Manual; submit for central adequacy confirmation (pass/fail for adequacy; not technique correctness) [1,2].
- Collection of demographics, diagnosis documentation (asthma and/or COPD) per GINA/GOLD definitions, current inhaler(s) and dosing, concomitant medications, clinical stability ascertainment [4,5].
- Smartphone compatibility and eID (BankID or equivalent) verification; willingness to use AsthmaTuner and inhalation app-module if randomized to intervention.
- Baseline participant-reported measures and usability/feasibility items [instrument(s) to be confirmed].
- AE/SAE history and spirometry/inhalation contraindication screen.

- V1 Randomization/Onboarding (post-SEC approval and central adequacy confirmation where required):

- Randomization release with inhaler-stratum confirmation.
- Control arm: standardized, guideline-based inhaler technique education using a prespecified checklist consistent with GINA/GOLD device-specific steps.
- Intervention arm: same standardized education plus app onboarding (AsthmaTuner version >5.4.13.5) and inhalation training module activation; device provisioning (CE-marked spirometer and Airflow Trainer) and competency check; secure pairing and test transmission verification; safety stop rules reiterated [2,4,5].
- Documentation of device/accountability and training completion; AE/SAE/device deficiency

assessment.

- V2 and V3 Interim checks (Weeks 2 and 4):

- Reinforcement of standardized inhaler steps (both arms).
- Intervention arm: troubleshooting, review of training module engagement and telemetry, optional technique refreshers.
- Remote safety check; capture of any AEs/SAEs/device deficiencies; confirm clinical stability.
- Optional collection of interim usability/acceptability items and adherence metrics [to be confirmed].

- V4 Primary endpoint visit (Week 6–12):

- Standardized inhalation technique artifact capture(s) per Adjudication Manual for centralized, blinded adjudication of correctness; ensure artifact adequacy (on-site QA) before submission [1,2].
- Spirometry per ATS/ERS with central core QC submission [1].
- Concomitant medications, exacerbations, healthcare utilization since last visit.
- Intervention arm: module usage summary captured; control arm: reinforcement session documented.
- AE/SAE/device deficiency assessment; privacy/data transfer confirmation if any changes.

- V5 Month 6 and V6 Month 12:

- Technique artifact capture strongly encouraged when feasible (for durability/exploratory analyses) with central submission; if remote, follow decentralized capture SOPs [3].
- Spirometry may be repeated per protocol [to be confirmed] when feasible; central QC if obtained [1].
- Usability/feasibility questionnaires [instrument(s) to be confirmed], training engagement (intervention), inhaler education reinforcement (both arms).
- AEs/SAEs/device deficiencies; exacerbations; concomitants.

- V7–V10 Years 2–5 annual contacts:

- Safety surveillance (AEs/SAEs/device deficiencies/UADEs), exacerbations and device-related issues if any persisting exposure; confirm ongoing consent and contact preferences.
- Technique artifact capture is optional at these contacts unless otherwise amended [to be confirmed].

Schedule of Assessments

Legend: E = eligibility-critical; R = required (non-eligibility); O = optional. “Mode” indicates preferred mode at that visit; decentralized execution must follow approved SOPs with identity verification and secure transfer [2,3].

Assessment/Procedure	Criticality (E/R/O)	V0 Screen/BL (On-site)	V1 Rand/Onboard (On-site)	V2 Wk2 (Remote/On-site)	V3 Wk4 (Remote/On-site)	V4 Wk6–12 Primary (On-site)	V5 Mo6 (Remote/On-site)	V6 Mo12 (Remote/On-site)	V7–V10 Yr2–5 (Remote/On-site)
Informed consent/assent/eID verification	E	XX							
Inclusion/exclusion checklist and SEC approval	E	XX							
ERC review (if referred)	E (conditional)	X (if needed)X (if needed)							
Diagnosis documentation	E	XX							

(asthma/COPD) per GINA/GOLD									
Current inhaler(s), dosing, and stratum confirmation	E	X	XX				R (update)	R (update)	R (annual update)
Smartphone compatibility and BankID/eID	E	XX							
Spirometry per ATS/ERS; central core QC submission	R	XX		O	O	X	O [TBC]	O [TBC]O [TBC]	
Baseline inhalation technique artifact capture; central adequacy check	E	XX							
Randomization release (1:1 within DPI/MDI/both strata)	RR		XX						
Standard inhaler technique education (both arms)	RR		X	X	X	X	X	X	O
App onboarding and device provisioning (intervention only)	R (intervention)R (intervention)		XX						
App-based inhalation training engagement/telemetry review (intervention)	R (intervention)R (intervention)		X (verify setup)	X	X	X	X	X	O
Primary technique artifact capture for blinded adjudication	RR					XX			
Technique artifact capture (durability/exploratory)	OO			O	OO		O	O	O
Concomitant meds, rescue use, exacerbations	R	X (baseline)	X	X	X	X	X	X	X
Usability/feasibility questionnaires [instrument TBC]	R (study-level)R (study-level)		X (baseline usability)	O	O	X	X	X	O
AE/SAE/UADE assessment and	R	X	X	X	X	X	X	X	X

device deficiency log									
Privacy/consent reaffirmation and contact preferences	R	XX		O	O	X	X	X	X
Device accountability (intervention)	R (intervention)R (intervention)		X	X (status)	X (status)	X (status)	X (status)	X (status)	O

Procedural standards and central processes

- Spirometry: Conduct per ATS/ERS 2019 standards including acceptability and repeatability criteria; document calibration/verifications; submit tracings for central QC grading. Avoid testing during acute exacerbations; follow contraindication precautions [1].
- Inhalation technique artifacts: Capture per Adjudication Manual using standardized positioning, prompts, and recording conditions; confirm adequacy locally; submit for centralized adequacy and endpoint adjudication; central reviewers remain blinded to allocation [1,2].
- Standardized education: Deliver device-specific critical step training consistent with GINA/GOLD guidance and the study's checklist; record content delivered, duration, and participant competency check [4,5].
- App onboarding and training (intervention): Verify AsthmaTuner version (>5.4.13.5), successful device pairing, test uploads, user competency, and safety stop rules. Software lifecycle and usability controls follow IEC 62304 and IEC 62366-1-aligned processes; device deficiencies are logged and escalated per Safety Reporting [2,6,7].
- Decentralized elements: Identity verification (e.g., BankID), secure data transfer, role-based access, and audit trails are mandatory for all remote procedures, consistent with EMA DCT guidance and site SOPs [3].

Rules for missed, late, or incomplete assessments

- General principles:

- Participant safety and scientific integrity supersede schedule adherence; document any deviations contemporaneously with rationale in source and eCRF per GCP/ISO 14155 [2,3].
- Within-window rescheduling is prioritized. If a planned contact cannot occur on the target date, schedule at the earliest time within the allowable window defined above.

- Primary endpoint (V4) window:

- Acceptable window is Week 6 through Week 12 post-randomization. If multiple artifacts are collected within this window, the prespecified hierarchy in the Adjudication Manual applies. If no acceptable artifact is obtained within the window despite documented attempts, the primary endpoint is considered missing for that participant; no post-window capture will replace the primary endpoint, and the case will be handled per SAP-defined missing data strategies [2,5].
- Justifications considered acceptable include intercurrent illness, technical failure documented as device deficiency, or participant scheduling constraints; each must be recorded with date/time, responsible staff, and corrective action.

- Spirometry:

- If baseline spirometry fails QC or is not obtained at V0 due to a transient contraindication, repeat prior to randomization where feasible. If operationally not feasible, SEC may defer or approve with documented justification and plan per Eligibility Governance; any repeats post-randomization follow protocol feasibility and safety rules [1,2].

- Interim and long-term visits:

- If V2/V3/V5/V6/V7–V10 are delayed within their windows, no protocol deviation is recorded. Outside-window completions require PI documentation of continued clinical relevance, SEC

confirmation that continued participation remains appropriate, and deviation logging per SOPs; data are included per SAP specification.

- Partial assessments:

- If a visit occurs but some procedures are incomplete (e.g., artifact captured but questionnaire omitted), record completed items and reason for missing elements; do not repeat procedures in a manner that compromises safety (e.g., excessive respiratory maneuvers) [1,2].

- Remote failures:

- If a remote capture fails (e.g., upload error), one repeat attempt is recommended within the same window. Persistent technical failures must be logged as device deficiencies and escalated; consider on-site reassessment when feasible [2,3].

- Documentation requirements:

- All missed/late/incomplete assessments require source documentation of the reason, impact on eligibility/evaluability (if any), participant communication, and corrective/preventive actions. Monitoring will verify contemporaneous completion and audit trails [2].

Training, quality assurance, and data flow

- Site personnel must be trained and documented as competent in: ATS/ERS spirometry coaching; standardized inhaler education steps per GINA/GOLD; artifact capture SOPs; app onboarding; decentralized procedures including identity verification and secure data transfer; AE/SAE/UADE and device deficiency reporting [1–5].
- Data flow:

- Source to eCRF transcription is contemporaneous with ALCOA principles; device telemetry and artifacts are transferred via validated, encrypted channels with role-based access. Central core/QC and adjudication systems maintain blinding and audit trails. Any software updates are version-controlled and documented in device accountability logs [2,3,6,7].

Withdrawal and early discontinuation procedures

- At any contact following withdrawal or discontinuation, perform safety assessment appropriate to participant permission and local law, reconcile device/accountability (intervention), and document the scope of ongoing data collection if allowed. Handling follows GCP/ISO 14155 and ethics approvals; no procedures are conducted without valid consent [2,3].

Rationale for schedule alignment

- The schedule concentrates resource-intensive, safety-relevant procedures (spirometry, primary artifact capture) at on-site visits while enabling decentralized interim monitoring to minimize burden, consistent with SPIRIT-aligned design and DCT guidance [3,5].
- The 6–12-week primary window reflects the expected timeframe to translate education/training into measurable technique proficiency while allowing operational flexibility and participant-centered scheduling [4,5].

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6.1 Pre-Procedure Assessments

Purpose and scope

This section defines mandatory pre-procedure assessments and readiness checks prior to any protocol-specified respiratory maneuvers (spirometry, standardized inhalation technique artifact capture) or app-based training sessions. Procedures ensure participant safety, data integrity, and compliance with ISO 14155/ICH-GCP, ATS/ERS spirometry standards, GINA/GOLD respiratory care guidance, and decentralized trial requirements where applicable [1–6].

Responsible personnel

- Principal Investigator (PI): final medical clearance to proceed or defer; oversight of safety decisions and documentation [1,2].
- Trained study clinician (physician/APRN/PA) or respiratory physiologist/technologist: targeted respiratory history, spirometry contraindication screen, technique coaching, and on-site observation [4].
- Trained research nurse/coordinator: vitals, device/app verification, identity/eConsent checks for remote procedures, questionnaire administration, source documentation [1–3,5].
- Technical specialist (as delegated): device pairing, software version control, telemetry test, and remediation; defect logging per usability and software lifecycle controls [3,7,8].

Pre-procedure readiness checklist (source-document template)

Domain	Required item	Timing window	Pass criteria	Action if not met
Consent/identity	Valid informed consent/assent; identity verification for remote contacts (eID)	Prior to any procedures; confirm at each session	Documentation present; eID validated (remote)	Stop; re-consent/verify before proceeding [1–3,5]
Eligibility status	No new exclusion since last review; background therapy stability per protocol	Within 7 days of session	Investigator attestation	Defer; SEC/ERC review if unclear [1,2]
Interim health status	No acute exacerbation/respiratory infection; no new ATS/ERS spirometry contraindications	Day 0–2 (in-person) or day 0 (remote)	Negative screen and clinician exam (in-person)	Defer ≥[TBC] days after recovery; re-screen [4]
Vitals/safety	Seated BP, HR, SpO2, RR; symptom screen (dyspnea, wheeze, chest pain, dizziness)	Within 2 hours pre-maneuvers	BP/HR within site norms; SpO2 ≥[TBC]% at rest; asymptomatic	Rest/reassess; if persistent or SpO2 <[TBC]% or unstable vitals, defer and evaluate [4]

Rescue medication	Participant has prescribed reliever available on-site or at home (remote)	Day of session	Confirm presence and expiry date	Provide/arrange per local care; proceed only once available [4–6]
Device/app status	AsthmaTuner version >5.4.13.5; module enabled; spirometer paired; test upload successful	Within 7 days (or same day)	Version/logs verified; telemetry OK	Troubleshoot/update/replace; if unresolved, log device deficiency and reschedule [3,7,8]
Infection control	Single-use mouthpieces; cleaning of non-contact components per IFU	Same day	Supplies available; area prepared	Replace supplies/clean area; do not proceed until compliant [4]
Data systems	eCRF access, audit trail active; central core/adjudication portals reachable	Same day	Access confirmed	IT remediation; if unresolved, proceed only with safe procedures and complete uploads ASAP with documentation [1–3,5]

Targeted history and physical examination (mandatory elements)

- Targeted history (collected or updated within 7 days pre-session; confirm on the day):

- Current respiratory symptoms and stability: increased dyspnea, wheeze, chest tightness, productive cough, fever; any exacerbation since last contact; healthcare utilization (urgent care/ER/hospitalization) [5,6].
- Recent events contraindicating forced maneuvers: thoracic/abdominal/ophthalmic/ENT surgery, pneumothorax, unstable cardiovascular disease, recent MI/PE, hemoptysis of unknown origin, uncontrolled hypertension, pregnancy-related high risk (site judgment) [4].
- Medication review: maintenance and reliever inhalers, oral/systemic therapies, recent changes; timing of last bronchodilator use if clinically relevant to spirometry interpretation [4–6].
- Device/app use issues: usability barriers, crashes, inconsistent feedback; prior device deficiencies and resolutions [7,8].
- Social/operational updates: smartphone/eID access, willingness to continue, ability to attend on-site visits [3].

- Physical examination (on-site sessions; within 2 hours of maneuvers):

- General appearance; work of breathing at rest.
- Vital signs: BP, HR, RR, SpO2 (at rest); temperature if infection suspected.
- Focused respiratory exam: wheeze, crackles, prolonged expiration.
- Focused cardiovascular exam: irregular rhythm, chest pain on exam.
- If abnormal findings suggest instability, defer maneuvers and arrange clinical evaluation; document rationale and plan [4].

Laboratory testing

- Routine laboratory testing is not required for participation or pre-procedure clearance, as the protocol involves non-invasive respiratory maneuvers only; investigators may order labs per clinical judgment if indicated by history/exam (e.g., suspected infection) [1,4].
- Pregnancy testing: not routinely required given non-pharmacologic, non-ionizing procedures; perform only if clinically indicated per site policy [1].
- Placeholder thresholds to guide defer/delay (to be finalized prior to first patient in):

- Resting SpO2 <[TBC]% on room air.
- Systolic BP >[TBC] mmHg or <[TBC] mmHg with symptoms; HR >[TBC] bpm at rest with symptoms.
- Febrile illness (temperature ≥[TBC] °C) with respiratory symptoms.
- Any ATS/ERS-listed absolute/relative contraindication identified; apply clinical judgment and document [4].

Required non-invasive tests and timing

- Spirometry:

- Conduct per ATS/ERS 2019 standards with acceptability and repeatability criteria; capture pre-bronchodilator maneuvers unless otherwise indicated; submit tracings to the central core for QC [4].
- Timing: mandatory at Screening/Baseline (V0) and at the primary endpoint visit (V4 Week 6–12); optional at Month 6 and Month 12 per feasibility [protocol TBC].
- Local quality steps: daily calibration/verification logs; seated testing when indicated; minimize repetitions to those needed for quality; stop for adverse symptoms [4].

- Standardized inhalation technique artifact(s):

- Mandatory video and/or inhalation flow-curve capture per Adjudication Manual at V0 (for adequacy confirmation) and at V4 for primary endpoint adjudication; encourage capture at Month 6 and Month 12 for durability/exploratory analyses when feasible [1].
- Timing windows: V0 within Day −28 to Day 0; V4 within Week 6–12 post-randomization; Month 6 ±4 weeks; Month 12 ±6 weeks (if performed) [1,5].

- ECG, chest imaging, echocardiography, CT, cardiopulmonary exercise testing, duplex ultrasound, and pulmonary function testing beyond spirometry are not required by protocol; obtain only if clinically indicated per investigator judgment. Results obtained for clinical care may be recorded as source if relevant to safety decisions [1,4–6].

Invasive diagnostic studies

- No invasive diagnostic procedures are required by this protocol. Arterial/venous blood sampling, bronchoscopy, or catheter-based assessments are not mandated and should not be performed for study purposes. If clinically indicated for standard care, record pertinent findings that impact maneuver safety and document any decision to defer study procedures accordingly [1,4].

Functional status and quality-of-life instruments

- Disease control/impact instruments: a validated, indication-appropriate instrument will be prespecified prior to first patient in:

- Asthma: Asthma Control Test (ACT) or ACQ-5 [instrument TBC; language versions TBC] [9].
- COPD: COPD Assessment Test (CAT) [language versions TBC] [10].

- Usability/feasibility: a standardized usability instrument (e.g., System Usability Scale [SUS]) and study-specific acceptability items will be prespecified, with validated translations where available [instrument TBC; languages TBC] [11].
- Administration timing:

- Baseline (V1) prior to or immediately after randomization for baseline usability and disease control.
- Primary endpoint visit (V4 Week 6–12).
- Month 6 and Month 12 visits.

- Administration mode: on-site ePRO or remote ePRO compliant with identity verification, data privacy, and audit trails per decentralized trial guidance; paper backup allowed per site SOP with prompt transcription and source retention [1–3,5].

Rules for repeat testing, deferral, or cancellation

- Spirometry or inhalation artifact capture must be deferred if any ATS/ERS-listed contraindication is present or if acute respiratory illness/exacerbation is suspected. Reassess after clinical stability is achieved for ≥[TBC] days without fever or escalating therapy; document clinician clearance [4–6].

- If local quality criteria are not met (e.g., repeated unacceptable attempts, cough interfering with tracings), allow rest, provide coaching, and attempt a limited repeat within the same session. Do not exceed ATS/ERS-recommended repetition to avoid fatigue/bronchospasm; if still unacceptable, reschedule within the visit window and document [4].
- Technical failure (e.g., upload error, device crash):

- Perform standard troubleshooting; if resolved, repeat capture within the same encounter.
- If unresolved, record a device deficiency, contact the sponsor helpdesk, and reschedule within-window. Consider on-site reassessment if prior attempts were remote [1,3,7,8].

- Safety stop rules during maneuvers:

- Abort immediately for presyncope/syncope, severe dyspnea/wheeze, chest pain, significant desaturation, or investigator concern; provide rest and clinical evaluation as needed; document as an AE if criteria met [1,4].

Device/app pre-session verification and order set (intervention arm)

- Verify AsthmaTuner version >5.4.13.5; confirm participant account identity and access; confirm inhalation app-module activation limited to study subjects (investigational feature flag checked) [3,7].
- Pair CE-marked spirometer; confirm Airflow Trainer availability; perform test maneuver upload and server receipt; review telemetry dashboard for integrity [3,7,8].
- Reconfirm safety instructions, availability of reliever inhaler, and stop criteria.
- If any element fails, remediate or replace hardware/software; if not correctable during the visit, document deficiency and reschedule within the allowed window [1,3,7,8].

Data capture, central submissions, and blinding safeguards

- Spirometry tracings and inhalation artifacts are uploaded via validated, encrypted channels with role-based access and audit trails; central core lab (spirometry QC) and blinded adjudicators (technique correctness) remain masked to allocation [1,3,7,8].
- Local staff confirm artifact adequacy prior to submission; any re-collection follows the same safety and quality rules and must remain within the visit window [1,4].

Documentation requirements

- Use ALCOA-compliant source templates to record: pre-session checklists, history and physical elements, vitals, device/app verification, reasons for deferral/repeat, technical issues and resolutions, AE/SAE/UADE assessments, and data transfer confirmations. Remote sessions require contemporaneous identity verification logs and system audit trails per decentralized guidance [1–3,5].

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6.2 Procedure Description

Overview and setting

- Procedure scope: Non-invasive respiratory maneuvers (spirometry and standardized inhalation technique artifact capture) and app-based education/training using the investigational inhalation app-module embedded in AsthmaTuner (version >5.4.13.5) paired with a CE-marked spirometer and used with an external Airflow Trainer. No incisions, catheterization, implants, or ionizing imaging are involved [1–5].
- Settings:

- On-site: Outpatient clinic or pulmonary function testing area equipped for spirometry, with trained personnel, emergency response access, and infection-control supplies [3–5].
- Remote (decentralized): Participant’s home with identity verification (eID/BankID), validated telemedicine platform, helpline access, and pre-shipped devices per site SOPs; remote procedures must follow approved decentralized trial safeguards and audit trails [2,6].

- Personnel: Certified spirometry technologist/respiratory clinician for coached maneuvers; investigator oversight for medical clearance and AE management; research coordinator for device/app setup and documentation [1–4].

Anesthesia and analgesia

- Anesthesia/analgesia: Not required. Procedures are performed with the participant awake and seated or standing per ATS/ERS standards. Supplemental oxygen is not routinely indicated and should be used only if clinically prescribed for underlying disease. No sedation is permitted [3–5].

Imaging and procedural guidance

- Imaging: None required or planned. No fluoroscopy, ultrasound, or radiography are used. Visual coaching and standardized prompts provide procedural guidance during spirometry and inhalation technique capture [3–5].

Access strategy and device preparation

- Physical access: Not applicable (non-invasive). Procedural “access” refers to safe participant positioning, mouthpiece interface, and confirmed pairing of the CE-marked spirometer with the AsthmaTuner app; the Airflow Trainer does not contact the mouth or skin [3–5].
- Digital access:

- Identity: eID/BankID verification for remote sessions per site SOPs [2,6].
- App/device: Confirm AsthmaTuner version >5.4.13.5; verify investigational inhalation module activation; pair spirometer; complete a successful test upload; ensure data encryption and role-based access controls [2,6–8].
- Contingency: If pairing or telemetry fails, remediate per IFU and site SOPs; log device deficiency and reschedule within the visit window if unresolved [1,2,7,8].

Anticoagulation and antiplatelet management

- Anticoagulation/antiplatelet therapy: No protocol-mandated changes. These medications do not affect the non-invasive respiratory maneuvers planned. Continue background therapy per standard care; defer procedures only if another clinical condition creates an ATS/ERS-listed contraindication to forced maneuvers (e.g., recent surgery with bleeding risk) [3–5].

Patient positioning and anatomic/mouthpiece requirements

- Position: Seated is preferred for safety; standing may be used if clinically appropriate and participant is stable [3].
- Seal and landmarks:

- Achieve a tight lip seal around a single-use, appropriately sized mouthpiece connected to the CE-marked spirometer per IFU; use a nose clip when indicated to prevent nasal leak during testing, consistent with ATS/ERS standards [3].
- Head and neck in neutral alignment; shoulders relaxed; for DPI/MDI technique artifacts, position and sequence the steps according to device-specific checklists aligned with GINA/GOLD guidance (e.g., exhale to functional residual capacity before DPI inhalation, slow-deep inhalation with actuation for MDI) [4,5].

- Sizing: Adult standard single-use mouthpieces are used unless local policy requires pediatric sizing; if an adapter is required for the spirometer, document model/size per IFU [3].

Pre-, intra-, and post-procedure medications

- Routine medications: Continue maintenance therapy as prescribed; record timing of last bronchodilator if clinically relevant to spirometry interpretation [3–5].
- Rescue bronchodilator: Must be immediately available during on-site sessions and available at home for remote sessions. Administer only if clinically indicated (e.g., bronchospasm) and document dose, route, and time [3–5].

Procedural workflow

- Pre-procedure verification (same day):

- Confirm valid consent and identity (eID for remote).
- Targeted stability screen; vitals (BP, HR, SpO2, RR) within site norms; no ATS/ERS-listed contraindications; rescue inhaler available [3–5].
- App/device check (version >5.4.13.5; pairing/telemetry OK); infection control setup (single-use mouthpiece; IFU-compliant cleaning) [3,6–8].

- Intra-procedure steps:

- Provide standardized coaching; minimize repeats to those needed for quality; allow rest between maneuvers [3].

- Collect inhalation technique artifact(s) per Adjudication Manual: device-specific step performance, inspiratory flow-curve when available, and optional video for central review; ensure adequate lighting/framing if video is captured [1,3–5].
- Perform spirometry per ATS/ERS 2019 standards with acceptability/repeatability criteria; seated when indicated; stop on safety triggers (e.g., presyncope, severe dyspnea, chest pain) [3].
- Abort criteria: Any concerning symptoms or technologist/investigator judgment of risk; provide rest and clinical evaluation as needed; document and report per safety procedures [1,3].

- Post-procedure:

- Reassess symptoms and SpO2 if indicated; reinforce inhaler steps and app safety rules; confirm data upload to central systems; log AEs and any device deficiencies [1–3].

Hemodynamic and physiologic measurements

- Required before and after on-site sessions: BP, HR, RR, SpO2 at rest within 2 hours pre-session; symptom check immediately post-session; repeat vitals if symptoms occur during or after maneuvers [3].
- Remote sessions: Symptom check mandatory; vitals optional per site SOP and available home devices; instruct participants to stop if symptomatic and contact the study team or urgent care as clinically appropriate [2,6].

Imaging and ancillary testing during procedures

- No protocol-required imaging. Additional clinical tests (e.g., ECG) are obtained only if clinically indicated due to symptoms or investigator concern; results, if obtained, are documented in source and reported per safety requirements [1–4].

Intra-procedural events and complication management

- Expected minor events: Cough, throat irritation, transient dyspnea, dizziness; manage with rest, fluids, and coaching adjustments [3–5].
- Potential complications: Bronchospasm, presyncope/syncope. Administer rescue bronchodilator if indicated; place participant seated/supine; obtain vitals; escalate to urgent care per site protocol if symptoms persist or worsen; record and report per ISO 14155/MDR safety reporting and study SAE/UADE workflows [1,9].

Documentation requirements

- Source documentation must be ALCOA-compliant and contemporaneous for all procedural elements, including device version/build, pairing status, calibration/verification logs, quality grades for spirometry, artifact adequacy, vitals, medications, events, and deviations. Electronic systems must maintain audit trails and role-based access controls; remote identity verification must be logged per SOPs [1,2,6].

Structured intra-procedure data capture form (source template)

Domain	Data element
Participant/session	Site; Participant ID; Date; Start time; Stop time; Mode (on-site/remote); Staff present/roles
Consent/identity	Consent version/date; eID verification (remote: Yes/No; method); privacy permissions confirmed (Yes/No)

Pre-procedure stability	Interim illness/exacerbation since last visit (Yes/No; details); ATS/ERS contraindications screen (Pass/Defer; rationale)
Vitals (on-site)	BP (mmHg); HR (bpm); RR (breaths/min); SpO2 (%); symptoms at baseline (None/describe)
Device/app verification	AsthmaTuner version (>5.4.13.5: Yes/No; exact build); spirometer model/serial; pairing OK (Yes/No); test upload OK (Yes/No); Airflow Trainer available (Yes/No)
Infection control	Single-use mouthpiece used (Yes/No); cleaning per IFU completed (Yes/No)
Inhalation artifact(s)	Inhaler type (DPI/MDI/both); steps performed per checklist (Pass/Fail per step); video captured (Yes/No); flow-curve captured (Yes/No); local adequacy (Adequate/Inadequate; reason); submission timestamp
Spirometry	Position (Seated/Standing); nose clip (Yes/No); number of acceptable maneuvers; best values; repeatability met (Yes/No); local QC grade; central submission timestamp
Medications during session	Rescue bronchodilator given (Yes/No; agent/dose/time); other meds (specify)
Events/complications	Event type; onset time; actions taken; outcome at end of session; AE/SAE status; relatedness (device/procedure/other); device deficiency (Yes/No; description)
Post-procedure check	Symptoms post-session (None/describe); vitals if indicated; discharge advice given (Yes/No)
Data integrity	Uploads verified (Yes/No; artifacts/spirometry); audit trail ID; any technical issues and resolutions
Signatures	Technologist/clinician signature/date; Investigator review/signature/date

Standardized procedure note template (medical record)

- Procedure: Spirometry and standardized inhalation technique assessment/training using AsthmaTuner inhalation module (v[record exact build]) with CE-marked spirometer; Airflow Trainer present.
- Indication: Asthma and/or COPD; assessment/training of inhaler technique per protocol.
- Setting and personnel: [Clinic/Remote]; names/roles.
- Pre-procedure status: Pertinent history update; stability confirmation; vitals (BP/HR/RR/SpO2); contraindication screen results.
- Technique:

- Positioning and safeguards (seated/standing; nose clip use; infection control).
- Inhaler(s) assessed (DPI/MDI/both); steps performed; artifact capture details (video/flow-curve); local adequacy judgment; time stamps.
- Spirometry per ATS/ERS: number of acceptable efforts; best values; repeatability; local QC; submission completed.

- Medications administered: Rescue bronchodilator or other (agent/dose/time) if applicable.
- Events: Any adverse symptoms/events; management; disposition; AE/SAE/UADE and device deficiency reporting initiated as applicable.
- Post-procedure: Immediate status; participant education provided; follow-up plan; remote/on-site next contact.
- Data and device: App version/build; pairing and telemetry status; calibration/verification logs referenced; uploads verified; device accountability status (if applicable).
- Signatures: Operator and investigator.

Data to be transmitted for central review

- Inhalation artifacts: Video and/or inspiratory flow-curves with associated metadata (date/time, device serials, app build, inhaler type/steps performed) for blinded adjudication of technique success [1–4].

- Spirometry tracings: Raw curves and best values with calibration/verification attestations for central QC per ATS/ERS [3].
- Event reports: AE/SAE/UADE narratives and device deficiency forms, with relevant logs and software versioning as required by ISO 14155/MDR and study safety procedures [1,9].

Quality and safety controls

- Calibration/verification: Perform and document per spirometer IFU and local lab policy before participant testing; retain logs for monitoring [3].
- Usability safeguards: Apply validated user interface and human factors controls; if prompts conflict with clinician judgment, pause app guidance and proceed per clinical standards; report algorithmic anomalies as device deficiencies [7,8].
- Decentralized safeguards: Identity verification, secure transfer, role-based access, and auditable data flows are mandatory for remote captures; reattempt failed uploads once within window; otherwise reschedule or convert to on-site per SOPs [2,6].

Deviations and contingency planning

- If primary artifacts cannot be obtained within the window due to illness or technical failure, document reason, corrective actions, and classify endpoint status per SAP. Do not exceed ATS/ERS-recommended repetitions to avoid fatigue/bronchospasm; participant safety has primacy [1–5].

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6.2.1 Placement of Device

Procedural approach and scope

- Approach: Non-invasive deployment of the investigational inhalation app-module embedded in AsthmaTuner (version later than 5.4.13.5; manufacturer MediTuner AB; SRN SE-MF-000028534) paired with a CE-marked spirometer and used with an external Airflow Trainer that does not contact the mouth or skin. No incisions, catheters, implants, anesthesia, or ionizing imaging are involved [1–6].
- Settings permitted:

- On-site: Outpatient clinic/pulmonary function testing area with trained personnel, emergency response access, infection-control supplies, and secure connectivity [1,4–6,9].
- Remote: Participant's home under approved decentralized procedures with eID/BankID identity verification, validated telemedicine platform, pre-provisioned devices, and audit-trailed data transfer [1–3,9].

- Operators: Trained respiratory technologist/clinician conducts coaching and captures artifacts; Principal Investigator (PI) provides medical clearance and oversight; coordinator manages app/device setup and documentation in accordance with ISO 14155/ICH-GCP and MDR [1–3].

Permitted device sizes and components

- App: AsthmaTuner mobile app, version >5.4.13.5 with investigational inhalation module enabled for study subjects only [7,8].
- Spirometer: CE-marked, site-approved model per IFU; disposable single-use mouthpieces:

- Adult standard mouthpiece (preferred).
- Pediatric mouthpiece/adapter if required by site policy [4].

- Accessories:

- Nose clips (adult and pediatric sizes per local policy) [4].
- Airflow Trainer (non-contact orientation aid) [1,4].

- Site must document exact spirometer model/serial, mouthpiece size/adapter used, and app build; substitutions require sponsor approval and documentation per device accountability SOPs [1–3].

Step-by-step deployment SOP (checklist)

- Pre-deployment verification

- Confirm valid informed consent and, for remote sessions, identity via BankID or approved eID (record method) [1–3,9].
- Reconfirm eligibility, clinical stability, and absence of ATS/ERS-listed spirometry contraindications; on-site vitals (BP, HR, RR, SpO2) within site norms; rescue reliever available [4–6].
- Verify environment: seated position available, adequate lighting for video artifacts, privacy, and infection-control readiness (single-use mouthpieces available; cleaning per IFU) [4].
- App/device readiness: AsthmaTuner version >5.4.13.5; investigational module enabled; spirometer paired and recognized; battery/charge adequate; successful test upload to server; role-based access active; audit trail confirmed [1–3,7–9].

- Participant positioning and interface

- Seat participant upright with feet supported; head/neck neutral; shoulders relaxed [4].
- Apply nose clip if indicated to prevent nasal leak; ensure correct mouthpiece size; instruct tight lip seal without tongue obstruction; Airflow Trainer positioned as per IFU without contacting mouth/skin [4].

- DPI/MDI procedure alignment (training sequence)

- DPI training: exhale to functional residual capacity away from device; seal; forceful/deep inhalation; breath-hold per device guidance; exhale slowly; avoid exhaling into device [5,6].
- MDI training: prime/shake per device; exhale; begin slow/deep inhalation with synchronized actuation; continue to full inspiration; breath-hold; use spacer per clinical routine if applicable [5,6].

- Artifact capture and spirometry

- Capture standardized inhalation technique artifact(s) per Adjudication Manual: video framing and audio clarity as applicable, and/or inspiratory flow-curve; confirm local adequacy before submission [1,4–6].

- Perform spirometry per ATS/ERS 2019 standards, minimizing repeats to those needed for acceptability and repeatability; seated when indicated; stop on safety triggers [4].

- Real-time quality and safety checks

- Monitor in-app quality indicators and flow/volume curves for artifacts (cough, early termination, leak); allow rest between maneuvers; abort immediately for presyncope, chest pain, severe dyspnea/wheeze, or investigator concern; manage per site emergency protocol and document [1,4].

- Data submission

- Verify successful, encrypted upload of artifacts and spirometry tracings; record timestamps, device serials, and app build; ensure central systems received files; maintain blinding of adjudicators [1–3,7–9].

- Session close-out

- Review symptoms; repeat vitals if symptomatic; provide post-session instructions; schedule next contact within protocol window [1,4–6].

Criteria to confirm appropriate “placement” and function

- App/module activation: Investigational inhalation module enabled for the correct participant account; version/build recorded; feature flag active [7,8].
- Device pairing and telemetry: Spirometer paired with stable connection; successful test transmission; server acknowledgement; no pairing errors during session [7–9].
- Interface/position:

- Adequate mouthpiece seal (no visible leaks, no cheek puffing); nose clip used if indicated; neutral head/neck alignment; Airflow Trainer oriented per IFU (non-contact) [4].

- Signal and quality targets:

- Inhalation artifact adequacy confirmed locally (lighting/framing; audible instructions followed; flow-curve free of major artifact) with central adequacy submission; spirometry meets ATS/ERS acceptability and repeatability where required [1,4].

- Output verification:

- In-app display of key inspiratory metrics (e.g., PIF, time to PIF, inspiratory time) present and plausible for patient profile; no conflicting/unsafe prompts; uploads verified in audit logs [4,7,8].

Actions for malposition or suboptimal deployment

- Indicators of malposition/suboptimal setup

- Persistent leaks, nasal breathing, poor lip seal; repeated unacceptable efforts (cough, early termination); absent/erratic flow signals; pairing/telemetry failures; implausible PIF/time-to-PIF metrics; video inadequacy (framing/lighting) [4,7,8].

- Corrective actions (apply sequentially; stop earlier if safety concern)

- Re-instruct and reposition: reinforce DPI/MDI steps; adjust nose clip; replace mouthpiece; confirm neutral head/neck; ensure Airflow Trainer correctly oriented off the face [4–6].

- Technical remediation: re-seat/re-pair spirometer; reboot device; confirm app version/feature flag; perform calibration/verification per IFU; try alternate USB/Bluetooth channel if applicable [7,8].

- Replace components: use a new mouthpiece; swap spirometer if hardware fault suspected; document serials and reason [1–3].

- Reschedule: if quality remains inadequate or participant becomes fatigued/symptomatic, defer within allowed window; record as device deficiency if technical cause; consider on-site conversion if prior attempt was remote [1,4,9].

- Escalation and reporting

- Any persistent malfunction impacting safety/data integrity: pause participant use; notify PI and sponsor helpdesk; log device deficiency and, if criteria met, report per ISO 14155/MDR safety reporting timelines [1–3].

Standards for closure and hemostasis

- Closure: Not applicable to non-invasive software-guided training. At session end:

- Remove and discard single-use mouthpiece; sanitize non-contact equipment per IFU/site policy; secure spirometer and Airflow Trainer for next participant [4].

- Reassess symptoms; provide rest as needed; no hemostasis required.
- Confirm that no invasive procedures or sedation occurred; document disposition and next steps [1,4].

Radiation exposure tracking

- No fluoroscopy, radiography, or ionizing imaging is used. For each session, document “No ionizing radiation used—N/A” in the procedure note; radiation dose logs are not required for this protocol [1,4].

Post-procedure documentation and accountability

- Required documentation (source and eCRF; contemporaneous, ALCOA-compliant)

- Session metadata: site, participant ID, date/time, on-site/remote mode, staff/roles; consent version and identity verification method (remote) [1–3,9].
- Clinical status: stability screen, vitals (on-site), symptoms pre/post, safety events and management [1,4].
- Device/app: AsthmaTuner version/build; investigational module enabled; spirometer model/serial; calibration/verification logs; pairing status; test and final upload confirmations; audit trail IDs [1–3,7,8].
- Procedural outputs: inhalation artifact adequacy (local) and submission timestamps; spirometry acceptability/repeatability, local QC grade, and central submission timestamps [4].
- Deviations and deficiencies: reasons for any missed/late/partial assessments; device deficiencies with descriptions and actions; UADE/SAE reports if applicable [1–3].
- Education/engagement: duration/content of standardized education; app training provided; participant comprehension/competency check; instructions given for home use [5,6,8].
- Device accountability: shipment/handover receipts; current custody; return plan if applicable; status of Airflow Trainer and spirometer [1–3].

- Remote-specific records

- eID verification captured; environmental suitability confirmed; troubleshooting steps taken; courier tracking (if devices shipped); confirmation of secure, encrypted data transfer and receipt [1–3,9].

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6.3 Post-Procedure Assessments (Inpatient)

Scope and applicability

This section defines standardized inpatient post-procedure assessments following on-site respiratory maneuvers (spirometry and standardized inhalation technique artifact capture) and any app-based training using the investigational inhalation app-module embedded in AsthmaTuner (version later than 5.4.13.5). Although no invasive procedures are performed, short, protocolized observation is required to detect and manage infrequent but recognized maneuver-related symptoms (e.g., cough, transient dyspnea, bronchospasm, dizziness/syncope) per ATS/ERS standards and good clinical practice [1–6].

Level and duration of monitoring

- Default level of care: ambulatory observation in a monitored clinic area; continuous ECG telemetry is not required.
- Minimum observation:

- Asymptomatic post-session: observe ≥15 minutes.
- If bronchodilator administered, symptoms occurred, or abnormal vitals were noted: observe 30–60 minutes, or longer per investigator judgment until resolution to baseline [4–6].

- Continuous pulse oximetry: not routinely required; use during observation if moderate symptoms or desaturation are suspected [4].
- Telemetry/ECG: obtain only if cardiac symptoms (palpitations, chest pain, syncope) or arrhythmia are suspected [4].

Vital signs and focused assessments

- Required measurements:

- Pre-session (recorded per Pre-Procedure section) and immediate post-session: BP, HR, RR, SpO2 (room air or prescribed oxygen), targeted symptom check [4].
- Reassessments:
  - Asymptomatic: symptom check at 15 minutes; additional vitals not required unless clinically indicated.
  - Symptomatic or treated with bronchodilator: repeat vitals and SpO2 at 15 and 30 minutes, and at discharge if extended observation is required [4–6].

- Orthostatic assessment: if presyncope/syncope reported, assess seated and standing vitals when safe [4].

Standardized post-procedure orders (inpatient/clinic)

- Activity

- Seated rest for 15 minutes minimum; longer if symptomatic.
- Assist with ambulation on discharge if dizziness occurred.

- Respiratory care

- Keep prescribed short-acting bronchodilator available at bedside/clinic.
- Administer short-acting bronchodilator for wheeze/bronchospasm per local practice; document agent/dose/time and clinical response [4–6].
- Provide fluids as tolerated for cough/throat irritation.

- Monitoring

- Vital signs per schedule above; add continuous SpO2 if moderate symptoms.
- ECG only if chest pain, palpitations, or syncope occur [4].

- Medications

- No protocol-mandated premedication or analgesia. Administer symptomatic therapy per investigator judgment; avoid sedatives.

- Infection control and device handling

- Discard single-use mouthpieces; clean non-contact equipment per IFU and site SOPs [4].

- Data and device verification

- Confirm successful encrypted upload of spirometry tracings and inhalation artifacts; verify app build (version >5.4.13.5), spirometer pairing, and absence of critical error messages [1,7,8].

- Log and escalate any device deficiency per ISO 14155/MDR and site SOPs [1,3].

Complications screening checklist (complete before discharge)

- Symptoms/signs

- Dyspnea, wheeze, chest tightness, persistent cough, hemoptysis.

- Dizziness, presyncope/syncope, headache, nausea.

- Chest pain or palpitations.

- New focal musculoskeletal chest/abdominal pain suggestive of strain.

- Objective checks

- SpO2 within acceptable limits and not clinically depressed from baseline [thresholds TBC].

- HR and BP within site norms and stable from baseline [thresholds TBC].

- Normal appearance, able to speak full sentences, ambulates safely.

- Device/app safety and function

- App functioning as intended; correct participant account; investigational module active; no conflicting or unsafe prompts observed [1,7,8].

- Spirometer paired; test and final data transmissions acknowledged by server; audit trail present [1,7].

- Any crashes, misclassifications, or usability concerns documented as device deficiencies and reported if safety-relevant [1,3,8].

Laboratory and imaging requirements

- Routine laboratory testing: not required post-procedure; order only if clinically indicated (e.g., suspected infection, metabolic cause of syncope) [1,4].

- Imaging:

- None routine. Obtain chest radiograph only if clinically suspicious for pneumothorax or other acute pathology (rare with spirometry) [4].

- ECG only if cardiac symptoms or arrhythmias suspected [4].

- Timing windows for clinically indicated tests:

- Perform during observation or within the same day if escalation is not immediately required; urgent testing per institutional emergency protocols takes precedence over research activities [1–4].

Criteria to assess device function prior to discharge

- App/module criteria

- AsthmaTuner version later than 5.4.13.5; investigational inhalation module enabled for the correct study account; no unresolved critical error notifications [1,7,8].

- In-app display of inspiratory metrics (e.g., PIF, time to PIF, inspiratory time) present and plausible for the participant profile [4].

- Hardware/telemetry criteria

- CE-marked spirometer recognized and paired; signal quality acceptable during session; at least one successful encrypted upload confirmed; server receipt timestamps recorded; audit logs accessible [1,7].

- Artifact/spirometry adequacy

- Inhalation artifact(s) judged locally adequate per Adjudication Manual; spirometry performed to ATS/ERS acceptability/repeatability standards where required by visit schedule [4].

- Deficiency and safety status

- No unresolved device deficiency with potential impact on participant safety or primary endpoint quality; if unresolved, document mitigation (e.g., device replacement, pause in home use) and provide

clear participant instructions; notify sponsor per safety reporting requirements [1,3].

Discharge criteria

- Clinical stability

- Symptom resolution or return to acceptable baseline; no ongoing moderate/severe dyspnea or wheeze after rest and/or bronchodilator.
- No chest pain, presyncope/syncope, or concerning neurologic symptoms.
- Vitals stable and within site-defined discharge thresholds: SpO2 ≥[TBC]% on baseline oxygen status; HR and BP within acceptable ranges; afebrile if infection suspected [4].

- Functional readiness

- Tolerates ambulation without symptom worsening; able to perform activities of daily living at pre-visit level.

- Safety and follow-up

- Participant understands stop rules and when to seek urgent care; rescue inhaler readily available.
- Next contact scheduled within protocol window; AE/SAE/device deficiency documentation completed as applicable; data submissions verified [1–3].
- If any criterion is not met, extend observation, convert to urgent clinical evaluation, or arrange hospital admission per institutional standards.

Escalation and emergency criteria

- Immediate escalation to urgent/emergency care and PI-led review:

- SpO2 persistently below site-defined threshold or clinically significant decline from baseline despite rest/bronchodilator [thresholds TBC].
- Persistent bronchospasm not resolving within 15–30 minutes after bronchodilator or associated with increasing work of breathing.
- Syncope, sustained arrhythmia, ongoing chest pain suggestive of acute coronary syndrome, focal neurologic deficit, or suspected pneumothorax [4–6].
- Any unanticipated serious adverse device effect (USADE/UADE) or device malfunction with potential to cause harm; initiate safety reporting per ISO 14155/MDR and MDCG 2020-10 timelines [1,3,9].

Documentation and reporting

- Record all post-procedure observations, vitals, interventions, and disposition in ALCOA-compliant source and eCRF; include app build/version, device serials, upload confirmation, and any device deficiencies [1–3,7,8].
- Classify and report AEs/SAEs/UADEs per protocol and regulatory guidance; retain devices/logs for analysis when safe and feasible [1,3,9].

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6.4 Discharge Procedures

Discharge readiness checklist (to be completed before the participant leaves the clinic or ends a supervised remote session)

Domain	Required item	Pass criteria	Action if not met
Clinical stability	Symptoms resolved or at acceptable baseline after rest ± bronchodilator	No moderate/severe dyspnea/wheeze, no chest pain, no presyncope/syncope; ambulates safely	Extend observation; provide treatment; escalate to urgent care if concerning signs persist [4–6]
Vitals (on-site)	HR, BP, RR, SpO2 stable from pre-session	Within site discharge thresholds; SpO2 ≥[TBC]% on baseline O2 status	Continue observation; clinician review; escalate if unstable [4]
Adverse events	AE/SAE assessment completed	All events documented and addressed; safety reporting initiated if criteria met	Initiate AE/SAE/UADE workflow per ISO 14155/MDR [1,3,9]
Device/app status	App build verified; module enabled; spirometer paired; uploads confirmed	AsthmaTuner >5.4.13.5; correct account; ≥1 successful encrypted upload; no unresolved critical errors	Troubleshoot/replace; defer home use if unresolved; document device deficiency and notify sponsor [1,7–9]
Data integrity	Central receipt of artifacts/spirometry verified	Server acknowledgement recorded; audit trail present	Re-upload; contact helpdesk; document and resubmit ASAP [1]
Education provided	Standardized inhaler steps reinforced; stop rules explained	Participant verbalizes understanding and demonstrates critical steps	Re-educate; provide written instructions; reassess comprehension [5,6]
Medications and rescue plan	Maintenance therapy unchanged; rescue inhaler available	Participant confirms access to reliever; understands when/how to use	Provide or arrange reliever; review action plan per guidelines [5,6]
Anticoagulation/antiplatelets	Plan reviewed (no routine changes)	No contraindications identified; placeholders updated if individualized changes are required	Defer only if separate clinical issue exists; document individualized plan [4]
Follow-up scheduled	Next visit within protocol window	Appointment(s) booked; reminders set; contact details confirmed	Schedule before discharge; document participant preference for mode [1,2]

Consent/privacy	Ongoing consent and contact preferences reaffirmed	Documented in source and eCRF	Reconfirm and document per ICH-GCP [1,2]

Mandatory checks prior to discharge

- Complete a targeted symptom review and confirm return to baseline tolerance for activity; verify that any bronchodilator administered achieved expected relief [4–6].
- Confirm stable vital signs (on-site) or symptom stability (remote) and absence of red flags requiring escalation [4–6].
- Verify successful, encrypted upload and central receipt of all required spirometry tracings and inhalation technique artifacts; confirm app version later than 5.4.13.5, correct account, investigational module enabled, and no unresolved critical errors; log any device deficiency and mitigation [1,3,7–9].
- Reiterate standardized inhaler technique steps tailored to DPI and/or MDI, including breath preparation, inhalation profile, actuation timing, and breath-hold, consistent with GINA/GOLD guidance; document competency check [5,6].
- Ensure participant has immediate access to a short-acting reliever inhaler and understands their individualized symptom response plan aligned with standard care [5,6].
- Schedule the next contact within the allowed protocol window and provide written/phone/electronic reminders; confirm preferred mode (on-site vs remote) and identity verification method for remote sessions [1,2].
- Reaffirm ongoing consent and privacy preferences; update contact information; provide 24/7 emergency instructions and site contact details [1,2].

Anticoagulation and antiplatelet management

- General rule: No protocol-mandated changes to anticoagulant or antiplatelet therapy are required for these non-invasive respiratory maneuvers; continue standard-of-care regimens [4].
- If a separate clinical condition poses concern (e.g., recent surgery with bleeding risk), defer strenuous forced maneuvers per ATS/ERS relative/absolute contraindications and arrange appropriate clinical follow-up; document rationale and SEC/PI review [4].
- Site-facing template for individualized plans (complete if applicable):

- Current agent(s)/dose: [TBC]
- Indication/INR or anti-Xa target (if applicable): [TBC]
- Temporary modification required for future visits? [Yes/No]; If Yes, specify: [TBC]
- Responsible clinician to manage changes: [Name/Contact]
- Participant counseling completed and written instructions provided: [Yes/No]

Supportive therapy and post-session care orders

- Rest and hydration; lozenges or warm fluids for throat irritation as needed.
- Short-acting bronchodilator for bronchospasm per local practice; document agent, dose, time, and response [4–6].
- Continue all prescribed maintenance respiratory therapies without change unless clinically indicated by the treating clinician [5,6].
- Spacer use for MDI if part of standard care; reinforce cleaning and replacement schedules per IFU [5,6].
- No sedatives or new medications are protocol-mandated; administer only per clinical judgment and document accordingly [1,2].

Patient instructions at discharge (plain language)

- What you may feel

- Mild cough, throat irritation, or brief lightheadedness can occur after breathing tests. These usually go away with rest and sips of water.

- What to do at home

- Rest if you feel tired. Drink water. Use your quick-relief inhaler if you wheeze or feel tight in your chest as your care plan describes.
- Keep using your regular (maintenance) inhalers exactly as prescribed.
- If you are in the app-training group, use the AsthmaTuner inhalation training module as shown. If the app or spirometer does not work or gives instructions that seem wrong, stop using it and call the study team.

- When to get help now (call emergency services)

- Severe shortness of breath, trouble speaking, blue lips or fingertips, chest pain, fainting, coughing up blood, or symptoms that get worse despite your quick-relief inhaler.

- When to call the study team or your clinic

- Ongoing wheeze or breathlessness after using your quick-relief inhaler, fever with cough, dizziness that does not improve, or any device/app problem.

- Keep handy

- Your quick-relief inhaler, this instruction sheet, and the study contact numbers.

These instructions align with standard asthma/COPD action plan principles and good clinical practice for post-test counseling [1,2,5,6].

Warning signs and escalation pathway

- Immediate escalation to urgent/emergency care:

- Persistent or worsening bronchospasm not responding to short-acting bronchodilator within 15–30 minutes; SpO2 decline below site-defined threshold or marked drop from baseline; chest pain, syncope, new focal neurologic deficit; suspected pneumothorax; hemoptysis [4–6].
- Any unanticipated serious adverse device effect (UADE) or malfunction creating an unsafe condition; stop device use, initiate safety reporting, and secure device/logs if feasible [1,3,9].

- PI review and same-day clinical evaluation:

- Moderate symptoms requiring repeated bronchodilator dosing, new arrhythmia/palpitations, or persistent dizziness without syncope [4–6].

Follow-up scheduling and discharge logistics

- Schedule the next protocol contact before discharge:

- Week 2 and Week 4 interim checks (remote or on-site per participant preference and site SOPs); Week 6–12 primary endpoint visit (on-site preferred). Book Month 6 and Month 12 contacts when feasible [1,2].

- Provide appointment confirmations and instructions for identity verification for any remote sessions (e.g., BankID/eID), along with secure data transfer guidance and helpdesk contacts [1,2].
- For intervention-arm participants:

- Confirm app version later than 5.4.13.5, feature flag enabled, and successful test upload at discharge; provide a quick-start card for home troubleshooting; document device custody and return plan if applicable [1,7,8].

- Ensure participant has study and emergency contact numbers, understands data privacy practices, and knows how to report AEs and device issues between visits. Reinforce that reporting safety concerns will not affect their clinical care or study participation rights [1–3].

Documentation and reporting at discharge

- Complete ALCOA-compliant source and eCRF entries for:

- Post-session vitals/symptoms, interventions, disposition, discharge readiness checklist, education provided, and next appointments [1,2].
- App build/version, device serials, upload confirmations, and any device deficiencies with remediation steps; initiate MDR/MDCG-compliant reporting for reportable events and notify the sponsor within required timelines [1,3,9].
- Participant reaffirmation of consent and contact preferences, including preferred mode for upcoming visits and identity verification method for remote sessions [1,2].

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6.5 Follow-Up Procedures

Overview and visit schedule

Follow-up is designed to capture the primary endpoint at 6–12 weeks and to monitor safety, usability, and feasibility, using a combination of on-site and telehealth contacts consistent with ISO 14155/ICH-GCP, ATS/ERS standards for respiratory maneuvers, decentralized-trial guidance, and disease-management guidelines [1–6]. The adjudication of inhalation technique remains blinded to allocation. Remote procedures are permitted when prespecified safeguards are met [1–3].

Visit ID	Nominal timing from randomization	Allowable window	Mode	Key purpose
V2	Week 2	±7 days	Telehealth preferred; on-site permissible	Early safety/usability check; reinforce technique; capture ePROs; app verification (intervention) [1–3]
V3	Week 4	±10 days	Telehealth or on-site	Interim assessment of technique and adherence; AE/SAE/device deficiency review; ePROs [1–3]
V4 (Primary endpoint)	Week 6–12	Entire window acceptable	On-site preferred; remote permitted if all quality/safety criteria met	Primary endpoint: successful inhalation technique rate; spirometry per ATS/ERS; central submissions; ePROs; safety [1,3,4]

V5 (optional)	Month 6	±4 weeks	Telehealth or on-site	Durability/exploratory outcomes: technique artifact(s), ePROs, safety [1–3]
V6 (optional)	Month 12	±6 weeks	Telehealth or on-site	Long-term exploratory outcomes: technique artifact(s), ePROs, safety [1–3]

Participants who discontinue the investigational app-module should continue scheduled follow-up and endpoint assessments whenever feasible, in line with intention-to-treat principles and SPIRIT recommendations for minimizing missing data [1,2,6].

Required assessments by visit and arm

- Universal assessments (all arms, all visits unless specified):

- Eligibility change screen; interim medical history since last contact; AE/SAE and UADE/device-deficiency review; concomitant medications; healthcare utilization (urgent care/ER/hospitalization) [1–3].
- Disease control/impact ePRO: ACT or ACQ-5 for asthma; CAT for COPD (instrument versions prespecified) [4–6].
- Usability/feasibility ePRO: SUS and study-specific acceptability items (intervention arm prioritized; control arm collects feasibility of standard education) [1,2].
- Identity verification for remote visits (eID/BankID) and audit-trailed data capture [2,3].

- Intervention arm (AsthmaTuner inhalation app-module) additional assessments:

- App/device verification: app version later than 5.4.13.5; feature flag enabled; spirometer pairing and telemetry check; successful test upload [1,7,8].
- Inhalation technique artifact(s): device-specific standardized capture for each prescribed DPI and/or MDI; submit to central adjudication [1,4–6].
- On-site visits: vitals pre-session (BP, HR, RR, SpO2), post-session symptom check; spirometry at V4 primary endpoint per ATS/ERS [1,4].

- Control arm (standard education only) additional assessments:

- Structured technique assessment using the site's standardized checklist aligned with guideline-based steps (DPI/MDI); local pass/fail per step; no app use or telemetry [4–6].
- On-site visits: same vitals/safety procedures when spirometry or coached maneuvers are performed per protocol [1,4].

Visit-specific procedures and quality controls

- V2 (Week 2; telehealth preferred):

- Confirm ongoing consent and contact preferences; identity verification (remote) [1–3].
- AE/SAE/UADE screen; medication and exacerbation review [1–3].
- ePROs (ACT/ACQ-5 or CAT; SUS for intervention arm) [4–6].
- Intervention arm: app version/build check; feature flag; brief guided technique practice with artifact capture if feasible remotely; confirm at least one successful encrypted upload [1–3,7,8].
- Control arm: checklist-based technique review/reinforcement; no artifact submission.

- V3 (Week 4):

- Repeat V2 assessments; reinforce device-specific steps (DPI/MDI) per guidelines [4–6].
- Consider remote artifact capture (intervention) to track progress; troubleshoot any device issues; log device deficiencies per MDR/ISO 14155 [1,3].

- V4 (Week 6–12; primary endpoint):

- On-site preferred to ensure ATS/ERS-grade quality; remote allowed only if decentralized safeguards and central submission quality are met [1–4].
- Pre-maneuver safety checks and vitals (on-site) per established readiness criteria; defer if contraindicated by ATS/ERS standards [4].
- Primary endpoint collection: standardized inhalation technique artifact(s) for each relevant inhaler; blinded central adjudication submission [1,4–6].
- Spirometry per ATS/ERS with central QC; seated testing preferred; apply acceptability/repeatability criteria; stop on safety triggers [1,4].

- ePROs (ACT/ACQ-5 or CAT; SUS and acceptability); AE/SAE/UADE review; device deficiency capture and escalation if applicable [1–3,7,8].

- V5 and V6 (Months 6 and 12; optional, exploratory):

- ePROs, safety review, and technique artifact(s) if feasible; spirometry not required by protocol for exploratory contacts [1–6].

Windows, rescheduling, and handling missed/partial assessments

- Visits should occur within the allowable windows in the schedule table. If a visit is missed:

- Attempt to complete within a 14-day grace period for V2/V3 and within the 6–12-week window for V4; document reason and mitigation [1,2].

- If primary endpoint artifacts cannot be collected within the V4 window due to illness/technical failure, classify per SAP, document corrective actions, and, if safe, collect as soon as possible for sensitivity analyses [1,2,4].

- Partial completes are allowed; record which assessments were obtained and reasons for omissions. Prioritize safety and the primary endpoint at V4 [1–4].

Telehealth conduct standards

- Remote visits require:

- Identity verification (eID/BankID), secure video platform, role-based access, and audit trails; contemporaneous source notes in compliant eCRFs [1–3].

- For remote artifact capture: confirm app version later than 5.4.13.5, pairing, and successful encrypted upload; provide real-time coaching as feasible; if quality is inadequate, schedule an on-site reassessment within window [1–3,7,8].

- Remote vitals are not mandated; instruct participants to stop if symptomatic and contact the study team or urgent care per stop rules [1,4].

Triggers for unscheduled visits and additional testing

- Initiate an unscheduled contact (telehealth or on-site) for any of the following:

- Suspected or confirmed exacerbation, ER visit, or hospitalization for respiratory symptoms [5,6].

- Safety signals during or after maneuvers (e.g., presyncope, severe dyspnea/wheeze, chest pain) [4].

- Device-related concern: app crash with unsafe prompt, telemetry failure preventing data capture, or suspected UADE; pause home use if safety-relevant and escalate per MDR/ISO 14155 [1,3,7,8].

- Central adjudication or core-lab feedback indicating inadequate or implausible artifacts requiring repeat within window [1,4].

- Additional testing:

- Repeat artifact capture if initial submission is inadequate and within window; minimize repeats to avoid fatigue per ATS/ERS [4].

- Spirometry is repeated only when required by protocol or if central QC indicates a quality failure and the participant is clinically stable [4].

- Any clinically indicated tests (e.g., ECG) per investigator judgment; safety takes precedence over research procedures [1,4].

Retention, reminders, and contact cadence

- Provide multimodal reminders (SMS/email/phone) 3–7 days before each visit and on the day of contact; confirm mode (on-site vs remote) and identity verification method for remote sessions [1–3].
- If unreachable, attempt a minimum of three contact attempts on different days/times; send a certified letter or secure message if permitted; document all attempts [1,2].

- Participants who stop using the investigational module remain in follow-up for outcomes and safety unless they withdraw consent; offer telehealth options to reduce burden [1–3].

Blinding safeguards during follow-up

- Central adjudicators of technique success remain blinded to allocation; submissions must omit allocation-identifying metadata and follow the Adjudication Manual [1–3].
- Site staff performing coaching should avoid disclosing allocation during source documentation and communications sent for central review [1,2].

Follow-up visit CRF templates

- V2 Week 2 Follow-Up CRF (telehealth preferred)
  - Contact metadata: date/time; mode; identity verification method/result; staff roles.
  - Interim events: exacerbations; ER/hospitalization; medication changes.
  - AE/SAE/UADE review: event description; onset/stop dates; severity; relatedness; actions; outcome.
  - Disease control ePRO: ACT/ACQ-5 (asthma) or CAT (COPD); completion timestamp.
  - Intervention arm only: app version/build; feature flag status; spirometer model/serial; pairing OK; test upload OK; artifact captured (Yes/No; inhaler type; local adequacy); submission timestamp; device deficiencies.
  - Control arm only: checklist-based technique review (per inhaler); step-level pass/fail; re-education provided (Yes/No).
  - Participant-reported usability: SUS (intervention); feasibility items (both arms as applicable).
  - Next steps: education reinforced; next visit scheduled; open issues.
  - Signatures: staff; investigator review.

- V3 Week 4 Follow-Up CRF
  - All V2 elements plus: repeat artifact capture status (intervention); cumulative device deficiency log; adherence to training (self-reported frequency).
  - If on-site: vitals (pre/post if maneuvers performed); safety notes.

- V4 Primary Endpoint CRF (Week 6–12; on-site preferred)
  - Pre-visit: consent status; eligibility changes; identity verification (if remote); visit window check.
  - Safety/vitals (on-site): BP, HR, RR, SpO2; ATS/ERS contraindication screen.
  - Primary endpoint artifacts: inhaler type(s); video/flow-curve capture; local adequacy; submission timestamps; blinding checks.
  - Spirometry: acceptability/repeatability; best values; local QC grade; central submission timestamp.
  - ePROs: ACT/ACQ-5 or CAT; SUS and acceptability items.
  - AE/SAE/UADE review; device deficiency reporting; concomitant medications.
  - Data integrity: encrypted upload confirmations; audit trail IDs.
  - Disposition: discharge criteria met; next contact plan.
  - Signatures: technologist/clinician; investigator.

- V5 Month 6 and V6 Month 12 Exploratory CRFs (optional)
  - Contact metadata; identity verification (remote).
  - Interim events and AE/SAE/UADE review.
  - ePROs: ACT/ACQ-5 or CAT; SUS/acceptability (intervention).
  - Technique artifact(s) capture status and submissions (if feasible).
  - Device deficiency log update (intervention).
  - Retention and future contact preference.
  - Signatures.

Data flow, documentation, and monitoring

- All follow-up data are captured in ALCOA-compliant source and eCRFs with audit trails; remote sessions require contemporaneous identity verification logs and secure data transfer confirmations [1–3].
- Encrypted submissions of artifacts and spirometry are verified locally with server acknowledgements; any failures prompt within-window reattempts or rescheduling and are logged as deviations or device deficiencies as applicable [1,3,7,8].
- The DSMB receives periodic aggregated, blinded safety summaries per the monitoring plan; reportable events are handled per MDR/ISO 14155 and sponsor SOPs [1,3].

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6.6 Annual Study Visit / Final / Premature Discontinuation / Unscheduled Visit

Purpose and scope

This section defines standardized procedures, minimum required datasets, optional assessments, and acceptable alternatives for the following visit types: Annual Study Visit (Month 12 exploratory), Final Study Visit (end-of-treatment within 6–12 weeks), Premature Discontinuation/Early Termination Visit (performed as soon as feasible after decision to discontinue), and Unscheduled Visit (safety, endpoint quality remediation, or device-related). Procedures apply to both on-site and decentralized (remote) conduct, with identity verification and audit trails for telehealth visits. Assessments align with ATS/ERS respiratory standards, ISO 14155/ICH-GCP, MDR safety reporting, and decentralized-trial guidance, and maintain blinding of central endpoint adjudication [1–6,9].

Definitions and timing windows

- Annual Study Visit (Month 12 exploratory):

- Nominal timing: 12 months post-randomization; allowable window: ±6 weeks.
- Purpose: durability/exploratory outcomes, safety, usability; no protocol-mandated spirometry.

- Final Study Visit (end-of-treatment):

- Timing: within the 6–12 week primary endpoint window. For participants completing per protocol, this coincides with the primary endpoint visit; for those completing outside the window, perform as soon as feasible and classify per SAP [1–4].

- Purpose: capture primary endpoint (successful inhalation technique rate), safety, usability, device accountability.

- Premature Discontinuation/Early Termination Visit:

- Timing: within 14 days of decision to discontinue device use or study participation, and before permanent withdrawal when feasible [1,2].
- Purpose: collect as much of the Final Visit dataset as is safely possible; document reasons for discontinuation; address safety and device return.

- Unscheduled Visit:

- Timing: initiated any time based on prespecified triggers (safety concerns, endpoint quality remediation, device issues, or clinical events).
- Purpose: targeted safety assessment, endpoint data remediation (e.g., repeat artifact capture), device troubleshooting/replacement, and AE/SAE/UADE handling per MDR/ISO 14155 [1,3,4,9].

Conduct standards and safeguards

- On-site visits: follow ATS/ERS maneuver safety, pre/post symptom checks, and vital sign collection when respiratory maneuvers are performed [4].
- Remote visits: verify identity (eID/BankID), use a secure telemedicine platform, ensure encrypted data transfers and audit trails; vitals not mandated unless clinically indicated; reinforce stop rules [2,3].
- Blinding: all inhalation technique artifacts are submitted for blinded central adjudication without allocation-identifying information [1–3].
- Safety oversight: AE/SAE/UADE and device deficiency management per ISO 14155 and MDR; reportability assessed against MDCG 2020-10 guidance [1,3,9].

Minimum required datasets and optional assessments by visit type

Visit type	Minimum required dataset (all arms unless specified)	Optional assessments	Acceptable alternatives if protocol tests cannot be performed
Final (6–12 weeks; end-of-treatment)	Identity verification (remote); confirmation of consent; visit window verification; interim medical history and exacerbations; AE/SAE/UADE review and device deficiency screen; concomitant meds; disease control ePRO (ACT/ACQ-5 for asthma; CAT for COPD); intervention arm: inhalation technique artifact(s) per prescribed DPI/MDI; control arm: standardized checklist technique assessment; spirometry per ATS/ERS with central QC (on-site preferred); app version/build and pairing check (intervention); encrypted upload confirmations; audit trail IDs; disposition and next contact	Usability/acceptability ePROs (e.g., SUS for intervention); healthcare utilization; optional video capture for control-arm checklist session (without app) if permitted by site SOPs	If spirometry contraindicated or unsuccessful: defer within window; if still not possible, document ATS/ERS contraindication and collect ePROs and technique assessments only [1,4]. If artifact capture not possible due to technical failure: perform checklist-based technique assessment and log device deficiency; reschedule artifact capture within window or classify per SAP [1,3,4].
Early Termination/Premature Discontinuation	Reason(s) for discontinuation; consent status and permission for continued	Usability/acceptability ePROs; healthcare	If participant declines further procedures: obtain minimal safety

	follow-up/data use; AE/SAE/UADE review; device deficiency and complaint check; disease control ePRO; intervention arm: attempt technique artifact(s) if safe; control arm: checklist technique assessment; device accountability (return/disable/replace); encrypted upload confirmations if any data captured; final contact and safety instructions	utilization; remote review of app logs (intervention)	dataset (reason for withdrawal; AEs; healthcare utilization; permission for future data linkage if applicable); document in source and eCRF per ICH-GCP [1,2].
Annual (Month 12 exploratory)	Identity verification (remote); interim medical history; AE/SAE/UADE review; concomitant meds; disease control ePRO (ACT/ACQ-5 or CAT); device deficiency review for participants who retained device access; disposition	Technique artifact(s) if feasible; usability ePROs (intervention); healthcare utilization	If remote connectivity unavailable: complete ePROs and safety review via telephone with identity confirmation per SOP; document mode and limitations; no spirometry required.
Unscheduled	Trigger documentation (safety, endpoint quality remediation, device malfunction, clinical event); focused history; AE/SAE/UADE review; device deficiency assessment; targeted coaching or remediation; disposition and follow-up plan	Repeat inhalation technique artifact(s); app version/build and pairing check; on-site vitals if maneuvers performed; spirometry only if clinically indicated or per SAP-directed remediation and participant is stable [4]	If artifact repeat is requested by central adjudication and cannot be obtained remotely with adequate quality, convert to on-site within window; if still unachievable, document reason and classify endpoint per SAP [1,4].

Modular CRF/source templates

- Final Visit CRF (end-of-treatment; on-site preferred)

- Visit metadata: date/time; on-site/remote; identity verification; window check; staff.
- Consent/retention: ongoing consent; permission for future contacts and data use.
- Clinical status: interim history; exacerbations; healthcare utilization; concomitant meds.
- Safety: AE/SAE/UADE review; device deficiency screen and actions taken; relatedness.
- Primary endpoint collection:
  - Intervention arm: inhaler type(s) and standardized artifact(s) captured (video and/or inspiratory flow-curve); local adequacy; submission timestamps; blinding check; encrypted upload confirmation.
  - Control arm: guideline-based checklist assessment per inhaler; step-level pass/fail; remediation.
- Spirometry (if indicated by protocol): acceptability/repeatability; best values; local QC; central submission timestamp [4].
- Usability/feasibility: SUS (intervention) and acceptability items.
- Data integrity: app version/build (>5.4.13.5), spirometer pairing; audit trail IDs; server receipt.
- Disposition: discharge readiness; next contact (Annual or safety follow-up); device accountability.
- Signatures: operator; investigator.

- Early Termination Visit CRF

- Trigger and rationale for discontinuation; consent status for continued data use/future contacts.
- Minimum safety dataset: AE/SAE/UADE, device deficiency, healthcare utilization.

- Endpoint salvage: attempt artifact capture (intervention) or checklist assessment (control) if safe and acceptable; document reasons if not performed.
- Device accountability: return logistics or remote deactivation; serials; status; deficiency/complaint forms if applicable.
- Participant communication: stop rules; when to seek care; contact details.
- Signatures and date.

- Annual (Month 12) Visit CRF

- Metadata and identity verification; interim history; AE/SAE/UADE; concomitant meds.
- ePROs: ACT/ACQ-5 or CAT; usability/acceptability (intervention).
- Optional technique artifact(s) if feasible; device deficiency log update.
- Disposition and retention planning.

- Unscheduled Visit Note

- Trigger description; immediate safety assessment; AE/SAE/UADE status; device deficiency triage.
- Targeted procedure: artifact repeat (if requested by adjudication), coaching, or device troubleshooting/replacement; app version/build and pairing.
- On-site vitals if maneuvers performed; stop criteria applied [4].
- Outcome and next steps; reporting initiated if applicable; signatures.

Operational rules and acceptable alternatives

- Safety-first rule: do not perform forced maneuvers in the presence of ATS/ERS-listed contraindications or if symptoms arise; reschedule within the window or collect alternative data as specified; document justification [4].
- Endpoint salvage hierarchy at Final/Early Termination:

- Primary: standardized artifact(s) with encrypted submission and audit trail.
- Alternative: guideline-based checklist technique assessment (no app) with detailed step-level scoring, if artifact capture is not feasible due to technical or access limitations.
- If neither is feasible: document reason; collect ePROs and safety dataset; classify endpoint per SAP [1–4].

- Remote data quality safeguards:

- Identity verification (eID/BankID), app version later than 5.4.13.5 with investigational module enabled, confirmed pairing and test upload prior to artifact capture; one reattempt permitted within window if initial quality inadequate; convert to on-site if unresolved [2,3,7,8].

- Device deficiency handling:

- Pause device use if safety-relevant; notify PI and sponsor; log deficiency; determine MDR reportability; preserve logs/serials; replace device if needed; document corrective actions [1,3,9].

Device accountability at Final/Early Termination/Annual

- Verify device/app status and custody:

- App build (>5.4.13.5) and feature flag active (intervention); spirometer model/serial; Airflow Trainer presence/condition.
- At Early Termination or study completion: arrange return via courier or in-clinic handover; confirm deactivation/lockout of investigational module; reconcile shipment and return logs; document any missing/damaged components [1–3,7,8].

Participant communication and retention

- Reconfirm consent and contact preferences; provide clear instructions regarding when to seek urgent care and how to report AEs or device issues; clarify that safety reporting does not affect clinical care or rights [1,2].
- For participants discontinuing the device but not research follow-up, offer remote Annual visit to minimize burden and reduce missing data; record preferences and update scheduling [1–3].

Data flow, documentation, and monitoring

- All visits require ALCOA-compliant source records and eCRFs with audit trails; remote visits require identity verification logs and encrypted upload confirmations where applicable [1–3].
- Blinded central adjudication receives artifacts stripped of allocation-identifying metadata; server acknowledgments are verified locally; any transmission failures prompt within-window reattempts or conversion to on-site [1–3].
- DSMB receives periodic, aggregated, blinded safety data per the monitoring plan; reportable events are processed per ISO 14155/MDR and MDCG 2020-10 [1,3,9].

Triggers for Unscheduled Visits

- Suspected device-related safety issue or unanticipated behavior (e.g., unsafe prompt, repeated crashes) [1,3,7,8].
- Adjudication/core-lab request for artifact repeat due to inadequate quality or implausible signal [4].
- Clinical events: exacerbation, ER visit, or hospitalization; significant symptoms during/after maneuvers (e.g., presyncope, severe dyspnea/wheeze, chest pain) [4–6].

Visit close-out and escalation criteria

- Discharge from on-site visits requires symptom stability, adherence to ATS/ERS stop rules, and completion of required uploads; remote visits require confirmation of data receipt when applicable [1,4].
- Immediate escalation is warranted for persistent bronchospasm, hypoxemia, syncope, chest pain, or suspected UADE; initiate MDR/ISO 14155-compliant reporting and clinical escalation per institutional standards [1,3–6,9].

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6.7 Patient Withdrawal

Definitions and principles

- Withdrawal refers to a participant's decision to stop some or all study activities at any time without penalty or loss of standard care, or the investigator's/sponsor's decision to discontinue participation for safety, non-compliance, or administrative reasons [1–3].
- Lost to follow-up (LTFU) is defined as the inability to complete required contacts or ascertain vital status after documented, reasonable contact attempts within prespecified windows [1,2].
- Participants who discontinue the investigational inhalation app-module should, whenever feasible, continue scheduled safety and outcome assessments, in line with intention-to-treat (ITT) principles and good clinical practice [1,2,4].

Standardized withdrawal workflow

- Trigger and timing

- Participant-initiated withdrawal of consent (immediate).
- Investigator- or sponsor-initiated discontinuation for safety, protocol ineligibility discovered post-randomization, or administrative reasons (as soon as decision is made) [1–3].

- Immediate actions (same day where feasible)

- Assess current safety status; manage and document any AE/SAE/UADE; apply reporting rules per MDR/ISO 14155/MDCG if applicable [1,3,5].
- Clarify scope of withdrawal: device use only, research procedures, future contacts, and/or data use. Reaffirm participant rights and options [1,2].
- Disable investigational module access and arrange device accountability (return/deactivation) if applicable; preserve device logs if safety-relevant [1,3].

- Early-discontinuation visit

- Schedule within 14 days to collect the minimum dataset and, if permitted, salvage endpoint data safely (on-site or remote with identity verification) [1,2].

- Documentation

- Complete the Early Discontinuation Form (see template) in source and eCRF; file contemporaneous notes with audit trails (ALCOA) [1,2].

Lost-to-follow-up (LTFU) procedures

- Pre-LTFU contact attempts (document all attempts)

- At least three contact attempts via different modes (phone/SMS/email/portal) on different days/times within the visit window; one attempt by certified mail or equivalent secure message where permitted; contact alternative person(s) only if previously consented [1,2].
- For remote-capable participants, offer a telehealth alternative within window; verify identity (eID/BankID) if contact is established [2].

- Escalation

- If unreachable, check allowed sources for vital status or hospitalization (e.g., medical records, national registries) per consent and local law; document outcomes and dates [1,2].

- LTFU designation

- If no contact or vital status confirmation after attempts above and grace period expiration, record as LTFU with last known contact date and data completeness; continue passive safety follow-up if permitted by consent [1,2].

Minimum data requirements at withdrawal or LTFU

- At the point of withdrawal or last contact, obtain at minimum:
  - Reason(s) for discontinuation (participant verbatim where possible) or LTFU status [1,2].
  - Consent status for continued follow-up and for use of previously collected data; permission for future data linkage if applicable [1,2].
  - Safety update: AEs/SAEs/UADEs since last visit, actions taken, outcomes; device deficiency/complaint screen [1,3,5].
  - Healthcare utilization since last contact (ER/hospitalization/exacerbations).
  - Disease control ePRO (ACT/ACQ-5 or CAT) if feasible.
  - Device accountability: app-module access status; spirometer and accessory return/deactivation; serials; preservation of logs if safety-relevant [1,3].
  - For the intervention arm, if safe and acceptable: one final standardized inhalation technique artifact capture; if not feasible, perform checklist-based technique assessment as an alternative per SAP [1].
  - Vital status (if allowable and feasible) [1,2].

Handling of consent scope at withdrawal

- Participant options must be respected and documented:
  - Stop all research procedures but allow use of data already collected.
  - Decline further contact but permit passive data linkage per consent/local law.
  - Withdraw all consent including use of previously collected data to the extent legally permissible; the sponsor may retain minimal data needed to meet regulatory and safety obligations [1–3].

ITT, analysis population, and missing data handling

- All randomized participants are included in the ITT analysis for the primary endpoint at 6–12 weeks, regardless of intervention adherence, to reduce bias and preserve randomization benefits [4].
- Participants who discontinue the investigational module remain in follow-up for endpoint and safety assessments whenever feasible; primary and secondary analyses will address missing data per the SAP using principled methods (e.g., multiple imputation and prespecified sensitivity analyses, including tipping-point analyses) consistent with regulatory guidance [4,6].
- Early discontinuation or LTFU will be flagged; endpoints obtained outside the nominal window will be handled per SAP rules and sensitivity analyses [4,6].

Participant replacement policy

- Replacement of randomized participants is not planned to maintain ITT integrity; recruitment may continue until the target sample size accounting for anticipated attrition is achieved per the SAP [4,6]. If a site-specific cap or recruitment stop is in place, any exception to allow replacement requires sponsor approval and documentation [1].
- Screen failures prior to randomization may be replaced per enrollment targets and site allocations.

Device accountability on withdrawal

- Intervention arm participants who withdraw should have:
  - Immediate deactivation/lockout of the investigational module; confirmation of app version/build and feature flag status at deactivation; documentation of device serials [1,3].
  - Return of spirometer and Airflow Trainer via courier or in-clinic handover; reconciliation against shipment logs; report and investigate any missing/damaged items as device deficiencies if applicable [1,3,5].
  - Preservation of device logs/data if a safety signal or complaint is involved, following chain-of-

custody procedures [1,3].

Safety reporting linkage

- If withdrawal is prompted by an AE/SAE or suspected UADE, complete expedited and periodic safety reporting per MDR/ISO 14155 and MDCG 2020-10 guidance; retain or quarantine implicated devices for analysis when safe and feasible [1,3,5].

Early Discontinuation Form (source/eCRF template)

Domain	Required element	Details to capture
Identification	Participant ID; site; date/time; staff	Mode (on-site/remote); identity verification method if remote [2]
Trigger and scope	Reason for discontinuation; scope of withdrawal	Participant verbatim; device-only vs full study; future contact permission; data use permission [1,2]
Safety	AE/SAE/UADE since last contact; actions/outcomes	Severity; relatedness to device/procedures; reporting status; hospitalization/ER visits [1,3,5]
Device deficiency/complaint	Presence/description; serials/logs preserved	Description; onset; recurrence; mitigation; MDR reportability; sponsor notification date [1,3,5]
Endpoint salvage	Technique artifact captured? If no, checklist assessment done?	Inhaler type(s); artifact adequacy; upload/audit IDs; or step-level checklist scores with rationale if artifact not feasible [1]
ePROs	ACT/ACQ-5 (asthma) or CAT (COPD); usability (intervention)	Instrument version; completion timestamps
Device accountability	App-module deactivated; device return/deactivation	App build; feature flag off; spirometer/Airflow Trainer return method; courier tracking; reconciliation [1,3]
Minimum dataset	Healthcare utilization; concomitant meds summary	Since last visit; changes relevant to safety
LTFU status	If applicable: attempts and outcomes	Dates/modes of attempts; alternative contacts; registry checks; vital status ascertainment [1,2]
Follow-up plan	Final instructions; emergency contacts; closure	Stop rules reiterated; who to contact; whether passive follow-up allowed
Signatures	Staff; PI review	Date/time; certification of completeness

Documentation standards

- Record all withdrawal/LTFU activities in ALCOA-compliant source and eCRFs with audit trails; maintain privacy and data security standards for all communications, including decentralized contacts [1–3].
- Any deviations from this workflow must be justified, documented, and reviewed by the PI and sponsor.

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7 ADMINISTRATIVE RESPONSIBILITIES

7.1 Institutional Review Board (IRB) Information

Overview and IRB/IEC governance

This Phase III, two-arm, parallel, single-blinded randomized clinical investigation of a Class II/III medical device software module (the investigational inhalation app-module embedded in AsthmaTuner >5.4.13.5; manufacturer: MediTuner AB; SRN: SE-MF-000028534) will be conducted only after Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form(s), recruitment materials, and any participant-facing documents. No participant will be screened or enrolled before receipt of a dated IRB/IEC approval letter for the site, and all approvals will be maintained current throughout the study in compliance with ISO 14155 and ICH-GCP [1,2]. Where applicable, national regulations governing human subject protections and medical device investigations (e.g., 21 CFR 50/56/812; 45 CFR 46; EU MDR) will be observed [3–6]. Oversight of minors (participants aged 16–17 where locally considered minors) will follow local law for assent and permission [2,4].

Type of IRB review and rationale

- Planned review type: Convened Full Board review.
- Rationale: The investigation prospectively evaluates an investigational device function (app-based inhalation training module available only within this trial) in patients with asthma and/or COPD, includes procedures that may exceed minimal risk for some individuals (e.g., coached inspiratory maneuvers; remote data capture), and may enroll participants aged 16–17 in some jurisdictions, warranting full-board risk assessment and continuing oversight per ICH-GCP, ISO 14155, and US/EU human subject protection frameworks [1–6]. If a site's IRB/IEC determines the research is minimal risk and eligible for expedited procedures, the IRB/IEC's determination will be documented in writing prior to initiation [4,5].

IRB initial submission checklist (site package)

Submit the following items for initial IRB/IEC review. Identify each document with protocol number, title, version, and date.

- Protocol: complete, version-controlled document with objectives, endpoints, eligibility, procedures, safety reporting, statistical plan, and data protection measures [1,2].
- Informed Consent Form(s) and, if applicable, Assent/Permission forms for minors; plain-language summaries; short-form consent if used; translated versions with certification where applicable [1,2,4].
- Recruitment and retention materials: advertisements, letters, scripts, emails, SMS templates, web content, social media posts, and any phone scripts; translations as needed [2].
- Privacy and confidentiality documentation:

- For US sites: HIPAA Authorization or waiver documentation; data flow diagrams; data security description [5].
- For EU/EEA and other jurisdictions: GDPR-compliant participant information, legal basis for processing, cross-border transfer mechanisms (if applicable), and data minimization/anonymization plans [6].

- Investigator's Brochure/Device Dossier or equivalent investigational plan for the inhalation app-module, including:

- Manufacturer details (MediTuner AB; SRN: SE-MF-000028534), device description, intended purpose, risk analysis, cybersecurity and software life-cycle overview (aligned to IEC 62304), usability/human-factors summary (aligned to IEC 62366-1), and instructions for use (IFU) [1,2,7,8].

- Regulatory determinations and letters (if applicable): device risk determination, IDE/competent authority notifications/waivers or MDR submissions, and any applicable local approvals [3].
- Data and Safety Monitoring Plan and DSMB Charter, including reporting pathways for AEs/SAEs/UADEs and stopping rules [1–3,9].
- Investigator qualifications: CVs, medical licenses, GCP training certificates, device/procedure training records; site facilities and equipment suitability [1,2].
- Study-specific training materials and manuals: site operations manual, adjudication manual, telehealth SOPs, identity verification processes, source/eCRF templates [1,2].
- Financial and conflict-of-interest disclosures; clinical trial insurance/indemnification statements consistent with local requirements [1,2].
- Recruitment site list, reliance arrangements (if any), and sIRB documentation for multi-site participation (see below) [4].

IRB continuing review calendar and reportable events template

IRB/IEC continuing review frequency will be as determined by the IRB/IEC, at intervals appropriate to the degree of risk and not less than annually where required under applicable regulations (FDA-regulated research and some local laws still require at least annual review) [1,4,5].

Element	Placeholder/Guidance
Approval period start date	[IRB Approval Date]
Approval period end/expiration date	[IRB Expiration Date]
Continuing review due date (internal)	[45–60 days prior to expiration]
Documents to submit	Current protocol and tracked-change version if amended; enrollment and withdrawal counts; AE/SAE/UADE summary; DSMB reports; deviation log; complaint/device deficiency summary; summary of new risk information/literature; updated consent/assent if needed; current recruitment materials
Reportable events (timelines)	Unanticipated problems/UADEs: prompt reporting per IRB policy and MDCG/FDA guidance; SAEs related/unexpected: expedited within IRB timelines; noncompliance/serious breach: report per local law and IRB policy [1,3,5,9]
Version control	Maintain version/date and IRB stamp on all active documents in the regulatory binder/eReg
Submission method	[IRB portal/email/mail per IRB SOP]
IRB acknowledgement/approval receipt	File dated approval letter and stamped documents; update site delegation/training as needed

Amendments, deviations, and urgent safety measures

- Substantial amendments:

- Definition: Any change that may affect participant safety, data integrity, scientific value, or ethical acceptability (e.g., eligibility, procedures, risk information, consent) [1,2].
- Process: Sponsor drafts and approves; PI reviews; submit tracked-change and clean versions to IRB/IEC (and competent authority if applicable) for approval before implementation, except when necessary to eliminate an immediate hazard [1–3].
- Responsibilities: Sponsor is responsible for global amendment control; PI is responsible for site submission and local implementation after approval; Regulatory Affairs maintains a master log [1,2].

- Non-substantial changes:

- Administrative or clarifying updates with no impact on risk/science may be filed with the IRB/IEC per local policy; maintain documentation and version control [1,2].

- Protocol deviations/violations:

- Definition and categorization per sponsor SOP and IRB/IEC policy. All deviations are documented; those impacting safety, rights, or data integrity are reported promptly to the IRB/IEC per policy [1,2,5].
- Root-cause analysis and corrective/preventive actions (CAPA) are documented; repeated or significant noncompliance is escalated to the sponsor and IRB/IEC [1,2].

- Urgent safety measures (USMs):

- If a change is required immediately to eliminate an apparent hazard to participants, the PI may implement without prior IRB/IEC approval; notify the IRB/IEC and sponsor as soon as possible, typically within 5 working days or per IRB policy, and submit a formal amendment if the change is permanent [1–3,9].

Multi-site IRB model and reliance

- Model: [To be confirmed] Single IRB (sIRB) for US federally funded multi-site research is required unless an exception is granted (45 CFR 46.114). For non-US or non-federally funded settings, either an sIRB/central IEC or local IRB/IEC oversight may be used per national law and sponsor strategy [4].
- Reliance agreements: If a sIRB/central IEC is used, execute reliance agreements specifying responsibilities for local context, ancillary reviews (radiation, pharmacy, privacy), reportable events, and continuing review. Maintain a reliance matrix and site-specific consent language addenda for local requirements [1,4].
- Local ancillary reviews: Regardless of sIRB use, sites must complete institutional ancillary reviews (e.g., data privacy officer/GDPR, IT security, telehealth platform approval) before activation [1,6].

Storage and access to IRB documents

- Regulatory binder/eReg system:

- Maintain an IRB/IEC section with current and superseded approvals, stamped consent forms, recruitment materials, investigator CVs/licenses, GCP training, safety reports, deviation logs, continuing review submissions/approvals, reliance agreements, and correspondence. Use ALCOA principles and audit trails for document control [1,2].
- Electronic systems must ensure role-based access, version control, and backups consistent with institutional policies and applicable privacy/security requirements [1,2,6].

- Site responsibilities:

- The PI or designee ensures only the current IRB-approved consent and recruitment materials are in use; staff are trained on the latest approved version before use; document training and delegation updates [1,2].

Roles and responsibilities

- Sponsor:

- Overall responsibility for scientific and ethical integrity, amendment control, DSMB oversight, and timely reporting of safety information to investigators, IRB/IECs, and competent authorities per ISO 14155/MDR/FDA requirements [1,3,9].

- Principal Investigator (PI):

- Submits initial and continuing review materials, amendments, and reportable events to the IRB/IEC; ensures informed consent is obtained using current IRB-approved documents; oversees protocol adherence and documentation; implements USMs when required and reports promptly [1,2].

- Study team:

- Maintains the site regulatory binder/eReg; tracks IRB approvals/expirations; logs and reports deviations; ensures only IRB-approved documents are used; coordinates version control and training [1,2].

Jurisdiction-specific privacy and consent considerations

- US sites: HIPAA Authorization or IRB waiver documentation will be submitted; data sharing plans and any transmission to external vendors will follow the HIPAA Privacy Rule and institutional policies [5].
- EU/EEA sites: GDPR-compliant participant information will describe purposes, legal basis for processing, data retention, data subject rights, and cross-border transfer safeguards; the IRB/IEC and, where required, the Data Protection Officer will review [6].
- All sites: Consent will align with ethical principles of the Declaration of Helsinki and ICH-GCP, emphasizing voluntariness, right to withdraw, and proportionality of risks and benefits [2,4].

Alignment with safety reporting

IRB/IEC reporting timelines and content for unanticipated problems, SAEs, UADEs, and device deficiencies will align with ISO 14155, IRB/IEC policies, and applicable regulatory guidance (e.g., MDR and MDCG 2020-10 for EU; FDA requirements for USA). The DSMB will receive periodic safety summaries and may recommend protocol modifications or pauses; IRB/IECs will be notified of DSMB recommendations that affect participant safety or consent content [1–3,9].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191–4. doi:10.1001/jama.2013.281053
5. US Department of Health and Human Services. 45 CFR 46 (Common Rule) and 45 CFR 164 (HIPAA Privacy Rule). 2018. https://www.ecfr.gov
6. European Union. Regulation (EU) 2016/679 (General Data Protection Regulation). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj
7. International Electrotechnical Commission. IEC 62304:2006/Amd1:2015 Medical device software—Software life cycle processes. Geneva: IEC; 2015. https://webstore.iec.ch/publication/22745
8. International Electrotechnical Commission. IEC 62366-1:2015/Amd1:2020 Medical devices—Part 1: Application of usability engineering to medical devices. Geneva: IEC; 2020. https://webstore.iec.ch/publication/26488
9. Medical Device Coordination Group (MDCG). MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations of Medical Devices. 2020. https://health.ec.europa.eu/publications/guidance-safety-reporting-clinical-investigations-medical-devices-mdcg-2020-10-1_en

7.1.1 Institutional Review Board Approval Letter

IRB approval confirmation requirements

No screening, consent, or study procedures may begin at a site until a dated IRB/IEC approval letter

covering the current protocol, informed consent/assent and HIPAA/GDPR materials (as applicable), recruitment/advertising content, and all participant-facing documents is on file. Ongoing conduct requires maintenance of current IRB/IEC approval throughout the study. These requirements are mandated by ISO 14155, ICH-GCP, and applicable human-subjects protection regulations (e.g., US 21 CFR 50/56/812, 45 CFR 46; EU MDR) [1–6].

IRB Approval Verification Form (one page)

Complete and file this form in the site regulatory binder/eReg before site activation and prior to each participant's enrollment.

Field	Entry
Protocol title and number	[Protocol title]; [Protocol No.]
Investigational device	Inhalation app-module embedded in AsthmaTuner (>5.4.13.5); Manufacturer: MediTuner AB; SRN: SE-MF-000028534
Site name and address	[Site legal name]; [Address]
IRB/IEC name	[IRB/IEC official name]
IRB/IEC FWA/registration ID (if applicable)	[ID]
IRB approval letter date	[YYYY-MM-DD]
IRB approval period (start → expiration)	[Start date] → [Expiration date]
Scope of approval checked	Protocol; ICF(s)/assent/permission; HIPAA/GDPR language (as applicable); recruitment/ads; participant materials; DSMB plan
Approved protocol version/date	Version: [vX.X]; Date: [YYYY-MM-DD]
Approved ICF version(s)/date(s) (all languages)	Main ICF: [vX.X; date]; Assent/permission (if applicable): [vX.X; date]; Translations: [list]
IRB-stamped consent(s) on file	Yes/No (attach copies)
Approved recruitment materials/version(s)	[List; version/date]; IRB stamps verified: Yes/No
Local privacy approvals (HIPAA/GDPR/DPO)	[Approved/Not applicable]; Date(s): [YYYY-MM-DD]
Ancillary reviews completed (IT security/telehealth/SOPs)	[List and dates]
Reliance/sIRB agreement executed (if used)	[Yes/No]; Agreement ID/date: [ ]
Investigator of record (PI)	Name; medical license active (Yes/No); GCP training valid through [date]
Delegation/training logs current	Yes/No
Device and app readiness verified	App build >5.4.13.5 with investigational module enabled; pairing test completed
Pre-enrollment IRB currency check completed by	Name, role, signature/date
Secondary verification (PI/designee)	Name, role, signature/date
Notes/conditions of approval to be met	[List any IRB conditions and their status]
Next continuing review due (internal reminder)	[YYYY-MM-DD] (45–60 days before expiration)

Process to verify IRB approval currency prior to each enrollment

- Pre-enrollment verification:

- The study coordinator confirms, on the calendar day of informed consent, that:
  - The IRB approval has not expired and the consent date falls within the approval period [1–3].
  - The protocol version in use matches the most recently IRB-approved version and any conditions of approval have been met [1,2].
  - The IRB-stamped consent/assent/permission forms (and HIPAA/GDPR language as applicable)

match the language, version, and date approved for the site [1–5].
- Any recruitment material used to reach this participant is an IRB-approved version bearing the correct stamp/date [1,2].
- The coordinator completes and signs the IRB Approval Verification Form; a second verifier (PI or designee) co-signs prior to presenting consent.

- Documentation:

- File the signed form in the eReg/binder; record the IRB approval and consent version/date in the screening/enrollment log and the consent source note; retain copies of the IRB approval letter and all stamped documents used that day [1,2].
- If decentralized consent is used, maintain electronic audit trails confirming the IRB-approved version presented and the timestamp within the active approval period [1,2].

- Ongoing oversight:

- The site maintains an electronic tracker with automated reminders 60 and 30 days before IRB expiration; the PI/designee submits continuing review materials per IRB policy to avoid lapses [1–3,5].

Procedures to halt enrollment if IRB approval lapses

- Immediate actions upon lapse detection:

- Suspend all screening, recruitment, new consent, and enrollment activities immediately; notify the PI and sponsor the same day; quarantine all recruitment materials and remove public postings [1,2].
- Assess whether any participants were consented on or after the lapse date; if yes, notify the IRB/IEC and sponsor and follow IRB guidance on remedial actions [1–3].

- Ongoing participant management:

- Continue only those clinical activities necessary for participant safety and welfare; do not perform protocol-specific research procedures until IRB approval is reinstated, unless required to eliminate immediate hazards and permitted by IRB policy [1–3].

- Reporting and remediation:

- Report the lapse and any associated noncompliance to the IRB/IEC per their timelines; submit continuing review/renewal materials promptly [1–3,5].
- Document the lapse, notifications, and corrective/preventive actions (CAPA) in the deviation log; the site may resume screening and enrollment only after receipt and verification of the renewed IRB approval letter and updated stamped documents, and completion of a fresh IRB Approval Verification Form [1,2].

Records and audit readiness

All IRB correspondence (initial approval, amendments, continuing reviews, stamped consent/recruitment documents, reportable event acknowledgments, reliance agreements, and lapse/resolution documentation) will be maintained with version control and audit trails in the regulatory binder/eReg. Only current IRB-approved documents may be used for participant interactions, per ISO 14155 and ICH-GCP [1,2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. US Food and Drug Administration. 21 CFR Parts 50, 56, and 812—Protection of Human Subjects; Institutional Review Boards; Investigational Device Exemptions. 2024. https://www.ecfr.gov
4. US Department of Health and Human Services. 45 CFR 46—Federal Policy for the Protection of Human Subjects (Common Rule). 2018. https://www.ecfr.gov
5. US Department of Health and Human Services. 45 CFR 164—HIPAA Privacy Rule. 2013. https://www.ecfr.gov
6. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj

7.2 Informed Consent

Overview and principles

Informed consent will be obtained prior to any study-specific procedures, in a manner that ensures voluntariness, adequate understanding, and documentation of authorization for use of health information. The process will comply with ISO 14155, ICH-GCP, the Declaration of Helsinki, applicable medical device regulations (e.g., EU MDR), and jurisdictional human subject protection and privacy laws (e.g., 21 CFR 50/56, 45 CFR 46, HIPAA; GDPR) [1–8]. Electronic informed consent (eConsent) may be used where permitted, following FDA and ICH/ISO expectations for identity verification, audit trails, and secure records [1–3,7,9].

Authorized personnel, training, and delegation

- Only investigators or site personnel formally delegated on the site's Delegation of Authority Log may conduct consent discussions and obtain signatures.
- Required training for consent-obtaining personnel includes current GCP training; protocol- and device-specific training; data privacy/HIPAA or GDPR training as applicable; and training in eConsent systems when used. Competency will be assessed by the Principal Investigator (PI) via observation or documented simulation prior to independent consent and re-assessed after substantive amendments [1–3,7].
- Documentation:

- Maintain delegation and training logs with dates, curricula, and competency assessments in the regulatory binder/eReg [1–3].
- For eConsent, maintain system access controls, role-based permissions, and audit trails consistent with 21 CFR 11 and ISO 14155 [1,3,9].

Timing, setting, and conduct of the consent discussion

- Consent will be obtained before any study-specific screening or baseline procedures and prior to randomization [1,2].
- Settings include on-site visits or remote/telehealth encounters. For remote encounters, identity will be verified using BankID or a similar electronic personal identification service, plus a secondary check (e.g., date of birth or two-factor authentication) per site SOPs [1,2,7].
- Participants will receive sufficient time to review the materials, consider participation, and ask questions without coercion. The discussion will address purpose, procedures, risks (including device- and maneuver-related), benefits, alternatives, confidentiality, data use and sharing, compensation/reimbursement (if any), voluntary nature, and the right to withdraw without penalty [1–5,7].
- Teach-back techniques will be used to confirm understanding (e.g., asking the participant to describe the study purpose, key procedures, and withdrawal rights) [1,2].

Consent modalities and documentation

- Modalities:

- Paper consent using the current IRB/IEC-stamped form.
- eConsent using a validated platform supporting version control, secure display of the IRB-approved form, identity verification, time-stamped eSignatures, and audit trails [1–3,7,9].

- Signatures:

- Adult participants (age of majority per local law) sign the consent.
- For participants aged 16–17 where they are minors under local law, parental/guardian permission is obtained, and the minor provides age-appropriate assent unless waived by the IRB/IEC [2,4,5].
- If a participant lacks decision-making capacity, consent will be sought from a Legally Authorized Representative (LAR) per local law; the participant's assent will be sought when feasible [2,4,5].

- For non-English readers when a full translation is not available, a short-form consent process with a qualified interpreter and an impartial witness may be used if approved by the IRB/IEC; both the witness and interpreter will document their roles. When certified translations are available, the translated long-form is preferred [2,5].
- For participants who cannot read or write, an impartial witness will be present for the entire discussion and will attest to the voluntariness and comprehension; the participant may mark the document, and the witness signs and dates per regulations [2,5].

- Date and time of signature(s) will be recorded, and the signer will receive a copy of the fully executed consent (paper or electronic) [1–3,7].

Supported languages and interpreter services

- Supported languages at study start: English and [site-specific languages to be confirmed]. Certified translations will be IRB/IEC-approved and version-controlled before use [1,2].
- Qualified medical interpreters will be offered at no cost for participants with Limited English Proficiency or hearing impairment; interpreter identity and modality (in-person/remote) will be documented [2,4,5].
- Consent will not proceed without appropriate language support to ensure comprehension [1,2,4,5].

LAR procedures and change in consent status

- Identification and verification of an LAR will follow local law and institutional policy; documentation of LAR authority will be filed in source documents.
- If a participant regains capacity, or if a minor reaches the age of majority during follow-up, re-consent from the participant will be obtained at the earliest opportunity using the current IRB/IEC-approved form [1,2,5].
- Any change in LAR status or guardianship will be documented, and consent will be refreshed accordingly [2,5].

Version control and re-consent

- Only the current IRB/IEC-approved consent versions (bearing version/date and, if applicable, IRB stamp) may be used. Site staff will verify currency on the day of consent per the IRB Approval Verification process [1–3,6].
- Active versions at study start will be listed in the site regulatory binder/eReg, along with certified translations.
- Amendments:

- When the consent is amended (e.g., to reflect new or increased risks, new procedures, or changes in data use), the sponsor will provide tracked and clean versions. Sites will implement the amended form only after IRB/IEC approval, except where required to eliminate immediate hazards [1–3,6].
- Re-consent is required for currently active participants when changes may affect willingness to continue, when new significant findings arise, when privacy practices change materially, upon transition to a new consent modality, or when a participant reaches the age of majority or regains capacity [1–3,5,6].
- The site will maintain a log of participants who require re-consent and completion dates.

Privacy, confidentiality, and HIPAA/GDPR authorization

- The consent will include required privacy language and authorization for collection, use, and disclosure of health information as applicable to the site's jurisdiction (HIPAA Authorization at US sites; GDPR-compliant information at EU/EEA sites) [4,7,8].

- Categories of data collected may include:

  - Identifiers: name, date of birth, contact details, medical record number, device/app identifiers, IP address, and time stamps (for eConsent and app interactions) [7,8].

  - Medical and research data: medical history, diagnosis (asthma/COPD), concomitant medications, inhaler type(s) and technique assessments, spirometry data, inspiratory flow parameters (e.g., PIF, time to PIF, inspiration time), usability and patient-reported outcomes, adverse events, device deficiency/complaint information, and health care utilization.

  - Operational and safety data: randomization assignment (blinded to adjudicators), visit dates, telehealth session metadata, and audit logs.

- Data sharing and recipients: sponsor, study sites, laboratories/core labs, contract research organizations, data monitoring committees, IRB/IEC, and regulatory authorities may access de-identified or coded data; direct identifiers will be limited to those with a need-to-know per consent and law [1–3,6–8].
- Cross-border transfers (if any) will follow approved mechanisms (e.g., Standard Contractual Clauses under GDPR) and institutional policies [8].
- Data retention: signed consent documents and essential source records will be retained for the period required by law and regulation ([to be confirmed] years or per local requirements), and not less than the period necessary to satisfy postmarket obligations and audits [1–3,6–8].
- Participants may withdraw consent for future data collection at any time; previously collected data may be retained as necessary to comply with legal, safety, and integrity obligations, as described in the consent and consistent with law [1–3,6–8].

Distribution of copies and storage of signed consents

- Participants will receive a copy of the signed consent and, where applicable, a copy of the HIPAA Authorization or GDPR information sheet. For eConsent, a PDF copy will be provided electronically and may be printed upon request [1–3,7].
- Storage:

  - Paper consents: stored in locked, access-controlled cabinets at the site.

  - eConsent: stored in validated, access-controlled systems with encryption at rest and in transit, with complete audit trails, electronic time stamps, and version history meeting ISO 14155 and 21 CFR 11 requirements [1,3,9].

- Access is restricted to authorized personnel; all records are subject to monitoring, auditing, and inspection by the sponsor, IRB/IEC, and regulators, in accordance with applicable privacy protections [1–3,6–8].

Documentation of the consent discussion and participant understanding

- A source note will document:

  - Date/time, location (on-site/remote), and modality (paper/eConsent).

  - Names/roles of staff present; interpreter and/or impartial witness if used.

  - Identity verification method (e.g., government ID on-site; BankID for remote) and confirmation that the consent version/date matched the current IRB/IEC-approved form.

  - Key topics discussed, participant questions, and use of teach-back to confirm understanding of purpose, procedures, risks/benefits, confidentiality, alternatives, and withdrawal rights.

  - Whether a copy of the signed consent and privacy authorization was provided and in what format.

  - Any LAR/assent procedures, capacity assessment, or special circumstances (e.g., short-form process) [1–5,7].

- For eConsent, the system’s audit trail will capture presentation of the correct version, time spent reviewing sections, identity authentication events, and time-stamped signatures, which will be filed with the source documentation [1,3,7,9].

Special considerations for the investigational device and decentralized processes

- Participants will be informed that the investigational inhalation app-module is embedded in AsthmaTuner (version later than 5.4.13.5) and is available only within this trial, and that related devices (spirometer and Airflow Trainer) may be provided for home use. The consent discussion will describe remote data capture, identity verification procedures (e.g., BankID), and safeguards for secure transmission and storage of device/app data [1–3,7].
- Participants will be advised that central adjudicators and sponsor personnel will review de-identified inhalation technique artifacts and logs, with blinding maintained for study allocation, and that safety events and device deficiencies may be shared with regulators per law [1,3].

Participant rights and contacts

- The consent will clearly state that participation is voluntary, refusal will not affect clinical care, and participants may withdraw at any time without penalty. Contact information for the PI (clinical matters), study team (scheduling), and an independent contact for questions about rights (IRB/IEC) will be provided [1–5].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191–4. doi:10.1001/jama.2013.281053
5. US Food and Drug Administration. 21 CFR Parts 50 and 56—Protection of Human Subjects; Institutional Review Boards. 2024. https://www.ecfr.gov
6. US Department of Health and Human Services. 45 CFR 46 (Common Rule) and 45 CFR 164 (HIPAA Privacy Rule). 2018/2013. https://www.ecfr.gov
7. US Food and Drug Administration. Use of Electronic Informed Consent in Clinical Investigations: Guidance for Institutional Review Boards, Investigators, and Sponsors. 2016. https://www.fda.gov/media/116850/download
8. European Union. Regulation (EU) 2016/679 (General Data Protection Regulation). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj
9. US Food and Drug Administration. 21 CFR Part 11—Electronic Records; Electronic Signatures. 2023. https://www.ecfr.gov

7.3 Confidentiality

Data privacy and confidentiality plan

Participant confidentiality will be protected throughout the study in accordance with ISO 14155, ICH-GCP, applicable privacy laws (e.g., GDPR for EEA sites; HIPAA for US sites), and institutional policies [10–13]. Personally identifiable information (PII) and protected health information (PHI) will be collected only as necessary, coded (pseudonymized) at the earliest opportunity, transmitted and stored using secure, validated systems with audit trails, and accessed solely by authorized personnel for protocol-related purposes [10–12,15]. Participants are informed of these practices in the approved consent/authorization documents, including that monitors, auditors, and regulators may review source data under confidentiality protections [10–13].

Data categories and legal basis

- Identifiers and operational metadata:

- Name, date of birth, contact details, medical record number (if used locally), site subject ID, randomized treatment arm (blinded to adjudicators), app- and device-generated identifiers (e.g., device serial, app instance ID), IP address and time stamps associated with eConsent and app interactions where applicable [10–12,15].

- Medical and research data:

- Diagnosis (asthma and/or COPD), inhaler type (DPI/MDI/both), medical history and concomitant medications relevant to inhalation therapy, spirometry and inhalation technique metrics (e.g., PIF, time to PIF, inspiration time), usability/feasibility questionnaires, adverse events and device deficiencies/complaints, healthcare utilization, and visit/telehealth scheduling data.

- Legal basis for collection and processing:

- EU/EEA and jurisdictions applying GDPR: lawfulness of processing will rely on informed consent for research and/or another permissible basis under Article 6, together with a special category condition under Article 9(2) (e.g., explicit consent or scientific-research basis), as confirmed by the site/institutional Data Protection Officer; data minimization and purpose limitation will apply [12].

- US sites: PHI use/disclosure will occur under a HIPAA Authorization or an IRB waiver, consistent with the Privacy Rule [13].

- All sites: processing is further grounded in obligations under clinical investigation regulations and GCP for safety reporting, monitoring, and record retention [10,11,17].

Data flow, coding, and re-identification key control

- Collection:

- Source data are recorded at the site (paper or validated electronic source) and within the AsthmaTuner ecosystem (iOS/Android) containing the investigational inhalation app-module (>5.4.13.5). Identity verification for remote procedures may use BankID or a comparable electronic personal identification service per local SOPs.

- Coding/pseudonymization:

- Each participant is assigned a unique study ID. Coded data transmitted to the sponsor, CRO, adjudicators, DSMB, core laboratories (if any), and analysis repositories will exclude direct identifiers. The site maintains the sole re-identification key (master subject identification log) in a separate, access-restricted location (locked file or encrypted folder on a secure institutional server), with access limited to the PI and designated site staff [10–12].

- Transfer:

- Data are transferred from sites and from the app/system to the electronic data capture (EDC) and other study systems via encrypted channels (TLS 1.2+). File transfers use secure managed services, with checksum or hash verification where applicable. No direct identifiers will be transferred to central adjudication, DMC/DSMB, or analytics environments unless strictly necessary and approved by the IRB/IEC and DPO [10–12,15].

- Storage and archiving:

- Coded clinical data and system audit trails are stored in validated environments with role-based access controls and encryption at rest. Backups follow institutional/business continuity policies. Final archives are immutable and access-controlled; the re-identification key remains exclusively at the site until destruction at the end of the retention period [10–12,15].

Technical and administrative safeguards

- Technical controls:

- Encryption in transit and at rest; strong authentication and least-privilege, role-based access; periodic access review; automatic log-off; firewalls and endpoint protection; vulnerability management and patching in accordance with institutional IT security; validated systems with audit trails consistent with ICH-GCP and 21 CFR Part 11 for electronic records/signatures [11,15].

- Administrative/physical controls:

- Staff training in GCP, privacy, and security; signed confidentiality agreements; documented SOPs for data handling, device logistics, telehealth, and identity verification; locked paper records; restricted server rooms and secure disposal of media [10–12].

- Vendor and cross-border safeguards:

- Written contracts and data processing agreements with CROs, EDC/hosting providers, adjudication and DSMB vendors; GDPR-compliant Standard Contractual Clauses or other lawful transfer mechanisms when applicable to international data transfers [12].

Access controls and permitted disclosures

- Site:

- Only authorized site personnel may access direct identifiers and the re-identification key. The PI is responsible for granting and periodically reviewing access.

- Sponsor/CRO/monitors:

- Access to coded data in study databases is restricted by role. Source documents, including identifiable information, may be reviewed on-site or via validated remote monitoring solutions by sponsor monitors, auditors, and regulatory authorities to verify data integrity and compliance, as permitted by consent and law [10,11].

- Regulators, IRB/IEC, and DSMB:

- Regulators and IRB/IECs may inspect or receive data as required. The DSMB receives coded datasets and safety narratives with minimal necessary identifiers; any exception requires governance approval and documentation [10,11].

- Participant disclosure:

- The informed consent/authorization discloses all categories of recipients, the possibility of audits/inspections, and the measures taken to protect confidentiality [11–13].

Data sharing outside the site

- Central adjudication and analytics:

- De-identified/coded inhalation technique artifacts and logs will be shared with central adjudicators and analytical teams; treatment allocation remains blinded where specified.

- Core laboratories and specialty vendors:

- If a core laboratory or specialty vendor is engaged (e.g., for spirometry over-reads), only coded data will be shared under contract and DPA terms approved by the sponsor and, where applicable, the DPO/IRB.

- Contracted service providers:

- CROs, EDC/hosting providers, and secure messaging/eConsent vendors act as processors, operate under written agreements, and are subject to security and privacy audits. No sale of personal data will occur.

Data retention and destruction

- Retention period:

- Essential documents and study records will be retained for at least 10 years after study completion or longer if required by local law or until the later of periods required for postmarket obligations and regulatory review; US IDE-related records will be retained for a minimum of 2 years after the later of study termination/completion or the date that the device is cleared/approved for the indication under study, whichever is longer, with the stricter rule prevailing [10,16,17].

- Sites:

- Sites retain the re-identification key and identifiable source documents for the full retention period. The sponsor retains coded datasets, analysis programs, audit trails, and essential correspondence for the same period.

- Destruction:

- After retention, paper records are cross-cut shredded or incinerated; electronic records and media are sanitized using industry-standard methods (e.g., NIST-aligned secure wipe) with destruction certificates where applicable. The site destroys the re-identification key last, upon sponsor confirmation that all regulatory obligations have been met [10–12].

Security incidents and breach response

- Detection and response:

- Suspected or confirmed data security incidents are reported immediately to the PI, sponsor, and institutional IT/security per SOPs. Containment, forensic investigation, risk assessment, and corrective actions are documented.

- Notifications:

- EU/EEA sites will notify the competent supervisory authority without undue delay and, where feasible, within 72 hours of becoming aware of a personal data breach; data subjects will be notified without undue delay when the breach is likely to result in a high risk to their rights and freedoms [12]. US sites will provide breach notifications to affected individuals without unreasonable delay and in no case later than 60 days following discovery, with required notifications to HHS and, if applicable, the media, consistent with the HIPAA Breach Notification Rule [14]. IRB/IEC and regulators will be notified per their policies and any device investigation requirements [10,17].

- Remediation:

- Access revocation, password resets/MFA enforcement, software patches, and process CAPAs will be implemented and tracked to closure.

Data subject rights and limitations

- EU/EEA data subjects may have rights to access, rectification, restriction of processing, and objection, with certain research exemptions or limitations applied where permitted by law and documented locally; requests will be coordinated by the site/institutional DPO [12].
- Under HIPAA, individuals have rights to access and amend designated record sets, subject to regulatory exceptions; requests will follow institutional HIPAA procedures [13].
- Withdrawal of consent for new data collection will be honored prospectively; previously collected data may be retained to meet scientific validity, safety reporting, and legal obligations as permitted by law and described in consent [10–13].

Confidentiality of shipping and device logistics

- Shipment of the spirometer and Airflow Trainer to participants uses verified addresses collected during consent. Carriers receive only minimum necessary information. Package contents are not labeled with study details. Any return logistics will follow chain-of-custody documentation without including medical information.

System validation, audit trails, and data integrity

- Electronic systems (eConsent, EDC, app-related study databases) will be validated and maintain audit trails capturing creation/modification, user, timestamp, and reason for change, consistent with ICH-GCP and 21 CFR Part 11 expectations [11,15]. ALCOA principles apply to all records [10,11].

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12. US Food and Drug Administration. 21 CFR 812.140—IDE Records. 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812/section-812.140
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8 ADVERSE EVENT REPORTING

8.1 Adverse Events (AEs)

Definitions and scope

- Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory finding), in a study participant, temporally associated with the use of a medical device, clinical investigation procedures, or study participation, whether or not considered related to the device or procedures [1,2].
- Serious Adverse Event (SAE): An AE that led to death, a serious deterioration in health (life-threatening illness or injury; permanent impairment of a body structure or a body function; in-patient or prolonged hospitalization; medical or surgical intervention to prevent life-threatening illness/injury or permanent impairment), fetal distress/death or a congenital anomaly/birth defect, consistent with ISO 14155 and EU MDR [1,3].
- Unanticipated Adverse Device Effect (UADE)/Device Deficiency that led to a serious adverse event: A serious adverse effect on health or safety or death caused by, or associated with, a device, which was not previously identified in nature, severity, or incidence in the investigational plan/IFU, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (FDA) and the corresponding concept under MDR/MDCG guidance [3–6].
- Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance such as malfunction, misuse or use error, and inadequate information supplied by the manufacturer; device deficiencies without subject harm are captured separately per protocol and reported per regulatory requirements [1,3,5].

AE assessment window and follow-up

- Collection window: All AEs will be collected from the time of informed consent through 30 days after the last protocol-specific interaction or last use of the investigational inhalation app-module (whichever is later). SAEs related to the device/procedures will be followed until resolution, stabilization, or return to baseline, even if this extends beyond 30 days [1,2,5].
- Post-withdrawal: For participants who discontinue early, AEs/SAEs emerging or ongoing within 30 days after last device exposure or protocol interaction will continue to be collected and followed as above, unless the participant withdraws consent for further safety contact as permitted by law; safety critical information may still be retained/reported per regulation [1–3].

Sources and methods of AE identification

Investigators will proactively and systematically ascertain AEs using multiple data sources:

- Clinical evaluations at scheduled and unscheduled visits (on-site or telehealth), including focused respiratory examination and assessment of inhalation maneuvers.
- Study procedures and measurements: spirometry and inhalation technique metrics (e.g., PIF, time to PIF, inspiration time), peak flow, oximetry if performed, and any clinically relevant abnormal findings [1].
- Participant-reported outcomes and symptom queries via the AsthmaTuner ecosystem and study ePROs, including app-based prompts and free-text reports; phone contacts between visits [2].
- Concomitant medications, rescue medication use, dose changes, and new therapies.
- Healthcare utilization: urgent care/ED visits, hospitalizations, outpatient procedures, and imaging/laboratory data obtained from medical records when available.
- Device/app logs and alerts suggestive of safety signals or use errors (e.g., repeated failed maneuvers temporally associated with symptoms), and device deficiencies/complaints captured per device procedures [1,3,5].

Identification of baseline conditions vs new or worsening AEs

- Baseline/pre-existing conditions present prior to first device exposure will be recorded in medical history. Such conditions are not AEs unless they worsen in frequency, severity, or character after baseline; in that case, the worsening component is recorded as an AE with onset at the time of change [1,2].
- Intermittent baseline symptoms typical of asthma/COPD (e.g., cough, wheeze) are not AEs unless there is a clinically meaningful exacerbation beyond baseline variability as judged by the Investigator, supported by objective or clinical criteria when available [1,2].
- Abnormal baseline findings repeated post-baseline without clinically meaningful change are not AEs; new abnormalities or clinically significant changes from baseline are AEs.

Severity grading

- Primary severity grading will use the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 where an appropriate term/definition exists (Grade 1–5) [7].
- If a CTCAE term is not applicable, the following device-appropriate scale will be used:

- Mild: transient, tolerable, no or minimal intervention; no impact on activities of daily living (ADLs).
- Moderate: local or systemic symptoms requiring noninvasive intervention; some limitation of instrumental ADLs.
- Severe: medically significant; limits self-care ADLs; requires intensive intervention or hospitalization; life-threatening consequences.
- Death: results in death.

Investigators must apply the most specific CTCAE term available; if none is suitable, justify use of the alternative scale in source notes and the AE CRF [1,7].

Causality attribution

Investigators will assess relatedness of each AE to:

- the investigational inhalation app-module (software function),
- associated devices/procedures (spirometer, Airflow Trainer, coached inspiratory maneuvers, app interactions),
- study participation (e.g., protocol-required assessments).

Attribution categories:

- Not related: no temporal relationship and a more likely alternative etiology.
- Unlikely related: temporal relationship improbable or a more plausible alternative explanation.
- Possibly related: reasonable temporal relationship and cannot be ruled out by alternative causes.

- Probably related: reasonable temporal relationship, plausible mechanism, improves on device/procedure discontinuation or recurs on re-challenge (if occurs inadvertently/ethically permissible).
- Definitely related: clear temporal relationship, biologically plausible, and supported by objective evidence or positive re-challenge.

Process and adjudication:
- The site Investigator assigns initial causality and severity at detection and updates assessments with new information. The Sponsor's Medical Monitor/Safety Physician independently reviews relatedness for SAEs, UADEs, and events of special interest. Disagreements are resolved through documented discussion; if unresolved, the Medical Monitor renders the final determination. Events meeting UADE criteria or material safety issues may be escalated to the DSMB for independent review per the DSMB Charter [1,5,6].

Responsibilities, frequency, and workflows

- Site responsibilities:

- Elicit and document AEs at every participant contact (in-person or remote) and through review of interim reports/app alerts. Enter non-serious AEs into the eCRF within 5 business days of awareness; enter SAEs within 24 hours of awareness; potential UADEs/device-related serious problems must be reported immediately per applicable regulatory pathways and Sponsor SOPs [1,4–6].
- Obtain and upload supporting source documentation (e.g., progress notes, discharge summaries, test results) promptly, ensuring protection of identifiers per confidentiality procedures.
- Update AE status at each follow-up until outcome is final (resolved, resolved with sequelae, ongoing at end of study, death).

- Sponsor/CRO responsibilities:

- Perform ongoing medical review, signal detection, reconciliation with device deficiency/complaint logs, and expedited reporting to competent authorities/IRB/IEC as required by ISO 14155, FDA IDE regulations, MDR, and MDCG guidance [1,3–6].
- Provide periodic safety summaries to the DSMB and all investigators; communicate new risk information and update the IB/Device Dossier and consent as needed [1–6].

- DSMB responsibilities:

- Review aggregated safety data at pre-specified intervals and ad hoc for potential safety concerns; recommend continuation, modification, or pause, per the DSMB Charter and governing regulations [1,5].

- Monitoring and verification:

- On-site or remote source data verification will confirm complete and timely AE capture, accurate grading/attribution, and concordance with source records and app/system logs, consistent with ICH-GCP and ISO 14155 [1,2].

Special considerations for software-enabled, respiratory maneuver procedures

- Transient symptoms related to coached inspiratory maneuvers or inhaler technique training (e.g., cough, lightheadedness) must be captured if they meet the AE definition, with careful attribution to device function, training procedure, underlying disease, or alternative causes, acknowledging the risk profile of inspiratory-flow–dependent DPI use and reduced respiratory muscle strength in some populations [1,8].
- Device deficiencies (e.g., app malfunction, connectivity errors, sensor pairing failures) will be logged and investigated; if they result in an AE, both the deficiency and the AE will be reported and cross-referenced [1,3,5].

Ongoing evaluation and closure of AEs

- Each AE will be assessed for seriousness, severity, causality, expectedness, action taken (e.g., device/procedure interrupted, medical treatment), and outcome. Investigators will

implement appropriate medical management and protocol-directed actions to protect participant safety [1,2].

- AEs will be considered closed when resolved to baseline, resolved with sequelae, or the participant is lost to follow-up with documentation of due diligence; SAEs related to the device/procedure require maximal feasible follow-up [1,2].

Standardized AE Case Report Form (CRF) fields

The following minimum data elements will be captured for each AE in the eCRF; sites will attach/source-upload supporting documentation when applicable:

CRF Field	Description
AE term (preferred term and verbatim)	Investigator's description; mapped to CTCAE v5.0 term if available [7]
Onset date/time	First date/time the AE met definition
Stop date/time	Date/time of resolution or last known status if ongoing
Seriousness	Yes/No; if Yes, select criterion(ia) per ISO/MDR definitions [1,3]
Severity grade	CTCAE Grade 1–5 or Mild/Moderate/Severe/Death with justification [7]
Relatedness to investigational app-module	Not/Unlikely/Possibly/Probably/Definitely related
Relatedness to procedures/devices (spirometer/Airflow Trainer/inhalation training)	Not/Unlikely/Possibly/Probably/Definitely related
Relatedness to study participation (other)	Not/Unlikely/Possibly/Probably/Definitely related
Expectedness	Expected/Unexpected based on IB/IFU and risk analysis [1,3]
Action taken with device/procedure	None; interrupted; discontinued; re-trained; software update; other (specify)
Medical actions taken	None; medication; outpatient visit; ED; hospitalization; procedure; other
Outcome	Resolved; Resolving; Resolved with sequelae; Ongoing; Fatal
Concomitant conditions/medications relevant to AE	List pertinent factors
Device deficiency link	Yes/No; if Yes, reference Device Deficiency/Complaint ID [1,3,5]
Hospitalization details (if applicable)	Admit/discharge dates; facility; diagnosis
Supporting documentation	Uploaded notes, test results, imaging, discharge summary; date obtained
Reporter and dates	Person recording AE, Investigator assessment date/signature
Causality adjudication notes	Medical Monitor/DSMB notes and final determination (if applicable)
Follow-up assessments	Dates and summaries until closure

All AE capture, documentation, and reporting will adhere to ALCOA principles and validated system audit trails per ICH-GCP and ISO 14155 [1,2].

References

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2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. US Food and Drug Administration. 21 CFR Part 812—Investigational Device Exemptions. 2024.

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8.2 Serious Adverse Events (SAEs)

Definition and scope of SAEs for reporting

An SAE is any adverse event that results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity or a substantial disruption of a person's ability to conduct normal life functions; results in a congenital anomaly/birth defect; or requires medical or surgical intervention to prevent permanent impairment or damage, consistent with ISO 14155 and EU MDR [1,3]. All SAEs will be collected from informed consent through 30 days after the last protocol-specific interaction or last use of the investigational app-module, whichever is later, and followed until resolution, stabilization, or return to baseline, as feasible [1,2].

SAE identification and immediate site actions

- Upon first awareness of a potential SAE from any source (participant report, clinical visit, hospitalization, app logs/alerts, device deficiency, medical record), the site must:

- Ensure appropriate medical evaluation and treatment; interrupt study device/procedures if clinically indicated to protect participant safety [1,2].
- Determine if the event meets the SAE definition and whether it may be related to the investigational app-module, associated devices/procedures, or study participation [1].
- Initiate reporting per timelines below and begin source documentation and evidence collection (e.g., progress notes, discharge summaries, test results) while protecting confidentiality [1,2].

Reporting timelines, recipients, and responsibilities

- To Sponsor (required for all SAEs irrespective of relatedness/expectedness):

- Initial notification: within 24 hours of the site's first awareness of the SAE [1,2].
- Follow-up information: within 10 calendar days of the initial report, and thereafter within 24 hours of any material update (e.g., change in seriousness, outcome, causality, or availability of key documents) until closure [1,2].

- To IRB/IEC (investigator responsibility):

- Fatal or life-threatening, related or unexpected SAEs: notify without delay and per IRB/IEC policy (typically within 24–48 hours); other SAEs per IRB/IEC reporting requirements (often within 5–10 business days), documenting local timelines followed [1,2].

- To Regulatory Authorities (sponsor responsibility; investigator supplies documentation promptly upon request):

- EU/EEA clinical investigations under MDR: sponsor will submit reportable serious adverse events and device deficiencies that might have led to an SAE to the Member State(s) in which the clinical investigation is being conducted per MDCG 2020-10/1 timelines: within 2 days for serious public health threats; within 7 days for deaths or unanticipated serious deterioration in health (with any incomplete information followed up within 8 days); within 15 days for other reportable SAEs [3,4].
- US IDE studies: for Unanticipated Adverse Device Effects (UADEs), the investigator reports to the sponsor and reviewing IRB within 10 working days of first learning of the effect; the sponsor reports to

FDA and all reviewing IRBs within 10 working days after first receiving notice of the UADE, consistent with 21 CFR 812.150. Other required IDE reports will be made per 21 CFR 812 and applicable FDA guidance [5].
- Postmarket MDR applicability: if any reporting under 21 CFR 803 is triggered for manufacturers, the sponsor/manufacturer will fulfill those obligations separately from IDE/MDR clinical investigation reporting, as applicable [6].

The Principal Investigator (PI) or sub-investigator listed on the Delegation of Authority Log is responsible for confirming seriousness, providing the initial assessment of causality and expectedness, and signing SAE submissions to the sponsor and IRB/IEC. The Sponsor's Medical Monitor/Safety Physician performs independent medical review, requests clarification as needed, and signs the final causality/expectedness determination for sponsor regulatory reporting [1,2].

After-hours and escalation procedures

- Sites must maintain 24/7 capability to notify the sponsor of SAEs:

- During business hours: send initial notification via the designated safety email and enter the SAE in the EDC; call the sponsor safety line for deaths, life-threatening events, potential UADEs, or events requiring urgent action.
- After hours/weekends/holidays: call the 24/7 safety hotline [number to be provided] and follow with an email to the safety mailbox [address to be provided] within 24 hours. Document the date/time and contact person reached.

- If the event suggests a new or increased risk (e.g., suspected UADE, cluster of similar SAEs, software malfunction leading to patient harm), the PI escalates immediately by phone to the sponsor Medical Monitor; the sponsor may convene an ad hoc DSMB review within 72 hours, per the DSMB Charter [1,4,5].

SAE reporting workflow

- Identification:

- Detect potential SAE and stabilize the participant; confirm SAE criteria.

- Immediate notification (within 24 hours):

- Site transmits the Initial SAE Notification to sponsor; logs the event in EDC/SAE module; notifies IRB/IEC per local policy for reportable events.

- Sponsor review and triage:

- Sponsor acknowledges receipt within 1 business day, confirms completeness, and assigns a safety case ID; Medical Monitor reviews seriousness, expectedness, and relatedness; assesses UADE criteria (US) and MDR reportability (EU) [1,3–5].

- Follow-up reporting:

- Site submits scheduled follow-up within 10 calendar days, including source documents and hospital records as available; answers sponsor/regulatory queries within 3 business days or as specified.
- Sponsor files expedited regulatory reports within mandated timelines (MDR/MDCG and/or FDA IDE) and provides copies/acknowledgments to sites as appropriate [3–5].

- Ongoing tracking and resolution:

- Site updates status at each contact until outcome is resolved/stable; cross-reference any device deficiency/complaint IDs if applicable [1,3–5].
- Sponsor maintains a query log and reconciliation tracker linking EDC AE/SAE entries, device complaint system, and regulatory submissions; all queries and responses are archived with date/time, responsible person, and closure status [1,2].

- Case closure:

- Site documents final outcome and PI signature; Sponsor Safety Physician signs final case assessment; closure communicated to site and, if applicable, to IRB/IEC/regulators in a follow-up report.

Events meeting SAE criteria in this study

- Examples include but are not limited to:

- Death, cardiopulmonary arrest, or life-threatening bronchospasm.
- In-patient hospitalization or prolongation of hospitalization for asthma/COPD exacerbation, pneumonia, syncope with injury, or other acute illness.
- Persistent or significant disability/incapacity (e.g., prolonged inability to perform activities of daily living due to event).
- Medically significant events requiring intervention to prevent permanent impairment (e.g., emergency airway management).
- Fetal distress/death or congenital anomaly/birth defect in participants who become pregnant during the study [1,3,4].

Any device deficiency that resulted in an SAE, or might have led to an SAE if it recurred, must be reported and cross-referenced to the device complaint/deficiency log [1,3,4].

Documentation standards and signatures

- Initial SAE submission must include minimum required data elements: participant study ID; demographics (coded); event term and narrative; onset date/time; seriousness criterion; initial severity and causality; actions taken; outcome (if known); relevant medical history/concomitant medications; device/exposure details; and reporter/PI signature/date [1,2].
- Follow-up submissions add hospital records, test results, discharge summaries, imaging, and updates to seriousness, causality, expectedness, and outcome, with PI re-signature and date. Sponsor Medical Monitor signs the final assessment used for regulatory reporting [1,2].

Templates

- Initial SAE Notification (email/phone)

- Subject/Opening: “Immediate SAE Notification – [Site], Subject [Study ID], [Event term], Onset [YYYY-MM-DD]”
- Patient/study info: Study ID; age/sex; randomized arm (if unblinding not required for safety, keep blinded).
- Event details: Event term; onset date/time; seriousness criterion; current clinical status; initial severity; initial causality to app-module/procedure/other; expectedness.
- Actions taken: Medical treatment; hospitalization details (admit date/facility); action with app-module/procedures (continued/interrupted/stopped).
- Supporting data: Key vitals/tests (if available); treating physician contact.
- Device information: App version; device serial(s); device deficiency/complaint ID (if any).
- Reporter: Name/role; 24/7 contact; PI confirmation that he/she is aware; date/time of report.
- Immediate needs: Any urgent safety concerns or requests for guidance.

- Scheduled Follow-up SAE Report (e.g., 10-day report)

- Case identifiers: Sponsor case ID; Site; Subject ID; Initial notification date.
- Updated clinical course: Interventions; test results; ICU/ward course; complications.
- Outcome status: Resolved/resolving/ongoing/fatal; dates; sequelae.
- Causality/expectedness update: PI reassessment; rationale; any contributory factors (e.g., inhaler misuse, comorbidities).
- Device/procedural details: App build; spirometer/Airflow Trainer use; retraining; software updates; device investigation summary and linkage to complaint/deficiency record.
- Regulatory/IRB notifications: Dates and recipients of IRB/IEC notifications; any regulator correspondence.
- Attachments: Discharge summary; lab/imaging; procedure notes; death certificate (if applicable).
- Signatures: PI signed/dated; Sponsor Medical Monitor review/notes; date of sponsor regulatory submission(s) if applicable.

Independent safety oversight (DSMB)

- The DSMB will review cumulative safety data, all SAEs, UADEs, and device deficiencies with potential clinical impact at regular intervals (e.g., quarterly) and ad hoc within 72 hours for deaths, life-threatening events, or emerging safety signals at the request of the sponsor or DSMB Chair. Reviews will be performed under a DSMB Charter specifying membership, meeting cadence, stopping/modification rules, unblinding procedures for safety, and communication pathways. DSMB recommendations (continue, modify, pause, or terminate) will be documented and communicated to the sponsor, who will notify investigators, IRB/IEC, and regulators as required [1,2,4].

Data integrity, traceability, and reconciliation

- All SAE data will be recorded in validated systems with audit trails, following ALCOA principles. The sponsor will reconcile SAEs across the EDC, safety database, device complaint/deficiency system, and regulatory submissions on a periodic basis and before database lock. Discrepancies will trigger documented queries and corrective actions. All correspondence, acknowledgments, and submissions will be archived for regulatory inspection readiness [1,2].

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8.3 Non-Serious Adverse Events

Definitions, scope, and collection window

- Non-serious Adverse Events (AEs) are untoward medical occurrences in a participant that do not meet any seriousness criteria (death, life-threatening, inpatient hospitalization/prolongation, persistent/significant disability, congenital anomaly, or other medically important conditions) but are temporally associated with use of the investigational inhalation app-module, related study devices/procedures (spirometer, Airflow Trainer, inhalation training/assessments), or study participation, regardless of relatedness [1–4].
- Collection window: Non-serious AEs will be captured from the time of informed consent through 30 days after the last protocol-specific interaction or last use of the investigational app-module, whichever occurs later, including after early discontinuation unless the participant withdraws consent for further contact, in which case safety-critical information will be retained/reported as permitted by law [1–4].

What non-serious AEs must be logged

- All non-serious AEs meeting the above definition, irrespective of relatedness, expectedness, or suspected mechanism, will be recorded in source documents and the eCRF [1,2].
- Examples relevant to inhalation technique training and app-guided maneuvers include:

- Transient cough, throat irritation, hoarseness, dysphonia, dry mouth, unpleasant taste, or rhinorrhea following inhalation attempts [5].
- Lightheadedness, dizziness, brief headache, chest tightness, or musculoskeletal discomfort related to forceful inspiratory efforts, particularly with DPI technique practice [5].
- Mild asthma/COPD symptom fluctuations not requiring hospitalization (e.g., increased short-acting bronchodilator use, unscheduled outpatient/telehealth contact) that exceed baseline variability per investigator judgment [1,2,5].
- Skin or local irritation from device handling (e.g., around mouthpiece vicinity even without direct contact) and non-harmful app usability issues associated with stress or frustration that result in symptoms (e.g., anxiety, transient insomnia).
- Events arising from use errors or device deficiencies that do not result in serious outcomes (e.g., repeated failed spirometer pairing with transient hyperventilation symptoms); these must be cross-referenced to the Device Deficiency/Complaint record [1,3,4].

- Not logged as AEs: pre-existing conditions without clinically meaningful worsening after baseline; normal variations of chronic symptoms within baseline variability; protocol-driven, asymptomatic, non-clinically significant measurement fluctuations, per investigator judgment documented in source [1,2].

Assessment intervals and methods

- At every participant contact (in-person or telehealth): screening/baseline, any interim/unscheduled contacts during the 6–12 week intervention, end-of-intervention, and safety follow-up 30 (±7) days after last app-module use [1,2].
- Between visits:

- App-based ePRO prompts: brief symptom and event checks at least weekly during the intervention window and at end-of-intervention; ad hoc prompts may be triggered by predefined app or device logs indicative of potential safety signals (e.g., repeated high-effort maneuvers) [2].
- Telephone/email contact: participants are instructed to report new or worsening symptoms at any time to site staff; these contacts are documented as unscheduled assessments.

- Sources: participant interview, app/ePRO reports, device/app logs, review of concomitant medications and health care utilization, and relevant medical records, consistent with ALCOA principles and audit-trailed systems [1,2].

Documentation, grading, relatedness, and coding

- Entry timelines: Sites must enter non-serious AEs into the eCRF within 5 business days of first awareness and update entries within 5 business days of receiving new information (e.g., outcome, attribution changes) [1,2].
- Severity grading: Use CTCAE v5.0 where terms exist (Grade 1–3 for non-serious events). If no suitable CTCAE term exists, apply the protocol's device-adapted Mild/Moderate/Severe scale with justification in source and eCRF [6].
- Causality: Investigators assess relatedness to the investigational app-module, associated devices/procedures, and study participation using the predefined categories (Not, Unlikely, Possibly, Probably, Definitely related) and update as new information emerges [1,2].
- Expectedness: Compare with the current risk analysis/IFU/Investigator's Brochure and training materials; classify as expected or unexpected [1,3].
- Coding: Verbatim AE terms will be coded to MedDRA preferred terms and system organ classes in the clinical database to support aggregate analyses and safety surveillance [7].
- Cross-referencing: Any non-serious AE associated with a device deficiency/use error must be linked in the eCRF to the corresponding Device Deficiency/Complaint ID; both records are maintained and reconciled by the sponsor [1,3,4].

Site-level non-serious AE log template

Sites will maintain a contemporaneous AE Source Log (paper or validated eSource), which mirrors the eCRF and supports monitoring. Minimum fields are:

Field	Entry guidance
Site and Subject ID	Coded identifiers only
AE verbatim term	Clinician description; later MedDRA-coded
CTCAE grade or Mild/Moderate/Severe	Select one and justify if not CTCAE [6]
Seriousness	No (this log is for non-serious AEs)
Onset date/time	First date/time criteria met
End date/time	Resolution/date last known status
Relatedness (app-module)	Not/Unlikely/Possibly/Probably/Definitely
Relatedness (spirometer/Airflow Trainer/procedure)	As above
Relatedness (study participation—other)	As above
Expectedness	Expected/Unexpected
Actions taken	Medical treatment, device/procedure change, retraining, none
Outcome	Resolved/Resolving/Ongoing/Resolved with sequelae
Device Deficiency/Complaint ID	Cross-reference if applicable
Source documents filed	Yes/No; list location/date
Investigator review/signature/date	PI or sub-investigator sign-off

The AE Source Log must be version-controlled, legible, and retained in the site regulatory/subject files per record retention requirements. Entries must be transcribed to the eCRF within 5 business days and reconciled at each monitoring visit [1,2].

Site review, reconciliation, and data-cleaning timelines

- Internal site review:

- Weekly: study team reviews new app/ePRO safety flags and AE Source Log for completeness and timeliness; escalates any uncertainty in seriousness or relatedness to the PI within 1 business day.
- Prior to each participant visit: pre-visit safety huddle to reconcile interim reports, app logs, and medical records.

- Data entry and query resolution:

- Initial eCRF entry for non-serious AEs: within 5 business days of awareness.
- Sponsor/CRO medical data review: rolling review; initial queries issued within 10 calendar days of eCRF entry.
- Site query responses and corrections: within 5 business days of query receipt; complex requests requiring medical records within 10 business days, or provide an interim response with an expected completion date [1,2].

- Reconciliation:

- Monthly: site reconciles AE entries against device deficiency/complaint records and app/system alerts; documents reconciliation outcome.
- At monitoring and prior to database lock: full reconciliation of the AE Source Log, eCRF, and device complaint system, with discrepancies resolved and documented [1,2,4].

Aggregate review and reporting of non-serious AEs

- Sponsor aggregate review: Non-serious AE incidence, severity, relatedness, and patterns by inhaler stratum (DPI/MDI/both) and treatment arm will be summarized at least quarterly for DSMB review, alongside SAEs and device deficiencies, per the DSMB Charter [1–4].

- Investigator communications: The sponsor will provide periodic safety line listings and summary tables to investigators at least quarterly and after material safety updates, to support ongoing risk assessment and site training [1,2].
- IRB/IEC reporting: Non-serious, non-unexpected, and non–device-related AEs are not subject to expedited reporting; they will be reported in aggregate at continuing review per IRB/IEC policy, at least annually or at the interval required by the reviewing IRB/IEC. Sites will follow local IRB/IEC requirements if more frequent summary submissions are mandated [1,2].
- Regulatory reporting: Non-serious AEs that do not meet reportability criteria under MDR/MDCG or FDA IDE regulations will not be submitted on an expedited basis to regulators but remain available in cumulative summaries and on inspection; events escalating in severity or meeting UADE criteria will be handled per SAE/UADE procedures [3,4].

Participant management and follow-up

- Clinical management is at investigator discretion and per standard of care. Non-serious AEs will be followed until resolution, stabilization, or end of safety follow-up, whichever occurs first.
- If a non-serious AE worsens and meets SAE criteria, it will be upgraded immediately and reported per SAE timelines; the original AE record will be updated to reference the SAE case [1–4].

Training and quality controls

- Before first participant enrollment, all site personnel will be trained on AE definitions, grading with CTCAE v5.0, relatedness assessment specific to software-enabled respiratory procedures, and documentation standards; competency is documented on the Delegation/Training Logs [1,2,6].
- Ongoing targeted re-training will occur when monitoring detects systematic under-reporting (e.g., missing transient maneuver-related symptoms) or misclassification (e.g., device deficiency logged without the associated AE), with CAPAs tracked to closure [1,2,4,5].

References

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8.4 Unanticipated Adverse Events (Unexpected AEs)

Definitions and scope

- Unexpected AE (unanticipated): Any AE whose nature, severity, or incidence is not consistent with the current device Reference Safety Information (RSI), including the Investigator's Brochure/Device Dossier, Instructions for Use (IFU), and the manufacturer's risk management file, or that represents a new risk not previously identified [1–3,8].
- Unanticipated Adverse Device Effect (UADE) (US IDE context): A serious adverse effect on health or safety or death caused by, or associated with, the device, if that effect was not previously identified in nature, severity, or incidence in the investigational plan/IB/IFU, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [4].
- In EU MDR clinical investigations, all SAEs and device deficiencies that might have led to an SAE are reportable; evaluation of expectedness informs risk assessment, IB/IFU updates, and corrective actions but does not limit reportability obligations for SAEs/device deficiencies under MDR [2,3].

Reference Safety Information (RSI) and expectedness assessment

- RSI sources:

- Investigator's Brochure/Device Dossier for the inhalation app-module embedded in AsthmaTuner (>5.4.13.5), MediTuner AB (SRN SE-MF-000028534).
- Current IFU and training materials for the investigational app-module, spirometer, and Airflow Trainer.
- Manufacturer's risk management file and current risk analysis per ISO 14971 (hazard identification, foreseeable misuse/use error, harm/severity, and frequency) [1–3,8].

- Version control:

- The sponsor maintains a version-controlled RSI index with document titles, numbers, versions, and effective dates. Each AE's expectedness is assessed against the RSI version effective at the AE onset date; material RSI updates trigger prospective reassessment of ongoing cases as appropriate [1–3].
- Changes to RSI (e.g., addition of a newly identified risk) are communicated to sites, DSMB, and IRB/IEC with revised consent where required [1–3].

- Assessment principles:

- Expected if the AE's nature, severity, and frequency are consistent with RSI for the device, associated procedures (spirometry, coached inspiratory maneuvers), or study participation.
- Unexpected if any of nature, severity, or frequency is inconsistent with RSI, or the event represents a new risk, new use error pattern leading to harm, or an unforeseen interaction between the device and standard inhaler use (DPI/MDI) [1–3,8].

Decision tree for classifying expectedness

14. Confirm event is an AE per protocol.
15. Determine seriousness (serious vs non-serious).
16. Assess relatedness to:

- investigational app-module,
- associated devices/procedures (spirometer, Airflow Trainer, inhalation training),
- study participation (other).

17. Compare the AE term and clinical course to RSI:

- Match in nature and severity within stated or reasonably inferred frequency → classify as Expected.
- No match in nature, greater severity than described, or materially higher frequency than anticipated → classify as Unexpected.

18. If Serious + related (possibly, probably, or definitely) + Unexpected → classify as UADE (US IDE context) and expedite per UADE timelines [4].
19. If Serious (regardless of expectedness) in EU MDR context → report per MDR/MDCG timelines; flag unexpectedness for risk evaluation and IB/IFU update considerations [2,3].

20. If Non-serious + Unexpected → record in eCRF/source; no expedited regulatory reporting; monitor for pattern/signals and escalate if severity increases [1–3].

Reporting timelines and recipients for unexpected AEs

- Investigator to Sponsor (all unexpected AEs that are serious or suggest a new risk):

- Serious, unexpected, and related (potential UADE): initial notification immediately/within 24 hours; provide comprehensive follow-up within 10 calendar days [1,4].
- Non-serious, unexpected: enter in eCRF within 5 business days; alert sponsor promptly if indicative of a potential safety signal or use-error pattern [1].

- Investigator to IRB/IEC:

- Fatal or life-threatening, related, and unexpected SAEs: without delay per IRB/IEC policy (typically within 24–48 hours) [1].
- Other unexpected SAEs: per IRB/IEC policy (commonly within 5–10 business days). Non-serious unexpected AEs are summarized at continuing review unless locally required sooner [1].

- Sponsor to Regulatory Authorities:

- US IDE UADEs: sponsor reports to FDA and all reviewing IRBs within 10 working days of first receipt; the investigator reports UADEs to the sponsor and IRB within 10 working days of first learning of the effect [4].
- EU/EEA MDR clinical investigations: sponsor reports SAEs and device deficiencies that might have led to an SAE to the concerned Member State(s) per MDCG 2020-10/1 timelines:
  - Serious public health threat: within 2 days,
  - Death or unanticipated serious deterioration in health: within 7 days (with follow-up within 8 additional days if information is incomplete),
  - Other reportable SAEs: within 15 days [2,3].
- Manufacturer MDR (21 CFR 803) obligations, if applicable, are fulfilled separately from IDE/MDR clinical investigation reporting [5].

- Communications to DSMB and investigators:

- UADEs and material unexpected risks are provided to the DSMB at the next review or ad hoc within 72 hours for deaths/life-threatening events; investigators receive safety letters and RSI updates promptly [1–3].

Coordinating Center/Sponsor responsibilities for expectedness confirmation and submissions

- The Coordinating Center (Sponsor Safety Management Team, including the Medical Monitor/Safety Physician) will:

- Acknowledge site reports; confirm seriousness, relatedness, and expectedness against the current RSI; and determine UADE status (US) and MDR reportability (EU) [1–4].
- Assign safety case IDs; ensure MedDRA coding; reconcile with device complaint/deficiency systems.
- Prepare, quality control, and submit expedited reports to FDA (UADE), EU/EEA competent authorities (per MDR/MDCG), and distribute copies/acknowledgments to sites and IRBs/IECs within mandated timelines [2–5].
- Lead signal detection and benefit–risk evaluation; propose and implement CAPAs, protocol amendments, RSI/consent updates, and training as warranted [1–3,8].

Documentation standards for unexpected AEs

- Minimum elements: AE term and narrative; onset/stop dates; seriousness criterion; severity grade; initial and final relatedness; expectedness rationale citing RSI; action taken with device/procedures; clinical outcome; device/app version and identifiers; cross-reference to device deficiency/complaint ID; PI and sponsor medical review signatures/dates [1–3].
- All records maintained in validated systems with audit trails; traceability to submissions and acknowledgments is required for inspection readiness [1,3].

Template: Unexpected AE/UADE notification letter (site to sponsor and IRB/IEC)

- Subject: Unexpected AE/UADE Notification – [Site], Subject [Study ID], [Event term], Onset [YYYY-MM-DD]
- Study/device: Phase III [study title]; Investigational device: AsthmaTuner inhalation app-module (>5.4.13.5), MediTuner AB (SRN SE-MF-000028534)
- Participant: Study ID; age; sex; inhaler stratum (DPI/MDI/both); randomized arm (blinded unless unblinding required for safety)
- Event summary:

- AE term and detailed narrative, onset/diagnosis dates, clinical course
- Seriousness criterion; severity grade (CTCAE v5.0 or alternative per protocol)
- Relatedness to app-module/procedures/study; justification
- Expectedness: Unexpected. Basis and RSI citation (document name, version, effective date)
  - Medical management and outcome: Interventions, hospitalization details, current status
  - Device/procedural details: App version/build; spirometer/Airflow Trainer use; device deficiency/complaint ID; preliminary investigation findings
  - Actions taken: With device (interruption/discontinuation/retraining/software update); with participant care
  - Reporting:
- Date/time first awareness; date/time initial sponsor notification
- IRB/IEC notification date/time (attach or provide copy if required)
- Other authorities notified (if any)
  - Contacts: Reporting investigator name/role, 24/7 contact; PI confirmation/signature/date
  - Attachments: Key source documents (de-identified as applicable), hospitalization/discharge summaries, test results

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8.5 Anticipated Adverse Events (Expected AEs)

Reference Safety Information (RSI) and source for expectedness

Expectedness will be determined against the current, version-controlled Reference Safety Information comprising: the Investigator's Brochure/Device Dossier for the inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB, SRN SE-MF-000028534), the Instructions for Use (IFU) and

training materials for the investigational app-module, spirometer, and Airflow Trainer, and the manufacturer's risk management file developed per ISO 14971 and usability engineering per IEC 62366-1 [1–4]. Where applicable, established clinical procedure risks (e.g., coached inspiratory maneuvers, spirometry) are informed by ATS/ERS standards, and background event rates typical of asthma/COPD populations are informed by GINA and GOLD [5,7,8]. Expectedness is judged at the time of event onset using the RSI version effective on that date, with prospective updates if the RSI is materially revised [1].

Prespecified list of anticipated AEs

Based on the RSI, known risks of coached inspiratory maneuvers and spirometry, and background morbidity in asthma/COPD, the following events are anticipated during the study. Events may occur irrespective of relatedness to the investigational app-module; relatedness will be assessed per protocol.

Anticipated AE	Typical severity/course	Rationale/source
Cough during or after inhalation attempts or spirometry	Mild–moderate, transient	Common with forceful inspiratory/expiratory efforts and inhalation technique practice; described in inhalation therapy and spirometry literature [5,6]
Throat irritation, hoarseness, dry mouth, unpleasant taste, rhinorrhea after inhalation attempts	Mild, transient	Local upper airway irritation related to repeated inhalation maneuvers and device handling [6]
Lightheadedness, dizziness, brief headache during training sessions	Mild–moderate, transient; resolve with rest	Hyperventilation/effort-related symptoms during coached maneuvers and spirometry [5]
Chest tightness or discomfort associated with forceful inspiratory efforts	Mild–moderate; usually self-limited	Effort-related symptoms during DPI-oriented training; monitor for exacerbation if persistent [6]
Musculoskeletal strain (intercostal/abdominal wall soreness)	Mild–moderate; self-limited	Repetitive high-effort breathing maneuvers [5]
Anxiety, frustration, transient insomnia related to app use or training feedback	Mild; self-limited	Usability-related effects identified in risk management/usability engineering (human factors) [3,4]
Local skin irritation from device handling (e.g., around hands/lips region without direct mucosal contact)	Mild; resolves with rest/hygiene	Device handling/contact; Airflow Trainer is not in direct contact with mouth/skin by design [1,3]
Transient abnormal spirometry values without clinical symptoms	Mild; no intervention	Procedure-related measurement variability inherent to spirometry [5]
Mild asthma/COPD symptom fluctuations requiring increased reliever use or outpatient contact, without hospitalization	Mild–moderate; expected in target population	Background variability in asthma/COPD control during 6–12 weeks follow-up [7,8]
Asthma/COPD exacerbations managed outpatient or requiring hospitalization	Variable; may be serious	Background events in the population; expected in aggregate irrespective of device relatedness [7,8]
Upper respiratory tract infection, acute bronchitis, pneumonia	Variable	Common intercurrent illnesses in asthma/COPD populations over similar durations [7,8]
Device deficiency/use error without harm (e.g., app crash, sensor pairing failure, incorrect maneuver sequence) potentially associated with transient symptoms above	Mild; managed by retraining/software update	Foreseeable use errors and malfunctions identified in risk management; cross-reference deficiency log [1,3,4]

This list is not exhaustive; it reflects events whose nature, severity, and frequency are consistent with RSI and the clinical context. Investigators should classify additional events as anticipated if they are

congruent with the RSI and recognized procedure/population risks [1–4,5–8].

Decision tree to classify an event as anticipated (expected)

21. Confirm the occurrence meets the AE definition.
22. Identify the primary context: device/app-module, associated procedures (spirometry, Airflow Trainer, coached inspiratory maneuvers), general study participation, or background disease.
23. Compare the AE's nature and severity to the RSI, procedure standards (ATS/ERS for spirometry/maneuvers), and known background events for asthma/COPD:

- If the AE's nature and severity are consistent with RSI and recognized procedure/population risks, classify as Expected (anticipated).
- If the AE is more severe than characterized in RSI, of different nature, or occurs at a materially higher frequency than anticipated, classify as Unexpected.

24. Independently assess seriousness and relatedness per protocol; serious events are reportable per regulatory requirements regardless of expectedness. In the US IDE context, serious, related, and unexpected events may meet UADE criteria; in EU MDR, all SAEs are reportable; unexpectedness informs risk updates [1,2].
25. Document the expectedness rationale citing RSI/standard(s) used.

Summarization of expected AEs

- Populations and denominators:

- Summaries will be provided for the Safety Set (all randomized participants with any post-baseline safety data), by randomized arm and stratified by inhaler type (DPI/MDI/both), and cumulatively overall [1,2].

- Metrics and displays:

- Incidence proportions and exposure-adjusted incidence rates for each anticipated AE (MedDRA PT and SOC), with 95% confidence intervals where prespecified in the SAP.
- Severity: CTCAE v5.0 grade distribution for each anticipated AE; where CTCAE does not apply, distribution by Mild/Moderate/Severe per protocol [1,2].
- Relatedness: counts and percentages by relatedness category to app-module, associated procedures, and study participation.
- Outcome, action taken (e.g., device interruption/retraining), and recurrence patterns.
- Device deficiency/use error linkage: cross-tabulation of anticipated AEs associated with a device deficiency/use error, by deficiency category [1,3,9].

- Timing and intervals:

- Site-level: ongoing entry; monthly internal reconciliation of anticipated AEs with device deficiency logs.
- Sponsor aggregate review: rolling medical monitoring with formal cumulative summaries at least quarterly for DSMB review and after any material RSI update; annual consolidated safety report per ISO 14155; final integrated safety analysis at database lock [1].
- DSMB: reviews anticipated AE summaries alongside SAEs/device deficiencies per charter-specified cadence (e.g., quarterly) and ad hoc as needed.

- Coding and classification:

- All AEs, including those anticipated, will be coded using MedDRA; grouping for analysis will follow the SAP and MedDRA Points to Consider [9].

- Signal detection:

- Although anticipated, any shift toward greater severity, clustering, or higher-than-expected frequency versus RSI or control arm will prompt targeted review, potential CAPAs, and consideration of RSI/consent updates per ISO 14155/ISO 14971 [1,3].

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8.6 Unanticipated Adverse Device Effects (UADEs)

Definition, criteria, and scope

For this study, a Unanticipated Adverse Device Effect (UADE) is defined per US IDE regulation as a serious adverse effect on health or safety, or death, caused by, or associated with, the investigational device, which was not previously identified in nature, severity, or incidence in the investigational plan/Investigator's Brochure (IB)/Instructions for Use (IFU), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [1]. Under EU MDR, all serious adverse events (SAEs) and any device deficiency that might have led to an SAE are reportable; "unanticipated" informs risk management and information updates but does not limit SAE reportability [2,3]. UADE assessment is made against the current, version-controlled Reference Safety Information (RSI) comprising the IB/Device Dossier for the inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB, SRN SE-MF-000028534), the IFU/training materials for the app-module, spirometer, and Airflow Trainer, and the manufacturer's ISO 14971 risk management file [2,4–6].

An event is a UADE if all apply:

- Serious (death, life-threatening, inpatient hospitalization or prolongation, persistent/significant disability/incapacity, congenital anomaly/birth defect, or other medically important condition) [2,7].
- Caused by, or associated with, the investigational app-module or associated study devices/procedures (spirometer, Airflow Trainer, coached inspiratory maneuvers) [1,2].
- Unanticipated: not previously identified in nature, severity, or incidence in the RSI, or any other unanticipated serious problem affecting subject rights, safety, or welfare [1–3].

Immediate actions and patient management

Upon first awareness of a potential UADE from any source (participant report, clinical contact, hospitalization, app log alert, device deficiency/complaint):

- Provide urgent clinical evaluation and standard-of-care treatment; interrupt the investigational app-module and/or associated procedures if clinically indicated to protect the participant [2,7].
- If a device deficiency or malfunction is suspected, quarantine the affected device(s) or software build where feasible; document identifiers (app build/version, device serials) and preserve relevant logs for investigation [2,5].
- Determine whether the event meets UADE criteria; if uncertain, treat as potential UADE and escalate [1–3].
- Initiate reporting without delay per timelines below and begin contemporaneous source documentation of all assessments, interventions, and outcomes [2,7].

Classification and reporting decision tree

26. Identify event and stabilize the participant; confirm SAE criteria.
27. Assess relatedness to the investigational app-module and/or associated procedures/devices (possibly/probably/definitely vs not/unlikely).
28. Compare the event's nature, severity, and incidence to the RSI (IB/IFU/risk file).
29. Classify:

- Not serious → Not a UADE; manage and report per non-serious AE process. Reassess if severity increases [2,7].
- Serious + related + expected → SAE; report per SAE timelines (expedited under MDR) [2,3,7].
- Serious + related + unexpected → Potential UADE (US IDE) and reportable SAE (EU MDR). Expedite per UADE and MDR timelines [1–3].
- Serious + unrelated (clear alternative cause) → SAE; report per SAE timelines (MDR) [2,3].

30. Escalate immediately by phone to the Sponsor Medical Monitor for all potential UADEs; consider ad hoc DSMB review for deaths, life-threatening events, or emerging clusters within 72 hours per charter [2,7].

Timelines, recipients, and required content

- Site to Sponsor (all potential UADEs):

- Initial notification: immediately/within 24 hours of first awareness by the site; include minimum case elements and clear flag as "Potential UADE" [2,7].
- Follow-up: submit comprehensive update within 10 calendar days and within 24 hours of any material change (seriousness, causality, outcome) until resolution/stabilization [2,7].

- Site to IRB/IEC:

- UADEs and fatal/life-threatening, related and unexpected SAEs: without delay per IRB/IEC policy (typically within 24–48 hours); other SAEs per local requirements (often within 5–10 business days) [2,7].

- Sponsor to Regulators:

- US IDE UADEs: report to FDA and all reviewing IRBs within 10 working days after first receipt of the UADE report; investigators must report to the sponsor and reviewing IRB within 10 working days of first learning of the UADE [1].
- EU/EEA MDR: report SAEs and device deficiencies that might have led to an SAE per MDCG 2020-10/1 timelines—within 2 days for serious public health threats; within 7 days for deaths or unanticipated serious deterioration in health (with additional 8 days for follow-up if incomplete); within 15 days for other reportable SAEs [2,3].
- Manufacturer MDR (21 CFR 803) obligations, if applicable, will be fulfilled separately from IDE/MDR clinical investigation reporting [8].

Regulator form checklist and minimum data set

Each initial and follow-up submission should include, as applicable [2,3,7]:

- Study identifiers; site and coded participant ID; age/sex; randomization arm (blinded unless unblinding is required for safety).
- Event term and narrative (chronology, diagnostics, clinical course); seriousness criterion; CTCAE grade or equivalent; outcome.
- Causality to app-module/procedures; expectedness rationale citing RSI (document, version, effective date).
- Actions taken with device/procedures (interruption/discontinuation, retraining, software update, corrective actions).
- Treating facility details; hospitalization dates; key clinical data (vitals, labs, imaging, discharge summary).
- Device/software identifiers: app name/build/version; spirometer/Airflow Trainer model/serial; any companion hardware; screenshots/log extracts if available.

- Device deficiency/complaint linkage: complaint/deficiency ID; preliminary investigation summary and returned device status.
- Reporter details; PI signature/date; sponsor case ID; dates of notifications to IRB/IEC and authorities and acknowledgments, if available.

Ongoing follow-up, tracking, and reconciliation

- Sites will update UADE cases at each clinical contact and upon receipt of new information until resolution, stabilization, or return to baseline. Maximal feasible follow-up is required for device-related SAEs/UADEs, even beyond the nominal safety window [2].
- The sponsor will maintain a reconciled safety case tracker linking the EDC AE/SAE module, the device complaint/deficiency system, and regulatory submissions, with query logs and closure documentation per ALCOA principles in validated systems [2,5,7].
- Root-cause analysis will be coordinated by the sponsor/manufacturer per ISO 14971 and usability engineering (IEC 62366-1), incorporating device log forensics and human-factors assessment where applicable; corrective and preventive actions (CAPAs) will be tracked to closure [4–6].

Roles and responsibilities

- Investigator/site:

- Ensure immediate clinical management; classify and report potential UADEs as above; obtain and upload de-identified source records; quarantine implicated device(s) where feasible; and document all interventions and counseling provided [2,7].
- Notify the sponsor immediately by phone/email of potential UADEs; notify the IRB/IEC per policy; support device investigation and return logistics when requested [1–3,7].

- Sponsor/Coordinating Center:

- Acknowledge receipt; confirm seriousness, relatedness, and expectedness; determine UADE status; code events (MedDRA); prepare and submit expedited reports to regulators/IRBs within mandated timelines; inform all investigators and the DSMB of material safety issues [1–3,7,8].
- Lead risk–benefit reassessment, update RSI/IB/IFU and training as needed, implement CAPAs, and propose protocol amendments when required [2,4–6].

- DSMB:

- Review UADEs and emerging signals at scheduled meetings and ad hoc within 72 hours for deaths, life-threatening events, or urgent concerns; provide recommendations to continue, modify, pause, or terminate the study per charter [2,7].

Participant communication, re-consent, and study modifications

- If a UADE or aggregate safety analysis identifies a new or increased risk, the sponsor will promptly update the RSI/IB/IFU and inform investigators, IRB/IEC, and regulators as applicable [2,4–6].
- Re-consent is required when new information may affect a participant's willingness to continue. Sites will:

- Communicate the new risk in clear language approved by the IRB/IEC.
- Obtain and document re-consent before continued participation, unless urgent safety measures necessitate immediate changes to protect participants, in which case consent updates will follow as soon as feasible [2,7].

- Urgent safety measures (e.g., temporary suspension of specific features, software rollback, enhanced monitoring, or retraining) may be implemented immediately to protect participants, with notification to IRB/IEC and regulators without delay per local requirements [2,3,7].

Study-specific considerations for the inhalation app-module

- Given the software-enabled coaching of inspiratory maneuvers and dependence of DPI performance on inspiratory flow, UADEs of interest include, but are not limited to, unanticipated serious bronchospasm, syncope with injury related to maneuver coaching, or serious events following a novel use-error pattern precipitated by app feedback or device malfunction [2,5].
- Any suspected software defect or connectivity failure temporally associated with a serious outcome must be logged as both a UADE (if criteria met) and a device deficiency, with cross-referenced investigations and expedited reporting per above [2,3,5].

Documentation standards and inspection readiness

- All UADE-related data must be contemporaneously documented in source records and the electronic case report form (eCRF), signed and dated by the PI/sub-investigator, and traceable to all submissions and acknowledgments. Systems must maintain audit trails, and records retained per regulatory requirements for device investigations [2,7].
- Sites and the sponsor must be prepared to provide complete case files, device investigation reports, correspondence, and CAPA evidence during monitoring visits and regulatory inspections [2,3,7].

References

1. US Food and Drug Administration. 21 CFR Part 812—Investigational Device Exemptions (including UADE definition and 812.150 reporting). 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812
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8.7 Adverse Event Follow-up

Principles and window for AE follow-up

- All adverse events (AEs), including serious adverse events (SAEs), will be followed from onset through resolution, stabilization, or return to baseline, with maximal feasible follow-up, consistent with ISO 14155 and ICH-GCP [1,2].
- The nominal safety follow-up window extends through 30 days after the last protocol-specific interaction or last use of the investigational inhalation app-module, whichever is later; SAEs

and device-related AEs may require follow-up beyond this window until medically resolved or adequately characterized [1,2].

- The investigator reassesses seriousness, severity (CTCAE v5.0 or protocol scale), causality, and expectedness at every update; the sponsor performs independent medical review and ensures regulatory reporting per MDR/MDCG and FDA IDE/UADE requirements when applicable [1–5].

AE follow-up schedule

Timepoint/period	AE follow-up activities	Minimum reassessment cadence	Documentation deadlines
During intervention (weeks 0–6/12)	Review AEs at each scheduled/unscheduled visit; monitor app/ePRO and device logs; instruct participants to report changes promptly	At every contact; between contacts via weekly app prompts and as-needed calls	Non-serious AE entry/updates within 5 business days; SAEs initial within 24 hours, follow-up within 10 calendar days [1–4]
End-of-intervention visit	Full AE review; determine status/outcome; plan post-intervention safety follow-up if not resolved	Same-day assessment	Same-day source; eCRF within 5 business days (non-serious); SAE per timelines
Safety follow-up 30 (±7) days after last app use	Reassess all ongoing AEs/SAEs; update outcomes; document sequelae	Single scheduled visit/contact minimum	As above
Ongoing unresolved non-serious AEs after the 30-day safety window	If clinically meaningful or related (possibly, probably, definitely) to device/procedures: continue follow-up to resolution/stabilization	Grade 1: at next routine contact or within 14 days; Grade ≥2: at least every 14 days until improvement; escalate if worsening	Update eCRF within 5 business days of new info [1,2,6]
Ongoing SAEs after the 30-day safety window	Continue active follow-up until resolution, stabilization, or return to baseline; obtain hospital records and specialist notes as feasible	Inpatient: at least weekly; Post-discharge: at least every 14 days for device/procedure-related SAEs; monthly thereafter if stable	Initial within 24 hours; substantive updates within 10 calendar days; further material changes within 24 hours [1–4]
Device deficiency–associated AEs	Cross-reference deficiency/complaint ID; incorporate device investigation outcomes; update causality as new evidence emerges	Align with AE/SAE cadence; additional contact within 7 days after device investigation findings	eCRF and complaint system linkage within 5 business days; expedited if reportable [1,3,4]

Criteria for AE outcome and closure

- Resolved: Symptoms/findings have ceased and clinically relevant measures have returned to pre-event baseline or to normal/acceptable limits without expected further sequelae [1,2,6].
- Resolved with sequelae: Event ended but resulted in persistent/significant change (e.g., impairment, new diagnosis) documented as sequelae; record date and nature of sequelae [1,2].
- Stabilized: No clinically meaningful change across at least two consecutive reassessments over ≥30 days (or ≥90 days for chronic conditions) and further change is not anticipated; document residual status [1,2].
- Ongoing: Event persists without meeting resolution/stabilization criteria at the last contact.

- Fatal: Death occurred; document date, cause (if known), and relation to device/procedures; obtain death certificate/autopsy if available [1–4].
- Not assessable/Lost to follow-up (LTFU): Despite reasonable documented efforts (minimum three attempts via different modalities over ≥14 days), outcome cannot be verified; classify as "not assessable" and close administratively with PI justification [1,2].

Outcome classification must be supported by contemporaneous clinical data (visit notes, hospital records, labs/imaging as relevant). Causality and expectedness must be reassessed at outcome or closure [1–4,6].

Reassessment procedures for unresolved AEs

- Non-serious AEs:

- Grade 1: Reassess by next scheduled contact or within 14 days; increase cadence if symptoms worsen or new information arises.
- Grade ≥2: Reassess at least every 14 days until improved to Grade 1 or resolved; consider targeted clinical evaluation or device retraining/modification per investigator judgment [1,2,6].

- SAEs:

- During hospitalization: obtain interim updates at least weekly; after discharge, reassess at least every 14 days if device/procedure-related or if outcome remains clinically uncertain; otherwise monthly until resolution/stabilization [1–4].

- At each reassessment: update severity grade, seriousness, causality (to app-module, spirometer/Airflow Trainer/procedures, study participation), expectedness versus current RSI, action taken, and outcome; recode MedDRA terms if the clinical concept changes materially [1–4,6,7].

Handling and reporting late, treatment-related SAEs after protocol-defined follow-up

- Investigator obligations:

- If the site becomes aware of a serious event reasonably related to the investigational app-module or associated devices/procedures after the formal safety window has ended, the event must be reported to the sponsor immediately/within 24 hours and to the IRB/IEC per local policy, and followed to resolution/stabilization as feasible [1–4].

- Sponsor obligations:

- Determine UADE status (US IDE) and MDR reportability; submit expedited reports within mandated timelines (e.g., UADE to FDA within 10 working days of first receipt; MDR/MDCG timelines of 2/7/15 days based on category) [3–5].
- Reopen the case in the safety database if previously closed; update RSI/IB/IFU, consent, and risk management file as warranted by new information [1,3–5].

- Documentation:

- Late SAEs are documented with the same minimum data set as in-window SAEs; the eCRF/safety database must reflect "late SAE" status with clear chronology and rationale for relatedness [1–4].

Procedures for updating outcomes and documentation

- Data entry and timelines:

- SAEs: initial sponsor notification within 24 hours; follow-up narrative and documents within 10 calendar days; material changes within 24 hours of awareness [1–4].
- Non-serious AEs: updates within 5 business days of new information [1,2].

- Source documentation must include: clinical course, interventions, diagnostics, outcome; device/software identifiers (app version/build; spirometer/Airflow Trainer model/serial); cross-reference to device deficiency/complaint ID where applicable; PI/signature/date [1–4].
- Causality/expectedness revision: Required when new evidence (e.g., device investigation, DSMB recommendations) emerges; document RSI version/date used for reassessment [1–4].

- MedDRA coding: Update preferred term and SOC if the medical concept changes (e.g., “dizziness” evolving to “syncope”); maintain audit trail of code changes per MedDRA Points to Consider [7].
- Query management: Address sponsor/monitor queries within 5 business days (or provide an interim timeline) and upload requested hospital records promptly; maintain a log of pending items until closure [1,2].

Participant contact, retention, and LTFU mitigation

- Preferred contact hierarchy: phone, secure messaging within the app, email, and mailed letter if needed; document each attempt with date/time and modality [1,2].
- If a participant withdraws from intervention but not from safety follow-up, continue AE follow-up per this section; if consent for further contact is withdrawn, retain and report safety-critical information already obtained and seek permission to access external records as permitted by law/IRB policy [1,2].

AE follow-up tracking tool (site-level)

Field	Description/entry guidance
Site/Subject ID	Coded identifiers only; match EDC
AE/SAE term (MedDRA PT)	Verbatim term and coded PT/SOC
Onset date/time	First date/time criteria met
Current severity/seriousness	CTCAE grade or protocol scale; SAE criterion if applicable [6]
Relatedness/expectedness	To app-module, spirometer/Airflow Trainer/procedures, study participation; expected vs unexpected with RSI citation/version [1–4]
Actions taken	Medical care; device/procedure changes; retraining; software update; quarantine
Next reassessment due date	Auto-calc per cadence rules; editable with justification
Latest update summary	Brief clinical course since last entry
Outstanding documents	e.g., discharge summary, imaging, device logs; target receipt date
Device deficiency/complaint ID	Cross-reference; investigation status
Outcome status/date	Resolved, resolving, stabilized, ongoing, resolved with sequelae, fatal, not assessable/LTFU
PI review/signature/date	Confirms current classification and plan

The tracking tool must be version-controlled, reconciled with the EDC and sponsor safety database, and retained per record-retention policy to ensure traceability and inspection readiness [1,2].

Case closure and reconciliation

- A case may be closed when outcome criteria are met and no further clinically meaningful information is expected. For device/procedure-related SAEs, closure requires confirmation that regulatory reporting is complete, device complaint investigations are linked, and CAPAs (if any) are documented to closure [1–4].
- Prior to database lock, the sponsor will reconcile AE/SAE cases across the EDC, safety database, and device complaint system and confirm alignment with regulatory submissions and acknowledgments; discrepancies require documented resolution and PI re-signature if substantive changes are made [1–4].

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1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical

devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
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9 DATA MONITORING AND QUALITY CONTROL

9.1 Case Report Forms (CRFs)

Overview and eClinical systems

Electronic case report forms (eCRFs) will be implemented in a validated electronic data capture (EDC) system compliant with ISO 14155, ICH E6(R2), FDA 21 CFR Part 11, and EU GMP Annex 11 requirements for electronic records, electronic signatures, system validation, security, and audit trails [1–4]. Role-based access control, encryption in transit and at rest, and full audit trails for all create/read/update/delete actions and data extracts will be enforced. Personal data will be processed in accordance with applicable privacy regulations (e.g., GDPR) and the sponsor’s data protection policies [5].

Device/app telemetry and spirometry data produced by the AsthmaTuner platform and associated devices (spirometer, Airflow Trainer) will be transferred to the EDC via validated data import processes using a standard interchange format (e.g., CDISC ODM-XML or equivalent), with reconciliation to eCRF fields and system-to-system audit trails maintained for each batch [1,3,6]. MedDRA will be used for adverse event coding and WHO Drug for concomitant medication coding [7,8].

CRF design, testing (IQ/OQ/PQ), and deployment will follow formal change control and version control procedures. All CRF revisions will be tracked with effective dates, rationale, and impact assessments; mid-study updates will be implemented only after user acceptance testing (UAT), site training, and IRB/IEC approvals as required [1–4].

CRF schedule by visit

Visit/timepoint	Forms to complete	Entry timeline
Screening/Baseline (Day −14 to 0)	Informed consent confirmation; Demographics; Medical history; Respiratory history; Baseline inhaler assessment; Concomitant medications; Physical exam/vitals; Baseline spirometry (if applicable); Baseline labs/imaging (if clinically indicated); Eligibility checklist; Randomization readiness	Within 5 business days of visit completion [1,2]
Randomization/Initiation (Day 0)	Randomization; Procedure/Training CRF (standardized education for both arms; app-module activation for intervention arm); Device	Randomization same-day; remaining

	accountability (spirometer/Airflow Trainer/app access provision); AE/SAE review; Concomitant medications update	within 5 business days [1,2]
Interim training/monitoring contacts (Weeks 1–2)	Procedure/Training CRF (session details or remote check-in); Device accountability; AE/SAE; Concomitant medications; Spirometry/app metrics import (if applicable)	Within 5 business days; SAEs within 24 hours [1–3,7]
Mid-program visit (Weeks 3–4)	Procedure/Training CRF; Usability/feasibility questionnaire; Device accountability; AE/SAE; Concomitant medications; Interim spirometry/app metrics	Within 5 business days; SAEs within 24 hours
Pre-endpoint visit (Weeks 5–6)	Procedure/Training CRF; Device accountability; AE/SAE; Concomitant medications	Within 5 business days
Primary endpoint visit (Weeks 6–12)	Primary endpoint assessment of inhalation technique success; Spirometry/app metrics; Usability/feasibility questionnaire; Device accountability; AE/SAE; Concomitant medications; Study status	Within 5 business days; SAEs within 24 hours
Safety follow-up (30 ± 7 days after last app use)	AE/SAE follow-up; Concomitant medications; Device accountability (final); End-of-study status	Within 5 business days; SAEs within 24 hours
Unscheduled/early termination	Reason for unscheduled/early termination; AE/SAE; Concomitant medications; Device accountability; Endpoint if feasible	Within 5 business days; SAEs within 24 hours

CRF templates

The following eCRF modules will be available. Mandatory fields are indicated in the data dictionary; system edit checks apply.

- Demographics

- Study/site/subject IDs; initials; date of birth; sex at birth; race/ethnicity (per local standards); height; weight; smoking status (current/former/never); pack-years; country; consent date; consent version.

- Medical history

- Asthma/COPD diagnosis (ICD code, year of diagnosis); exacerbation history (number past 12 months); comorbidities (cardiovascular, diabetes, OSA, other pulmonary); allergy history; prior inhaler technique training (yes/no; date).

- Respiratory history and baseline inhaler assessment

- Inhaler type(s) used: DPI, MDI, or both; device brand/model; daily controller and reliever regimen; baseline inhalation technique assessment per standardized criteria (pass/fail items); baseline PIF (if available); baseline symptoms scores (if applicable to protocol).

- Procedure/Training

- Visit type (in-person/remote); arm (intervention/control); standardized education delivered (Y/N; checklist); app-module activation (Y/N; date/time; app build/version); training session count/duration; number of coached inspiratory attempts; PIF/time-to-PIF/inspiration time summary (mean/best); retraining provided (Y/N; reason); protocol deviations.

- Laboratory results

- Only if clinically indicated: test name, specimen date/time, value, unit, normal range, clinical significance (Y/N), action taken.

- Imaging

- Only if clinically indicated: modality, date, body region, key findings (narrative), clinical significance (Y/N), action taken.

- Spirometry/app metrics

- Device type (spirometer/Airflow Trainer); model/serial; calibration check; FEV1, FVC, FEV1/FVC, PEF (predicted/reference, unit); PIF/time-to-PIF/inspiration time from app-module; data import batch ID; verification status (import confirmed Y/N).

- Concomitant medications

- WHO Drug coded generic name; brand; route; dose; unit; frequency; indication; start/stop dates; ongoing at visit; changes since last visit (Y/N).

- Adverse events/Serious adverse events

- Event term (verbatim and MedDRA PT); onset/stop dates; seriousness; severity grade (CTCAE v5.0 or protocol scale); outcome; relatedness (app-module; associated devices/procedures; study participation); expectedness versus RSI; action taken with device; hospitalization details; device/software identifiers; device deficiency/complaint ID; narrative; PI assessment; follow-up.

- Device accountability

- Device category (spirometer/Airflow Trainer/app access); device ID/serial; date dispensed/returned; condition; software/app build; updates applied; quarantine status; loss/damage; reconciliation status.

- Follow-up/End of study

- Visit completion status; primary endpoint status assessed (Y/N); reason if not; early termination reason; safety follow-up plan; re-consent (if applicable); overall study status.

Data dictionary, data types, ranges, and edit checks

Field name	Module	Data type	Allowed values/range	Key edit checks
subject_id	All	Text (regex)	Site-unique per format [A-Z]{2}[0-9]{4}	Must be unique; immutable after randomization
date_of_birth	Demographics	Date	1900-01-01 to today	Age at consent ≥ 16 years; else hard stop [1]
sex_at_birth	Demographics	Categorical	Male; Female; Intersex; Prefer not to say	Required; cannot be blank
height_cm	Demographics	Integer	100–220 cm	If outside 120–210 trigger query
weight_kg	Demographics	Decimal	30.0–250.0 kg	BMI auto-calc; extreme BMI > 50 prompts confirmation
smoking_status	Demographics	Categorical	Current; Former; Never	If Current or Former, require pack_years
pack_years	Demographics	Decimal	0.0–200.0	Required if smoking_status ≠ Never
diagnosis_code	Medical history	Text (ICD-10)	J45.x, J44.x, etc.	Must be valid ICD-10 code
diagnosis_year	Medical history	Integer (YYYY)	1950–current year	Cannot be > current year
inhaler_type_stratum	Baseline	Categorical	DPI; MDI; Both	Must match randomization stratum
baseline_technique_pass_items	Baseline	Integer	0–N (per checklist)	N derived from standardized criteria

app_build_version	Procedure	Text	>5.4.13.5 (semantic version)	Must be parsable; flag if downgraded
session_count	Procedure	Integer	0–10 per visit	>10 requires deviation note
coached_attempts	Procedure	Integer	0–50 per visit	>50 triggers alert for overuse
pif_l_min	Procedure/Spirometry	Decimal	0.0–300.0 L/min	≤0 or >300 hard stop; biologic plausibility check
ttpif_ms	Procedure/Spirometry	Integer	0–5000 ms	Missing requires reason
insp_time_ms	Procedure/Spirometry	Integer	0–10000 ms	Cross-check with maneuver count
fev1_l	Spirometry	Decimal	0.2–8.0 L	If change >20% vs prior, prompt confirmation [5]
fvc_l	Spirometry	Decimal	0.3–10.0 L	Ratio FEV1/FVC auto-calc
med_name_generic	Medications	Text (coded)	WHO Drug dictionary	Code to ATC; require route
med_route	Medications	Categorical	Inhaled; Oral; SC; IV; IM; Other	If Other, require specify text
ae_term_verb	AE/SAE	Text	Free text	MedDRA coding required [7]
meddra_pt	AE/SAE	Text (coded)	MedDRA v25.x+	Mandatory for lock; SOC auto-link [7]
ae_onset_date	AE/SAE	Date/time	1900-01-01 to today	Must be ≤ report date
ae_serious	AE/SAE	Categorical	Yes; No	If Yes, require SAE criterion, 24h clock
sae_criterion	AE/SAE	Categorical	Death; Life-threatening; Hospitalization; Disability; Congenital anomaly; Other medically important	Required if serious
ae_severity	AE/SAE	Categorical	CTCAE Grade 1–5 or Mild/Moderate/Severe	Required; Grade 5 implies Death outcome [7]

ae_relatedness	AE/SAE	Multi-categorical	Relatedness to app-module; associated devices/procedures; study participation: Not/Unlikely/Possible/Probable/Definite	At least one relationship required
ae_expectedness	AE/SAE	Categorical	Expected; Unexpected	If Unexpected + Related + Serious, flag UADE [1–3]
device_deficiency_id	AE/SAE/Device accountability	Text	Alphanumeric	Required if deficiency suspected [1]
device_id_serial	Device accountability	Text	Manufacturer format	Cross-check with site inventory
dispense_date	Device accountability	Date	Today or past	Cannot be future-dated
return_date	Device accountability	Date	≥ dispense_date	If missing at closeout, require explanation
imaging_modality	Imaging	Categorical	CXR; CT; MRI; US; Other	Required if imaging performed
lab_test_name	Laboratory	Text (coded)	Local lab dictionary	Unit and reference range required

System edit checks will include range checks, cross-form consistency (e.g., inhaler stratum equals randomization stratum), temporal plausibility (e.g., AE onset after consent), conditional requirements (e.g., SAE criterion if serious = Yes), and dictionary compliance for coded fields [1–4,7,8].

User-role matrix and account request

Role	Permissions	Typical users	Training prerequisites
Principal Investigator (PI)	Approve/reject user access; enter/edit data; respond to queries; e-sign CRFs; SAE attestations; lock-ready sign-off	Site PI	GCP; protocol; EDC; safety reporting; Part 11/Annex 11 overview [1–4]
Sub-Investigator	Enter/edit data; respond to queries; e-sign assigned CRFs	Sub-I/Clinician	GCP; protocol; EDC
Study Coordinator	Enter/edit data; manage queries; device accountability; import verification	Study nurse/coordinator	Protocol; EDC; device handling
Unblinded Device Specialist	Device accountability; app activation; import verification; no access to treatment assignments beyond role	Device tech	Device SOPs; EDC
Pharmacovigilance/Safety	Read AE/SAE; create queries; code AEs; lock AEs	Sponsor safety staff	Safety systems; MedDRA [7]
Medical Monitor	Read all; SAE review; sign medical assessments; unlock/lock AEs	Sponsor physician	GCP; safety

Data Manager	CRF design; dictionary management; listings; queries; database lock	Sponsor DM	EDC admin; CDISC/ODM [6]
Biostatistician	Read-only; exports; blinded data reviews	Sponsor statistician	SAP; EDC reports
Monitor (CRA)	Read; SDV/SDR; create/close queries; source upload view	CRA	GCP; monitoring; EDC
Auditor/Inspector	Read-only; audit trail and documents	QA/regulatory	Audit SOPs
System Administrator	User provisioning; role assignment; configuration; backups; release management	EDC vendor/sponsor IT	CSV; security; change control [3,4]

Account request form (electronic):

- User details: name, email, phone, organization, site number.
- Requested role(s) and justification; supervisor/PI approval.
- Certifications: GCP completion date; protocol and EDC training completion dates.
- Data privacy acknowledgment and confidentiality agreement.
- Sponsor authorization and system admin activation date.

CRF completion guidelines

- Source data and ALCOA+: All eCRF entries must be attributable, legible, contemporaneous, original, accurate, complete, and consistent with source documents (clinic notes, app/device logs, hospital records). Each data item must be traceable to a verifiable source; any transcription must be verified during monitoring [1,2].
- Timeliness:

- Baseline/procedure/endpoint/device accountability/medication updates: within 5 business days of visit.
- AE/SAE: initial SAE within 24 hours of awareness; follow-up within 10 calendar days; non-serious AE entries and updates within 5 business days [1–3].
- Query responses: within 5 business days or provide an interim timeline.

- Signatures: The PI or delegated Sub-I will e-sign CRFs per delegation log. SAE assessments require PI/Sub-I signature; safety follow-up updates require prompt re-signature after material changes [1–4].
- Corrections: Corrections must not obscure original entries; the EDC audit trail must capture prior value, new value, user ID, date/time, and reason for change. No overwriting of signed data without documented unlock by Data Management [3,4].
- Coding: AEs will be coded with MedDRA; medications with WHO Drug. Sites must provide sufficient clinical detail to enable accurate coding (e.g., diagnoses rather than symptoms when confirmed) [7,8].
- Endpoint integrity: Primary endpoint fields must be complete and consistent with app/telemetry summaries and source checklists. Any imputation or adjudication will follow the SAP; sites must not infer values [1].
- Deviations: Data affected by protocol deviations must be flagged and described in the Deviation log; related data points require reviewer attention notes.

Paper CRFs and eSource handling

- Primary data capture will be electronic. If paper worksheets are used (e.g., downtime or participant-facing checklists), they are controlled documents with version numbers and must be completed in indelible ink, signed/dated by the author, and transcribed into the EDC within 2 business days after system restoration. Reconciliation logs will link paper source to eCRF entries; originals will be filed in the Investigator Site File (ISF) [1–4].

- eSource from the AsthmaTuner app and associated devices will be retained in validated repositories with audit trails. Any direct data imports will be documented with batch IDs; site verification of successful import is required on the Spirometry/App Metrics CRF [1,6].

Audit trail requirements

- The EDC will maintain a non-modifiable audit trail capturing user ID, timestamp (UTC), old/new values, reason for change, and electronic signature events. Audit trail review will be available to monitors, auditors, and inspectors. Data exports for analysis will be checksum-verified and logged [1–4].

CRF version control and change management

- All CRFs will carry a system version and effective date. Changes require:

- Impact assessment (data integrity, statistics, safety).
- Updated specifications and testing (UAT evidence archived).
- Site notification and training completion records.
- IRB/IEC notification/approval where required.
- Controlled go-live with cutover plan and migration rules; legacy data mapping documented [1–4,6].

Training prerequisites for site access

- Mandatory trainings: protocol/procedures, GCP, EDC use, safety reporting, device/app handling, privacy/security. Completion must be documented before account activation and repeated upon significant amendments or system upgrades [1–4,5].
- Competency checks: role-appropriate proficiency testing during UAT or sandbox sessions; remediation if deficiencies are identified.

Data listings, reconciliation, and lock

- Routine reconciliations: AE–device deficiency linkage, randomization vs stratum, device accountability vs inventory, telemetry imports vs eCRF summaries, and concomitant medication changes vs AE narratives.
- Data lock: requires resolution/closure of all queries, completion and signature of all required CRFs, coding finalization, and PI confirmation. A formal database lock procedure will be executed with role-based locks and documented approvals per SOPs [1–4].

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9.2 Data Reporting

Data entry service-level agreement (SLA) and escalation

- Scope and timing standards:

- Visit-based CRFs (baseline, procedure/training, spirometry/app metrics, device accountability, concomitant medications, endpoint): entered and submitted within 5 business days of visit completion, aligned with ALCOA+ and system audit-trail requirements [1,2].
- Non-serious AE entries and updates: within 5 business days of awareness; SAE initial reporting within 24 hours and follow-up within 10 calendar days; UADE/expedited safety per regulatory timelines described elsewhere in the protocol [1,2].
- Data import verification for device/app telemetry: site verification of each batch within 5 business days of import availability in EDC; unresolved mismatches escalated within 2 business days to Data Management (DM) [1–4,8].
- Coding turnaround (MedDRA for AEs, WHO Drug for medications): within 10 business days after site submission; coding queries raised within 5 business days of coding attempt [2,7].

- Quality thresholds:

- ≥95% of required CRFs complete within SLA during active enrollment; ≥98% before scheduled data review meetings/data cuts.
- ≤5% overdue queries (>5 business days open) per site at any time; corrective plans required if exceeded.

- Escalation pathway and timelines:

- Day 6 (business): automated reminder to assignee and study coordinator for any overdue CRF or query.
- Day 8: CRA notifies Site PI and Sponsor DM; site provides a written catch-up plan within 2 business days.
- Day 12: escalation to Sponsor Medical Monitor and Clinical Operations Lead; site may be placed on enhanced monitoring or temporary enrollment hold pending remediation.
- Persistent non-compliance (>2 consecutive months below thresholds) triggers CAPA per sponsor QA SOPs, with retraining and targeted monitoring [1,2].

Data query workflow: roles, timelines, documentation

- Roles:

- Site staff (PI/Sub-I/Coordinator): primary responders; ensure source verification and PI/sub-I medical attestations where required.
- CRA/Monitor: raises/clarifies queries, verifies source, closes when resolved; prioritizes critical data affecting primary endpoint, safety, and randomization per risk-based monitoring plan [1,2].
- Data Manager: configures edit checks, generates listings, triages system queries, adjudicates complex discrepancies, manages unlocks and freezes.
- Safety/Pharmacovigilance: initiates and manages safety-critical queries; ensures alignment with regulatory submissions.
- Biostatistician: conducts blinded data reviews; requests data clarifications via DM.

- Query lifecycle and timelines:

- Creation: automated at entry via programmed edit checks, or manual by CRA/DM/Safety after review [1–4].
- Notification: system email within 1 hour of query creation to assigned site users.
- Response: within 5 business days with corrected data or documented explanation and supporting

source uploads. If additional time is required, provide an interim response with a target date.
- Verification/closure: within 3 business days by CRA/DM after site response; safety-critical queries are prioritized for same-day review when feasible.
- Documentation: each query retains full audit trail (originator, timestamp, text, classification, responses, attachments, closure rationale) per 21 CFR Part 11/Annex 11; cross-referenced to subject, visit, and form [3,4].

- Query priority classes:

- Critical: impacts participant safety, UADE/SAE reporting, primary endpoint integrity, treatment allocation concealment, or subject eligibility. Response expected within 2 business days; immediate same-day phone escalation by CRA for UADE/SAE discrepancies [1,2].
- Major: affects key secondary endpoints or important covariates; standard 5 business days.
- Minor: formatting, administrative fields; 10 business days when not on critical path to data cut.

- Freeze/unfreeze rules:

- Forms/fields may be frozen by DM after resolution to prevent further edits. Unfreeze requires written justification and DM approval; if post-signature changes occur, PI re-signature is required with documented reason for change [1–4].

Standard operational reports and templates

- Reporting cadence:

- During active enrollment: weekly site-level and program-level reports for enrollment, timeliness, missing forms, and open queries; biweekly protocol deviation and device accountability reports; monthly safety summaries.
- During follow-up only: biweekly operational reports; monthly safety summaries and AE reconciliation; quarterly DSMB packages in blinded aggregate unless unblinding is safety-necessary [1,2].
- Pre–data cut/lock: targeted daily listings and exception reports until all locks are complete.

- Distribution and blinding:

- Site-facing reports: blinded to randomized assignment; show “Intervention” vs “Control” only if blinding is preserved for site team as per design. Unblinded reports limited to designated unblinded personnel (e.g., device specialists, selected sponsor DM/IT staff) under access controls [1,2].
- Sponsor aggregate: blinded to treatment unless SAP-approved unblinded review is triggered and restricted to an independent unblinded team; DSMB receives unblinded or partially unblinded data per charter [1,2].

- Templates (field minimums):

- Enrollment report (site and overall)
  - Site ID; active subjects; weekly enrollments; screen failures (counts and top reasons); randomizations by inhaler stratum (DPI/MDI/Both); time from consent to randomization (median, range); pending eligibility verifications.
- Data timeliness report
  - Site ID; visits due in period; visits entered on time (%); median days from visit to entry; overdue forms (count/list); telemetry import verification status (% verified); SLA compliance flags.
- Open queries report
  - Site/Subject/Visit/Form/Field; query class (Critical/Major/Minor); open date/age; last site activity; CRA/DM owner; next action date; overdue flag; count per category and per subject.
- Missing and partial forms
  - Site/Subject; scheduled visit/date; form name; status (missing/partial); criticality (endpoint/safety/other); target resolution date; comments.
- Protocol deviations
  - Site/Subject; date; deviation category (eligibility, consent, visit window, treatment, endpoint assessment, data entry, device accountability); severity (major/minor); impact (safety/data integrity); corrective action; status (open/closed); IRB/IEC notification required (Y/N).
- Safety summary (aggregate, blinded by arm unless otherwise approved)
  - Reporting interval; subjects at risk; AE/SAE counts; incidence by MedDRA SOC/PT; severity distribution; relatedness; expectedness; device deficiency–linked events; exposure-adjusted rates; cumulative overview; reconciliation status with complaint/deficiency system [1,2,7].

- Output formats:

- Interactive dashboards within EDC for real-time views; exportable CSV/PDF listings with version/time stamps and checksum logs. All distributions tracked and archived per sponsor SOPs [1–

4].

Automated and manual data checks

- Automated checks (at entry/import):
  - Field-level range, format, and conditional logic checks; cross-form/temporal plausibility (e.g., AE onset after consent); dictionary compliance (MedDRA, WHO Drug); telemetry–eCRF reconciliation (batch ID, subject, timestamps, device IDs) [1–4,7,8].
- Batch edit checks and statistical surveillance:
  - Routine listings to detect outliers, heaping, improbable repeats; duplicate subjects; unusual site-level distributions; primary endpoint completeness; re-randomization risks; timeliness metrics. Signal detection listings reviewed by DM/biostatistics monthly.
- Manual reviews:
  - Source data verification (SDV)/source data review (SDR) per risk-based monitoring plan; targeted review of primary endpoint and safety-critical fields; reconciliation of AE–device deficiency–regulatory submissions [1,2].
- Discrepancy management:
  - Exceptions documented in the EDC with CAPA tracking for systematic issues; retraining assigned where patterns recur.

Blinding rules for reports and exports

- General principle:
  - Maintain single-blind integrity at sites and for the sponsor’s blinded team; only the minimum necessary personnel may access unblinded treatment information, segregated by role and system permissions [1,2].
- Site reports:
  - Mask treatment allocation; present arm-agnostic subject IDs; any operational data that could reveal allocation (e.g., app activation specifics) is restricted to unblinded device specialists and excluded from PI-facing summaries.
- Sponsor/DSMB:
  - Blinded aggregate for routine operational and safety oversight; DSMB receives unblinded or partially unblinded summaries per charter. If safety requires unblinding for a subject, implement subject-level unblinding with audit trail; do not cascade to broader datasets unless mandated by DSMB recommendation/SAP [1,2].
- Exports:
  - Blinded analysis data sets by default; unblinded exports permitted only under SAP-approved workflows executed by an independent unblinded statistician/DM with access controls and documented approvals.

Regulatory inspections, remote access, and data sharing with oversight bodies

- Access provisions:
  - Monitors, auditors, and regulatory authorities will have direct access to source data, eCRFs, audit trails, device/app logs, and essential documents, on site or remotely, to verify data accuracy, subject protection, and compliance, consistent with ISO 14155/ICH-GCP and privacy laws [1,2,5].
- Remote access:
  - When remote SDV/SDR or inspection is used, systems will provide secure, role-based, time-bounded read-only access; transmission uses encrypted channels; no local storage of PHI/PII unless authorized and protected per GDPR and sponsor policy. Site redaction procedures apply where required by local law [3–5].
- Preparation and conduct:
  - Sponsor provides an inspection readiness package: current protocol/IB/IFU, data management and monitoring plans, EDC validation package (IQ/OQ/PQ), user access logs, audit trails, listings, and CAPA evidence. A single point of contact is designated for each inspection; document requests are logged and tracked to closure [1–4].
- Regulator data requests:

- Fulfilled within requested timelines; all extracts are checksum-verified, labeled with dataset specifications, and accompanied by data provenance and blinding status. Any post-lock changes follow formal unlock/change control with full audit trail [1–4].

Inspection readiness checklist

- Governance and documentation

- Current and historical versions of protocol, SAP, DM plan, monitoring plan, risk assessment, and vendor/SOP indices [1,2].
- Training logs for all system users (GCP, protocol, EDC, device) and delegation logs.
- EDC validation documentation (requirements, UAT, IQ/OQ/PQ), Part 11/Annex 11 compliance evidence, and change control records [3,4].

- Data integrity and traceability

- Complete audit trail access for CRFs, queries, signatures, and exports.
- Reconciliation packages: AE/SAE vs safety database vs device complaint/deficiency logs; randomization vs stratum; device accountability vs inventory; telemetry imports vs CRFs [1,2,8].
- Coding dictionaries versions (MedDRA, WHO Drug) and lock certificates [7].

- Operational evidence

- SLA performance dashboards; query metrics; deviation logs and CAPAs; DSMB communications and decisions (blinded as appropriate) [1,2].
- Evidence of timely safety reporting to IRB/IEC and authorities, including acknowledgments.

- Privacy and security

- GDPR/data protection impact assessment (if applicable); data processing agreements; breach response SOPs; user access reviews; periodic security audits [4,5].

- Site-level essentials

- Investigator Site File completeness; source documentation indexed to eCRF entries; device logs and identifiers; calibration/maintenance records for spirometer/Airflow Trainer where applicable.

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9.3 Data Review

Overview and governance

This section describes the end-to-end plan for ongoing data review, data cleaning, missing-data handling, endpoint and safety adjudication triggers, quality-control (QC) listings, interim data cuts, and database lock for this confirmatory, randomized, single-blinded, stratified device study. Processes adhere to ISO 14155, ICH E6(R2), SPIRIT 2025, FDA 21 CFR Part 11, and EU Annex 11 for

computerized systems, with dictionary-based coding and controlled exports for analysis [1–5]. Device/app telemetry transfers and eCRF data are reconciled under a documented data flow and audit trail (CDISC ODM/traceability) [1,4–6].

Responsibilities:

- Site: timely entry, source verification, PI sign-off, clarifications, and proactive correction of errors; documentation of reasons for missing/late data [1,2].
- Sponsor Data Management (DM): configure edit checks, listings, and reconciliation; manage queries, freezes, interim cuts, and lock; ensure coding and system validation [1–5,7,8].
- Monitors (CRAs): risk-based SDV/SDR, on-site/remote review, escalation of critical discrepancies, verification of source–eCRF concordance [1,2].
- Safety/Medical Monitor: alignment of AE/SAE/UADE cases with safety and regulatory submissions and device complaint logs [1].
- Biostatistics: blinded data reviews, statistical surveillance, and derivation rules consistent with the SAP and estimand framework for handling intercurrent events and missingness [3,10].

Data cleaning plan with defined review cycles

Risk-based, multi-layered review is performed throughout enrollment and follow-up to ensure completeness, accuracy, consistency, and traceability [1–3].

- Real-time automated checks (continuous):

- At data entry/import: range, format, conditional logic, temporal plausibility, cross-form checks; dictionary compliance (MedDRA/WHO Drug); telemetry-to-eCRF batch match (subject ID, visit window, timestamps, device/app build) [1–2,7,8].

- Weekly review (during active enrollment/follow-up):

- Listings for overdue forms, open queries, endpoint and safety-critical missing fields, telemetry import verification, and device accountability reconciliation; CRA targeted follow-up [1–2].

- Monthly statistical surveillance:

- Outliers, heaping, improbable repeats, unusual site distributions; primary endpoint completeness by stratum; randomization/stratum concordance; duplicate subject detection; safety signal screening aligned with DSMB cadence [1–3].

- Pre-DSMB cut review (per DSMB schedule):

- Lock-grade resolution of critical data (eligibility, treatment assignment integrity, primary endpoint fields, SAEs/UADEs and device deficiencies), coding finalization to date, reconciliation with safety and device complaint systems [1–3].

- Interim analysis/cut(s):

- Timing: planned when approximately [to be confirmed] of randomized participants have completed the 6–12 week primary endpoint; no unblinded comparative analyses are shared with the blinded team per SAP/charter [1–3].

- Scope: completeness of primary endpoint, safety data through the data-cut date, coding status, key protocol deviations; freeze datasets for DSMB per charter [1–3].

- Pre-lock review (T−30 to T−5 days before targeted lock date):

- 100% resolution of critical queries; ≥98% completion for required CRFs; final coding pass; AE/SAE/UADE and device deficiency reconciliation complete; site PI re-signatures as needed [1–3].

Turnaround standards:

- Non-serious issues: query within 5 business days of detection; site response within 5 business days; closure within 3 business days after response.
- Critical issues (safety/eligibility/primary endpoint integrity): same-day notification; site response within 2 business days; immediate escalation if unresolved [1,2].

Missing-data decision tree

Missingness is minimized through preventive design, visit reminders, and telemetry imports. When missingness occurs, decisions follow SPIRIT 2025/ICH E9(R1) principles to protect the primary estimand and preserve trial integrity [3,10,11].

- Step 1: Identify the data element and criticality
  - Is the field critical to safety, eligibility, randomization, or the primary endpoint?
  - If critical, classify as Critical Missing; otherwise Non-critical Missing.
- Step 2: Confirm scheduling and window
  - Was the assessment scheduled? Is it still within the visit window? If yes, trigger immediate re-collection within window; if window closed, proceed to Step 3.
- Step 3: Attempt recovery from alternate verifiable sources
  - For endpoint components and safety data: source hospital records, device/app telemetry batches, certified paper source, or validated eSource repositories [1,9].
  - Document the source, retrieval outcome, and any limits to verification.
- Step 4: Clarify with site
  - Issue a targeted query requesting clarification, corrected entry, reason for missingness (e.g., subject refusal, technical failure), and confirmation that no source exists [1,2].
- Step 5: Classify missingness mechanism (operational, technical, clinical/intercurrent)
  - Operational (e.g., missed visit), Technical (e.g., telemetry transfer failure), Clinical/intercurrent (e.g., hospitalization) per SAP; record classification and impact [10,11].
- Step 6: Apply analysis rule per SAP and endpoint hierarchy
  - Primary endpoint:
    - If objective app/telemetry data exist and pass verification, use imported values as primary source; if conflicting with eCRF, reconcile and follow adjudication as necessary.
    - If no verified data and no retrievable source, mark endpoint missing; apply SAP-defined handling (e.g., prespecified imputation rule or missing = failure if justified) with sensitivity analyses under plausible missing-not-at-random scenarios [3,10,11].
  - Safety data: no imputation for incidence; narrative completeness pursued; classify as “not assessable” only after documented reasonable efforts [1,2].
- Step 7: Document and lock
  - Record final disposition, rationale, and SAP clause used; ensure audit trail and PI acknowledgment; flag for sensitivity analyses in the statistical review [3,10,11].

Adjudication charter outline

An independent Endpoint Adjudication Committee (EAC) will be convened to adjudicate prespecified cases where endpoint integrity or safety classification requires independent confirmation, operating under a written charter aligned with ISO 14155/ICH-GCP and the SAP [1,2].

Scope of adjudication:

- Primary endpoint discrepancies:
  - Discordance between site-rated inhalation technique success/failure and objective app/spirometry-derived metrics.
  - Suspected protocol deviations that could bias endpoint ascertainment (e.g., incorrect device pairing, out-of-window measurement) [1–3].
- Safety classification triggers:
  - Complex relatedness determinations for SAEs potentially linked to investigational app-module or associated devices/procedures when site and sponsor medical review remain inconclusive after reconciliation [1].
- Eligibility exceptions:
  - Rare, pre-defined borderline cases escalated by the Medical Monitor before randomization; only under exceptional, charter-defined conditions to preserve blinding and avoid selection bias [1–3].

Committee composition and blinding:

- At least two independent reviewers with respiratory/airway device expertise; a third tie-breaker when needed; members operate blinded to randomized assignment unless unblinding is essential for determination and approved per charter [1,2].

Case package content and workflow:

- Redacted source documents, relevant eCRF excerpts, telemetry summaries (PIF, time-to-PIF, inspiration time), device/software identifiers, visit window records, and site narrative.
- Timelines: case distribution within 5 business days of trigger; adjudication votes within 10 business days; consensus/third review within an additional 5 business days; final adjudication logged with rationale and version-controlled outcome [1–3].

Governance:

- Conflict-of-interest management; training and calibration exercises; periodic drift checks; decision rules and version control; audit trail for every vote; data privacy safeguards [1–3].

Outputs and integration:

- Final adjudication results written back to the EDC as read-only fields with timestamp; overrides initial assessments for analysis populations per SAP; all changes traceable with audit trails [1–4].

Quality-control listing shells

The following standardized listing shells will be generated at defined cadences to detect errors, omissions, and inconsistencies. Columns may be extended per DM plan but minimums must be retained.

Site	Subject	Visit	Form	Field	Current value	Expected/Range	Query status	Source verified	Notes
001	0012	Week 6	Primary endpoint	Technique success	Missing	Y/N	Open	N	Window closed

Site	Subject	Visit date	Visit window	Required forms completed (%)	Missing forms	Partial forms	Critical fields missing	Telemetry verified (Y/N)	Deviations (Y/N)
001	0012	2026-03-14	In-window	83	2	1	1	Y	N

Site	Overdue forms	Open queries	Critical open queries	Median days to entry	% endpoint complete	% AE coded	Telemetry match rate (%)	Device accountability match (Y/N)	SLA status
001	6	23	2	4	92	96	98	Y	On track

Additional safety reconciliation listing (aggregate, blinded where required):

- Subject, AE/SAE ID, MedDRA PT/SOC, seriousness/relatedness, device deficiency ID, complaint system ID, expedited report status, reconciliation status [1,7].

Quality metrics and thresholds

- Timeliness: ≥95% visit CRFs within 5 business days; SAEs within 24 hours initial and 10 days follow-up; telemetry batch verification within 5 business days [1–3].
- Completeness: ≥98% completion of required fields before interim cuts and ≥99% before lock; 100% for primary endpoint and safety-critical fields.
- Query burden: ≤5% queries open >5 business days per site; ≤1 critical query aging >2 business days.
- Concordance: ≥98% telemetry-to-eCRF match on key identifiers and timestamps; ≥99% randomization–stratum concordance; 100% AE–device deficiency–regulatory reconciliation before lock [1–3].

Sites below thresholds trigger corrective actions, retraining, and enhanced monitoring per RBQM [1,2].

Interim data cuts: process and timelines

- Planning: DM publishes a cut specification and schedule at least 21 days in advance; sites receive targeted cleanup listings within 14 days of cut; a freeze window of 3 days precedes extraction [1–4].
- Execution: role-based dataset freeze; extraction with checksum; generation of blinded analysis datasets; QC by DM/biostatistics; DSMB package compiled per charter [1–3].
- Post-cut: unlock only by DM with documented justification; any post-cut changes require tracked change logs and, if analysis-impacting, re-issuance of datasets with updated versioning [1–4].

Database lock checklist

The database will be locked only after all criteria below are met and documented per SOPs and regulatory expectations for electronic systems [1–5].

- Governance and approvals
  - Final protocol/SAP/DM plan versions in effect; all amendments implemented and trained; lock authorization signed by DM, Biostatistics, Medical Monitor, and Sponsor Representative.
- Data completion and signatures
  - 100% of enrolled subjects have end-of-study disposition; all required CRFs complete; all critical fields present; all CRFs e-signed by PI/sub-I as applicable [1,2].
- Queries and freezes
  - All queries closed or documented with final rationale; all critical forms/fields frozen; unlocks controlled and justified; audit trail reviewed for late changes [1–5].
- Coding and dictionaries
  - Final MedDRA and WHO Drug versions applied and documented; coding QC complete; coding deviations logged and resolved [7,8].
- Reconciliations complete
  - AE/SAE/UADE in EDC fully reconciled with safety database and device complaint/deficiency logs; expedited reporting acknowledgments on file; randomization vs stratum alignment confirmed; device accountability vs inventory balanced; telemetry imports vs eCRF verified [1–3].
- Adjudication integrated
  - All triggered endpoint/safety adjudications complete; EAC outcomes ingested to EDC; overrides documented and time-stamped [1–3].
- Protocol deviations
  - Deviations logged, categorized, and assessed for impact; major deviations flagged for analysis populations as per SAP.
- Data privacy and security
  - User access review completed; roles appropriately restricted; any security incidents resolved; GDPR and local privacy requirements met [2,5].
- Extracts and archival
  - Final locked datasets and define.xml/specifications generated; checksum-verified; blinding status documented; archival packages prepared (EDC export, audit trails, listings, coding, reconciliation evidence) [1–5].
- Readiness for inspection
  - EDC validation package (Part 11/Annex 11), training logs, monitoring records, DSMB documentation (blinded where applicable), and CAPAs compiled and indexed [2–5].

Handling unclear or inconsistent data

- Discrepancy classification:
  - Critical (safety/eligibility/primary endpoint), Major (key secondary or covariate), Minor (administrative/format).
- Resolution pathway:
  - Immediate site clarification with supporting source; correction with audit trail; if unresolved and analysis-impacting, escalate to Medical Monitor/EAC per charter [1–3].
- Source precedence:

- When both eCRF and validated telemetry exist, verified telemetry takes precedence for objective inhalation metrics; eCRF is updated to reflect reconciled values or flagged per SAP rules with adjudication if discordant [1,9].

Documentation, audit trails, and version control

All detections, queries, adjudication triggers, decisions, corrections, imports, freezes, unlocks, and exports are captured with non-modifiable audit trails and version-controlled outputs consistent with Part 11/Annex 11 and ISO 14155 [1–5]. Dataset versions include date/time stamps, checksum, and derivation notes tied to the SAP.

References

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9.4 Records

Essential documents, TMF/ISF index, and folder structure

Essential documents will be created, filed, and maintained in a sponsor Trial Master File (TMF) and an Investigator Site File (ISF) to permit evaluation of the conduct of the clinical investigation and the quality of the data, consistent with ISO 14155, ICH E6(R2), EU MDR, and applicable FDA IDE regulations. Electronic TMF/ISF systems must be validated with audit trails and role-based access per 21 CFR Part 11/Annex 11; paper files must be controlled, indexed, and secure [1–6].

Recommended top-level TMF structure (sponsor) with ISF alignment (site):

- Governance and trial-level documents

- Final protocol and all amendments; Synopsis; SPIRIT 2025 checklist; Investigator’s Brochure (IB)/Risk Summary Information (RSI); Statistical Analysis Plan (SAP); Monitoring Plan; Data Management Plan; Safety Management Plan/Pharmacovigilance Plan; Randomization/Blinding Documents; Device Accountability Plan; Risk Management File cross-references; DSMB Charter and membership [1–3,5].

- Regulatory and ethics
  - IRB/IEC approvals/acknowledgments for protocol/consent/advertising; correspondence; Clinical Investigation Application/notifications; Competent Authority approvals/acknowledgments (as applicable); FDA IDE/NSR determinations and correspondence; MDR Annex XV documentation [1,3–5].
- Site management
  - Site selection, qualification, initiation, and closeout reports; signed Clinical Trial Agreements; Financial Disclosure forms; Delegation and Training Logs; CVs/licenses and GCP/protocol training certificates [1,2].
- Investigational device
  - Device description; manufacturing and quality certificates; CE-mark status of AsthmaTuner system; investigational app-module specifications (AsthmaTuner version > 5.4.13.5); device labeling/IFU; shipping records; calibration/maintenance; device deficiency/complaint records with CAPA linkages; manufacturer identifiers: MediTuner AB, SRN SE-MF-000028534 [1,3].
- Participant-level documents
  - Screening and enrollment logs; signed ICFs; source document worksheets; eligibility checklists; medical records extracts; subject ID code list (secured, limited access); re-consent records [1,2].
- Data capture and coding
  - EDC/eSource validation package (IQ/OQ/PQ, UAT), Part 11/Annex 11 compliance; CRF versions and change control; data transfer agreements/specifications; coding dictionary versions (MedDRA, WHO Drug); data listings/cuts and lock documentation [1–4].
- Safety
  - AE/SAE/UADE reports and narratives; expedited regulatory submissions and acknowledgments; DSMB safety reviews; aggregate safety summaries; reconciliation evidence with complaint system [1,3,5].
- Monitoring, auditing, inspection
  - Monitoring visit reports and follow-up letters; issue logs and resolutions; CAPAs; audit reports and responses; regulatory inspection requests and closeout [1,2].
- Deviations and CAPA
  - Protocol deviation/violation logs; impact assessments; IRB/authority notifications; CAPA records and effectiveness checks [1–3].
- Reports and dissemination
  - Annual/periodic progress reports to IRB/IEC and authorities; Clinical Investigation Report (CIR)/Final Study Report; lay summary; publications; trial registry updates [1,3,5].
- Archival and access controls
  - Record retention statements; access control matrices; audit trail exports; index of archived datasets and documents; GDPR/Data Protection Impact Assessment (if applicable) [2,4,6].

ISF mirrors site-specific subsets: current approved protocol/ICF, approvals, delegation/training, subject source and consent files, drug/device accountability, monitoring correspondence, deviations, safety submissions, and closeout/archival certificates [1,2].

Document storage, access control, and retention

- Storage and systems:
  - eTMF/ISF systems must be validated with complete audit trails, username/time-stamped actions, version control, and secure backups; paper records stored in locked fire-resistant cabinets in controlled-access areas [1–4].
- Access:
  - Role-based, least-privilege access; monitors, auditors, and regulatory authorities granted direct access to relevant source documents and essential records as needed for verification; subject identifiers segregated with additional protections [1,2,6].
- Retention:
  - Retain sponsor and investigator records for at least the longest applicable period: not less than 10 years after the end of the clinical investigation or after the last device has been placed on the market in the EU (non-implantable), and 15 years for implantables (if applicable) under MDR; and at least 2 years after the later of FDA marketing approval or study termination/withdrawal under 21 CFR 812.140(d), whichever is longer [1,3,5].
  - Electronic data and signatures retained in compliance with 21 CFR Part 11/Annex 11; personal

data retained no longer than necessary per GDPR storage limitation, with documented justification and secure destruction at end of retention [2,4,6].

- Transfers and archival:

- Any custody transfer (e.g., site consolidation, vendor change) is documented with inventories, checksums for electronic records, and updated indices; archival media must ensure readability over time with format migration plans [1–4].

Logs and trackers: controlled templates

All templates are controlled documents with version numbers and effective dates; complete in indelible ink (paper) or validated e-system; corrections must preserve original entries with audit trail [1–4].

Delegation and signature log (site)

- Columns: Version; Site ID; PI name/signature/date; Staff name/role; Qualifications/CV on file (Y/N); GCP training date; Protocol/device training date; Tasks authorized (screening, consent, eligibility confirmation, device handling, AE/SAE assessment, eCRF entry, e-signature); Start date; End date; PI authorization signature/date; Notes [1,2].

Training log (site and sponsor)

- Columns: Version; Name; Role; Organization; Training type (GCP, protocol, EDC, safety, device/app handling); Trainer; Format (in-person/remote/e-learning); Date; Assessment/competency check (Y/N, score if applicable); Retraining due date; Signature; Certificates filed (Y/N) [1,2].

Screening/enrollment log (site)

- Columns: Version; Site ID; Screening ID; Subject ID (assigned at consent); Date of pre-screen/screen; Consent date/version; Eligibility result (eligible/ineligible); Key exclusion reason (coded); Randomization date; Stratum (DPI/MDI/Both); Allocation (blinded as applicable); Early withdrawal (Y/N); Reason/date; Notes [1,2].

AE/SAE/UADE log (site)

- Columns: Version; Site ID; Subject ID; Event ID; MedDRA PT/SOC; Onset date; Severity grade; Serious (Y/N, criterion); Relatedness (app-module; spirometer/Airflow Trainer/procedures; study participation); Expectedness vs RSI; Outcome/date; Device deficiency/complaint ID; Initial report date/time; Follow-up submissions (dates); Regulatory submissions and acknowledgments; PI assessment signature/date [1,3,5].

Device accountability log (site)

- Columns: Version; Site ID; Device category (spirometer/Airflow Trainer/app access); Device model/serial; App build/version; Received date; Dispensed to subject ID/date; Returned date/condition; Updates applied; Loss/damage (Y/N; description); Quarantine status; Inventory balance; Reconciliation status; Responsible staff/signature/date [1,3].

Monitoring visit log (site)

- Columns: Version; Visit type (selection/initiation/routine/for-cause/closeout/remote); CRA name; Date(s); Scope; Findings summary; Action items; Due dates; Items closed (Y/N; date); PI acknowledgement/signature/date [1,2].

Correspondence tracker (site and sponsor)

- Columns: Version; Date; From; To; Subject; Medium (email/letter/portal); Summary; Related file location (TMF/ISF index); Required action; Due date; Closed (Y/N; date); Archivist initials [1,2].

Protocol deviation/violation form with CAPA

Use for any departure from the approved protocol, consent, or GCP that may affect subject safety, rights, or data integrity. Major vs minor classification per Monitoring Plan; report to IRB/IEC/authorities

as required [1–3,5].

- Administrative header: Version; Site ID; Subject ID (if applicable); Date discovered; Visit/timepoint; Reporter.
- Deviation details:

- Category (eligibility, consent, visit window, endpoint assessment, treatment/exposure, device accountability, safety reporting, data entry, other).
- Description (verbatim, including chronology).
- Dates/times of occurrence and detection.
- Root cause analysis (e.g., human error, training gap, system failure, process deficiency, technical issue).
- Severity (major/minor) with rationale and potential/actual impact on safety and data integrity.
- Immediate containment/correction taken (dates).

- CAPA plan:

- Corrective actions (what, who, when); Preventive actions (process change, retraining, system enhancement); Effectiveness criteria and verification date.

- Notifications and approvals:

- IRB/IEC notification required (Y/N; date sent/acknowledgment); Competent Authority/FDA notification required (Y/N; basis and regulation); Sponsor Medical Monitor review (name/date); PI acknowledgement/signature/date; Closure date and effectiveness outcome [1–3,5].

Periodic and final reporting responsibilities

- Investigator (per site):

- Submit progress reports to IRB/IEC at least annually and as requested; promptly report SAEs/UADEs and significant new findings; provide device accountability and enrollment status on request; submit final report/closure package to IRB/IEC at study completion or site closeout [1–3,5].

- Sponsor:

- Safety: expedited UADE/MDR reporting and annual/periodic safety updates per MDR and FDA IDE requirements; maintain safety file and acknowledgments [3,5].
- Progress/final: provide required progress reports to authorities where applicable; submit final clinical investigation report to relevant authorities and IRB/IECs; for FDA IDE studies, submit a final report within 6 months of completion or termination per 21 CFR 812.150; ensure registry postings and lay summaries per jurisdictional rules [1,3,5].

- DSMB:

- Review periodic blinded/unblinded safety summaries per charter; provide recommendations to sponsor; records filed in TMF with appropriate blinding [1,2].

Final study report skeleton (ISO 14155-compliant CIR)

The Clinical Investigation Report (CIR)/Final Study Report will be authored under sponsor QA with medical, statistical, and clinical review, conforming to ISO 14155 and MDR Annex XV content expectations; consistency with the SAP and the locked database is mandatory [1,3].

- Title page: study title; identifiers; device details (inhalation app-module embedded in AsthmaTuner > 5.4.13.5; MediTuner AB; SRN SE-MF-000028534); version/date; confidentiality.
- Synopsis: objectives; design; populations; endpoints; results; conclusions.
- Administrative information: roles/responsibilities; investigators and sites; ethics and regulatory approvals; trial registration(s).
- Background and rationale: clinical context; risk–benefit summary; prior data.
- Objectives and endpoints: primary, secondary, exploratory; hypotheses.
- Study design and methods:

- Design overview; randomization/blinding; stratification; eligibility criteria; interventions and procedures; visit schedule; data sources and handling; device accountability; protocol deviations.

- Statistical methods: analysis populations; endpoints; estimands; handling of missing data; interim analyses; software and versions.
- Study population disposition: screening, randomization, follow-up, withdrawals; protocol deviations (major/minor).

- Baseline characteristics: demographics and clinical characteristics by stratum.
- Device exposure and compliance: app usage metrics; training sessions; device accountability outcomes.
- Efficacy endpoints:

- Primary endpoint results with estimates, confidence intervals, and p-values; sensitivity and subgroup analyses; secondary/exploratory outcomes.

- Safety results:

- AE/SAE/UADE summaries (incidence, severity, relatedness, expectedness); device deficiencies/complaints and outcomes; fatalities; discontinuations due to AEs; exposure-adjusted analyses.

- Adjudication outcomes: EAC results and impact on endpoints/safety.
- Discussion and conclusions: interpretation vs objectives; limitations; generalizability; risk–benefit.
- Changes to protocol and analysis: amendments and deviations from planned analyses with justifications.
- Quality management: monitoring, audits, data integrity, and compliance statements.
- Ethics and participant protection: consent process; privacy/GDPR; compensation/insurance if applicable.
- Regulatory reporting and dissemination: submissions performed; lay summary plan; publication intentions.
- References.
- Appendices:

- Final protocol and amendments; SAP; IB/RSI; monitoring plan summary; list of investigators and sites; sample ICF; core CRFs; major deviations listing; detailed statistical outputs and shells; AE/SAE listings; device accountability reconciliation; adjudication charter; DSMB charter and recommendations (blinded as appropriate); eDC validation summary; coding dictionary versions and coding rules; CSR data definition files (e.g., define.xml) [1–5].

Deviation handling, documentation, and escalation

- Identification and documentation:

- All deviations documented within 5 business days of awareness using the controlled form; serious non-compliance escalated same day to sponsor and IRB/IEC as required [1–3].

- Classification and impact:

- Major deviations with potential impact on safety/rights or primary endpoint integrity trigger immediate containment, CAPA, and Medical Monitor review; EAC review may be requested per charter; data may be excluded from per-protocol analyses per SAP with justification [1–3].

- Reporting:

- Report significant deviations to IRB/IEC/authorities per local regulation and ISO 14155; maintain acknowledgments in TMF/ISF [1,3,5].

- Effectiveness checks:

- CAPA effectiveness verified by CRA/QA within defined timelines; repeat deviations trigger retraining or process revision; persistent non-compliance may result in enrollment hold or site termination [1,2].

Version control, indexing, and audit trails

- Every essential document carries a version number, effective date, and authorizer; superseded versions retained and indexed; change histories preserved with rationale [1–4].
- The TMF/ISF index is maintained in real time; quarterly QC checks verify completeness and legibility; deficiencies are corrected with documented timelines; audit trails for eTMF/ISF are exportable on request [1–4].

References

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10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Role of the Sponsor-Investigator

Overview and accountability

As the Sponsor-Investigator (SI), the Principal Investigator assumes full and unified responsibility for both sponsor and investigator obligations for this late-phase confirmatory clinical investigation of the investigational inhalation app-module integrated in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) in subjects aged ≥16 years with asthma and/or COPD using DPI and/or MDI devices. The SI is responsible for scientific validity; participant safety, rights, and well-being; compliance with the approved protocol, ISO 14155, ICH-GCP, applicable medical device regulations (including MDR and, if applicable, FDA IDE), and IRB/IEC decisions; quality management; data integrity; and transparent registration and reporting [1–6].

Key SI responsibilities include:

- Design, approval, and maintenance of the protocol, risk management, statistical analysis plan, monitoring and data management plans, safety management plan, and DSMB charter, with timely amendments, training, and approvals prior to implementation [1–3].
- Regulatory and ethics submissions and approvals prior to initiation, including clinical investigation notifications/approvals where required; maintenance of essential documents and readiness for inspection [1–5].
- Selection, qualification, training, and oversight of all study personnel and vendors; documentation of competency and delegation; continuous performance oversight and corrective/preventive actions (CAPA) as needed [1,2].
- Provision, accountability, and traceability of the investigational device and associated equipment/software; management of device deficiencies and complaints with appropriate reporting and CAPA linkages [1,3].
- Implementation of a risk-based monitoring program, pharmacovigilance/safety surveillance, DSMB oversight, and prompt safety reporting (including UADE/SAE/expedited reports) per jurisdictional timelines [1,3,5].
- Assurance of data integrity and confidentiality, including validated electronic systems, audit trails, ALCOA+ principles, and compliance with 21 CFR Part 11/Annex 11 and applicable privacy laws (e.g., GDPR) [1,2,4,6].
- Public registration before first participant enrollment and timely disclosure of summary results and lay summaries in applicable registries per SPIRIT and regulatory requirements [2,3,5].
- Adequate insurance/financial coverage for potential subject injury and indemnification provisions per contracts and applicable law [1,3].

Registration and transparency

- Register the clinical trial in a public, WHO-ICTRP–recognized registry (e.g., ClinicalTrials.gov) before enrolling the first participant; maintain accurate, current entries (objectives, endpoints, eligibility, device, oversight) [2,7].
- In the EU, ensure submission to the appropriate competent authority and registry (e.g., EUDAMED/competent authority per MDR) as applicable; provide a summary of results and a lay summary according to jurisdictional timelines [3].
- Post summary results within mandated timeframes and ensure consistency with the final Clinical Investigation Report (CIR) [2,3].

Safety management and expedited reporting

- Maintain an independent Medical Monitor and a DSMB per written charter to periodically review safety and study conduct; implement recommendations promptly while preserving blinding per plan [1,2].
- Collect, assess, and report AEs/SAEs/UADEs and device deficiencies in accordance with ISO 14155 and applicable regulations (e.g., MDR Article 80/Annex XV; FDA 21 CFR 812.150 for IDE studies), including expedited timelines to authorities and IRB/IECs, with reconciliation to the device complaint system [1,3,5].
- Ensure continuous safety surveillance, trend analysis of device deficiencies/complaints, and prompt risk mitigations with CAPA documentation [1,3].

Monitoring oversight and quality management

- Implement risk-based monitoring (RBM) covering site qualification, initiation, routine/for-cause visits, and close-out; verify consent, eligibility, endpoint integrity, safety data, device accountability, and source–data concordance [1,2].
- Ensure monitors (CRAs) are trained, independent of site conduct, and operate to written SOPs; document all findings and resolution timelines; escalate persistent non-compliance [1,2].
- Maintain a quality management system and TMF/ISF per ISO 14155 and MDR, including validated computerized systems, change control, and audit trails for all critical processes and data [1,3,4].

Data integrity, privacy, and records

- Use validated eClinical systems compliant with Part 11/Annex 11; enforce role-based access, audit trails, electronic signatures, and ALCOA+; perform periodic access reviews and security audits [1,2,4].
- Protect personal data in alignment with GDPR and applicable local privacy law; minimize and pseudonymize data where feasible; restrict re-identification to authorized personnel; implement incident response procedures [2,6].
- Retain essential documents and data for the longest applicable period under MDR and FDA IDE; maintain inspection-readiness and ensure orderly archival and retrieval [1,3,5].

Training and delegation

- Ensure all personnel complete and document training in GCP, protocol/procedures, safety reporting, device handling (app-module/Airflow Trainer/spirometer), EDC, and privacy/security prior to performing tasks; retrain after significant amendments or system changes [1,2].

- Maintain a current, signed Delegation-of-Authority (DoA) Log that details roles, qualified tasks, start/stop dates, and signature authority; the SI remains accountable for all delegated activities and their oversight [1,2].

Insurance and indemnification

- Secure clinical investigation insurance or equivalent financial coverage for subject injuries as required by ISO 14155 and MDR; inform participants of compensation/medical care provisions in consent materials [1,3].
- Execute site/vendor agreements that define indemnification, liability limits, and notification duties; ensure coverage extends to investigational activities and device-related risks [1,3].

Organizational chart

The SI ensures clear lines of authority, decision-making, and segregation of blinded/unblinded functions. The following study organization will be maintained; named incumbents and alternates will be documented in the DoA Log and TMF/ISF.

Function	Role/Title	Core responsibilities	Blinding status
Sponsor-Investigator	Principal Investigator (PI)	Overall responsibility; protocol and amendments; regulatory/IRB liaison; safety oversight; final data sign-off	Blinded
Sub-Investigators	Physician Co-Investigators	Eligibility, clinical assessments, AE/SAE evaluations, medical oversight	Blinded
Clinical Operations	Clinical Operations Lead	Site activation and oversight; monitoring management; CAPA tracking; training coordination	Blinded
Monitoring	CRA(s)	RBM execution; SDV/SDR; device accountability checks; visit reports	Blinded
Safety/Pharmacovigilance	Safety Officer	Case processing; expedited reports; RSI maintenance; safety listings; reconciliation with complaints	Blinded to treatment; unblinded only if necessary for safety
Medical Monitor	Independent Physician	Medical review of safety; complex causality; unblinding decisions per charter	May access unblinded data if required
DSMB	Independent Committee	Periodic safety/efficacy oversight; recommendations to SI	Unblinded per charter
Data Management	Lead Data Manager	EDC build/validation; edit checks; coding; listings; database lock	Blinded; limited unblinded access per SAP if applicable
Biostatistics	Lead Biostatistician	SAP; randomization; blinded data review; analyses; CSR support	Blinded; independent unblinded statistician as needed
Device Management	Unblinded Device Specialist	Device/app provisioning; telemetry reconciliation; complaint initiation	Unblinded (limited)
Quality Assurance	QA Lead	Audits; inspection readiness; SOP compliance	Blinded
Manufacturer liaison	MediTuner AB contact	Technical support; device deficiency/complaint processing; CAPA	Unblinded (device-specific)

Delegation-of-Authority Log template

A controlled, versioned DoA Log will be maintained at each site and centrally. The PI authorizes, dates, and signs each delegation; qualifications and training must be verified before task performance.

Field	Description
Log version/effective date	Controlled document metadata
Site ID and address	As per site regulatory file
PI name/signature/date	Acknowledges overall accountability and delegations
Staff name/role	Full name, title, affiliation
Qualifications on file (Y/N)	CV/license; GCP certificate date
Training completed	Protocol; device/app; safety/PV; EDC; privacy/security (dates)
Delegated tasks	Screening; consent; eligibility confirmation; clinical assessments; device handling; AE/SAE assessment; eCRF entry; e-signature; safety reporting; monitoring liaison
Signature authority	Forms each individual may sign electronically/in ink
Start date	Date delegation becomes active
End date	Date delegation ceases
PI authorization/signature/date	For each individual and any updates
Notes	Restrictions/conditions; re-training requirements

Public trial registration and results disclosure obligations

- Before first participant enrollment, register the study with a WHO-ICTRP–compliant registry containing all mandatory data elements; include device identification and version constraints (AsthmaTuner >5.4.13.5) [2,7].
- Update registry records at least annually and within mandated timelines for recruitment status, amendments, and results; provide a plain-language lay summary consistent with MDR/ISO 14155 expectations and SPIRIT guidance [1–3,7].

Inspection readiness and communications

- Permit and facilitate direct access for monitors, auditors, and regulatory inspectors to source documents, eCRFs, device logs, and essential documents; maintain an inspection response plan, single points of contact, and document request tracking [1,2].
- Notify competent authorities and IRB/IECs of reportable events, urgent safety measures, and significant deviations; provide periodic and final reports as required (e.g., MDR, FDA IDE) [1,3,5].

Sponsor-Investigator attestations

By initiating and conducting this investigation, the SI attests that:

- The investigation is scientifically sound, ethically justified, and conducted per ISO 14155, ICH-GCP, MDR, and applicable national regulations [1–3,5].
- Adequate resources, training, and oversight are in place to protect participants and ensure reliable data.
- Safety signals will be acted upon promptly, and results will be disseminated responsibly and transparently.

References

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10.2 General Duties

Compliance framework and overarching responsibilities

All parties will conduct, supervise, and document study activities in accordance with ISO 14155, ICH E6(R2), applicable national regulations (including EU MDR and, if applicable, FDA IDE requirements), IRB/IEC determinations, and SPIRIT 2025 principles for protocol transparency and reporting [1–5]. Personal data processing follows GDPR and any local privacy laws [6]. The Sponsor-Investigator (SI) retains ultimate responsibility for participant safety, data integrity, and regulatory compliance; each investigator is responsible for conduct at their site, including oversight of delegated tasks and vendors, maintenance of essential documents, and readiness for monitoring, audit, and inspection [1–3].

Regulatory submissions and approvals

- Pre-initiation:

- Obtain required IRB/IEC approvals for the protocol, consent/assent, recruitment materials, and any country-specific documents prior to site activation [1,2].
- Submit clinical investigation application/notification to the relevant Competent Authority where required by MDR Annex XV and national law; obtain authorization or non-objection before first enrollment [3].
- For FDA-jurisdictional sites where the investigation constitutes a Significant Risk device study, obtain IDE approval; otherwise document Non-Significant Risk determination with IRB concurrence and IDE-abbreviated requirements; ensure all IDE reporting obligations are met if applicable [4].
- Register the study in a WHO-ICTRP–recognized public registry prior to first participant enrollment and maintain current entries [5,7].

- During conduct:

- Submit and obtain prior approval for substantial amendments from IRB/IEC and, where required, authorities before implementation, except when necessary to eliminate immediate hazards [1–3].
- Notify authorities and IRB/IEC of UADEs, SAEs, urgent safety measures, and significant deviations in accordance with jurisdictional timelines (e.g., MDR Article 80, FDA 21 CFR 812.150 if IDE) [1,3,4].

- Closeout:

- Submit final reports to IRB/IEC and applicable authorities within required timelines (e.g., within 6 months for FDA IDE studies); post summary results and lay summary per MDR/registry rules [3–5].

Investigator and site selection

- Selection criteria:

- Documented qualifications and experience in asthma/COPD care and inhaler technique education; active medical license(s); GCP training within sponsor-defined currency; adequate time and resources to conduct the trial [1,2].
- Infrastructure to perform device handling and training; secure storage for investigational equipment; validated eClinical systems access; capability for remote monitoring and teleconferencing as needed [1].
- Demonstrated data quality and compliance performance in prior research, or satisfactory pre-study qualification assessment.

- Activation requirements:

- Executed clinical study agreement; IRB/IEC approval; regulatory greenlight (if applicable); completed site initiation training; finalized Delegation-of-Authority and training logs; device/accountability setup and calibration/verification per sponsor procedures [1–3].

Site monitoring and oversight

- Monitoring strategy:

- Risk-based monitoring with a combination of on-site and remote visits to verify informed consent, eligibility, source–data concordance, endpoint and safety data accuracy, device accountability, and compliance with the protocol and GCP [1,2].

- Visit cadence and triggers:

- Site initiation visit before first enrollment; first routine visit within approximately 4–8 weeks after first randomization; subsequent visits at risk-based intervals (e.g., every 6–10 weeks during active enrollment and as needed thereafter), with ad hoc remote reviews; for-cause visits when significant risks or non-compliance are suspected [1,2].

- Escalation:

- Non-compliance triggers corrective and preventive actions (CAPA), enhanced monitoring, temporary enrollment hold, or site termination if unresolved, with notifications to IRB/IEC/authorities as required [1–3].

Informed-consent verification

- Process controls:

- Consent must be obtained before any trial-specific procedures by appropriately delegated, trained staff using the current IRB/IEC-approved form/version; participants receive adequate time for questions and a signed copy of the form [1,2].
- Verify participant identity per local law and site policy; where legally acceptable, validated electronic consent and national electronic identification (e.g., BankID or similar) may be used with appropriate audit trails and version controls [1,2,6].
- Re-consent is required when new safety information emerges or when protocol amendments materially affect participation; documentation of discussion and signatures must be filed in the ISF/TMF [1,2].

- Ongoing oversight:

- Monitors verify consent documentation for each enrolled participant and confirm use of the current approved version; deviations are documented and reported per IRB/IEC and regulatory requirements [1,2].

Compliance reporting schedule (template)

Report type	Responsible party	Recipient(s)	Timing/frequency	Minimum content	Regulatory basis
Trial registration and updates	SI/designee	WHO-ICTRP–recognized registry	Initial before first enrollment; updates per registry rules and within 30 days of key changes	Study identifiers; device details; design; objectives/endpoints; status; amendments; results/lay summary when due	SPIRIT 2025; WHO ICTRP [5,7]

DSMB safety/conduct review	Sponsor medical/safety team; DSMB	DSMB; SI receives recommendations	At predefined intervals (e.g., quarterly) and ad hoc	Aggregate safety; enrollment/exposure; protocol deviations; recommendations	ISO 14155; ICH E6(R2) [1,2]
Annual progress report (site)	PI	IRB/IEC	At least annually and on request	Enrollment status; deviations; SAEs/UADEs; risk–benefit; changes; continuing review materials	ISO 14155; ICH E6(R2) [1,2]
Annual report (sponsor/IDE)	SI (if IDE)	FDA (if applicable)	Every 12 months from IDE approval date	Summary of progress; safety; deviations; device deficiencies; investigational plan changes	21 CFR 812.150(b)(5) [4]
UADE/SAE expedited reports	PI/SI	IRB/IEC; Competent Authority/FDA as applicable	Per local law; without delay for UADEs/SAEs; IDE timelines if applicable	Event narrative; assessment of relatedness/expectedness; outcomes; actions; device info	ISO 14155; MDR; 21 CFR 812.150 [1,3,4]
Significant deviation/non-compliance	PI/SI	IRB/IEC; authorities as required	Promptly after awareness	Description; impact assessment; CAPA; preventive measures	ISO 14155; ICH E6(R2) [1,2]
Final report/closeout (site)	PI	IRB/IEC	Upon site completion/termination	Participant disposition; safety; deviations; device accountability; data status	ISO 14155; ICH E6(R2) [1,2]
Final clinical investigation report and registry results	SI	Competent Authority (as required); public registry	Within mandated timelines (e.g., ≤6 months to FDA for IDE; MDR timelines for EU)	CIR/CSR synopsis; results datasets/summary; lay summary	MDR; 21 CFR 812.150; SPIRIT 2025 [3–5]

Documentation and essential records

- Maintain complete, contemporaneous essential documents in the TMF/ISF to permit evaluation of the trial's conduct and data quality, with version control, audit trails, and secure access; retain records per the longest applicable retention period under MDR and national regulations [1–3,6].
- Ensure device accountability and traceability for the investigational app-module (AsthmaTuner version later than 5.4.13.5; MediTuner AB; SRN SE-MF-000028534) and associated equipment, including receipt, assignment, updates, returns, loss/damage, and complaint/deficiency linkages [1,3].

Training, delegation, and vendor oversight

- Prior to performing study tasks, all personnel complete GCP, protocol/procedure, device handling, safety reporting, and data privacy training, with competency documented; retrain after significant changes [1,2].
- The PI/SI documents delegation of duties and maintains oversight of all delegated activities and service providers; vendor qualifications, contracts, and performance oversight are maintained and auditable [1,2].

Deviation management and CAPA

- Identify, document, assess, and report protocol deviations and non-compliance; implement and verify CAPA effectiveness; escalate persistent issues to the SI and, when required, IRB/IEC and authorities; consider enhanced monitoring or site suspension/termination if risks persist [1–3].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/2017/745/oj
4. US Food and Drug Administration. 21 CFR Part 812—Investigational Device Exemptions. 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812
5. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). SPIRIT 2025 Statement and Checklist. 2025. https://www.spirit-statement.org/
6. European Parliament and Council. Regulation (EU) 2016/679 (General Data Protection Regulation). 2016. https://eur-lex.europa.eu/eli/Reg/2016/679/oj
7. World Health Organization. International Clinical Trials Registry Platform (ICTRP): Minimum Trial Registration Data Set. 2021. https://trialsearch.who.int/ICTRP/RegistryNetwork

10.3 Selection of Investigators

Overview and selection strategy

Investigators and sites will be selected, qualified, trained, and activated under a documented, risk-based process consistent with ISO 14155, ICH E6(R2), EU MDR, and, where applicable, FDA IDE requirements and SPIRIT 2025 transparency principles [1–5]. Selection prioritizes outpatient pulmonary/allergy clinics with demonstrated expertise in asthma/COPD care, inhaler-technique education for dry powder inhalers (DPI) and metered dose inhalers (MDI), operational capacity for single-blind randomized device studies, and the infrastructure required to support the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5) with associated spirometer/Airflow Trainer workflows [1–3].

Site feasibility assessment

Prospective sites will complete a standardized feasibility assessment and undergo a qualification visit (remote or on site) to confirm capabilities, resource commitments, and compliance frameworks [1,2].

- Clinical capabilities

  - Access to the target population (≥16 years; asthma and/or COPD) routinely treated with DPI and/or MDI; historical monthly volumes sufficient to meet enrollment targets within planned timelines [1].
  - Clinicians and educators experienced in inhaler technique assessment, including DPI flow-dependent performance considerations in elderly and patients with reduced lung function [1].

- Operational readiness

  - Capacity to support single-blind, 1:1 stratified randomization by inhaler type (DPI/MDI/both) and timely follow-up at 6–12 weeks.
  - Facilities and SOPs for receipt, secure storage, configuration, dispensation, return, and reconciliation of investigational devices (CE-marked AsthmaTuner spirometer, Airflow Trainer) and app access; ability to manage shipment to participants' homes when applicable [1–3].
  - Capability for remote and on-site monitoring; timely source document provision; Part 11/Annex 11-compliant eClinical access (EDC/eSource) and secure internet connectivity [2,4].

- Digital and identity verification

- Experience with validated electronic consent where permissible; capacity to support national e-identity solutions (e.g., BankID or comparable) or equivalent compliant consent workflows; audit trails for consent versioning and signatures [1,2].
- Smartphone and app support processes (iOS/Android), participant onboarding, troubleshooting, and telemetry transfer verification aligned to sponsor plans [1].

- Data integrity and quality systems

- GCP-compliant SOPs for consent, eligibility, AE/SAE/UADE reporting, device deficiency/complaint initiation, data entry, and CAPA; GDPR-compliant privacy controls where applicable [1–3,6].
- Acceptable performance history (or equivalent demonstration) regarding enrollment reliability, data timeliness/completeness, and inspection readiness [1,2].

- Staffing and time commitment

- Named Principal Investigator (PI) with dedicated time; adequate sub-investigators and coordinators; documented backup coverage; commitment to meeting query turnaround and visit windows [1,2].

Minimum feasibility evidence to file prior to activation:

- Completed feasibility questionnaire and qualification report signed by sponsor and PI [1,2].
- Draft enrollment plan with source of potential participants and projected screening/randomization rates [1].
- Confirmation of device handling/storage capacity and secure shipment processes [1,3].
- Confirmation of eConsent/eSignature and identity verification capabilities or approved alternative processes [1,2].
- IT questionnaire confirming secure networks, access controls, and browser/device compatibility for EDC/app [2,4,6].

Investigator qualification criteria

Each site's PI must meet all of the following criteria; sub-investigators must collectively assure equivalent coverage across all protocol-required competencies [1,2]:

- Medical credentials and experience

- Active, unrestricted medical license(s) for the site jurisdiction; board certification or equivalent demonstrated expertise in pulmonology, allergy/immunology, internal medicine with respiratory focus, or general practice with substantial asthma/COPD experience [1,2].
- Documented experience in conducting interventional clinical investigations or, at minimum, successful completion of sponsor-provided investigator training with mentorship/heightened monitoring until competency demonstrated [1,2].
- Demonstrated proficiency in DPI/MDI technique education and assessment.

- GCP and regulatory training

- ICH-GCP training completed within the sponsor-defined currency period (e.g., ≤3 years) and prior to first study activity; protocol-, safety-, device-, and EDC-specific training completed pre-activation; retraining after substantial amendments or system changes [1,2].

- Time and oversight

- Commitment to personal supervision of the investigation, oversight of delegated tasks, and availability for monitoring/audit/inspection; maintenance of a current Delegation of Authority log [1,2].

- Independence and disclosures

- Completion of financial disclosure forms for investigators and covered staff per 21 CFR Part 54 (if FDA-jurisdictional) or equivalent local requirements; assessment and management of any conflicts of interest per site policy and sponsor procedures; prohibition of individuals with unmanaged significant conflicts from key roles [2,5].

Documentation required in the Investigator Site File (ISF) before activation:

- Signed PI and sub-investigator CVs (dated within 2 years) and medical license(s) [1,2].
- GCP and study-specific training certificates; device/app competency records [1,2].
- Financial Disclosure/Conflict of Interest forms for all covered individuals [2,5].
- IRB/IEC approval documentation and approved consent/assent materials [1,2].
- Signed Clinical Study Agreement/financial contract and insurance/indemnification proof as applicable [1,3].

Activation checklist

A site may enroll only after sponsor issues written authorization confirming completion of:

- Successful qualification assessment and Site Initiation Visit (SIV) with documented training attendance and competency checks [1,2].
- IRB/IEC approval(s), registry prerequisites, and competent authority authorization/notification where required by MDR or IDE regulations [1,3,5].
- Executed agreements; finalized Delegation of Authority and Training Logs; device/accountability records initiated; eClinical user accounts provisioned with role-based access [1–4].
- Verification of data privacy measures (e.g., GDPR compliance statements, privacy notices, and secure handling of personal data) [6].

Ongoing competency, retraining, and performance oversight

- Competency maintenance

- Refresher training will be required at least annually or following substantial amendments, major deviations, or evidence of knowledge drift; attendance and competency outcomes will be filed in the ISF/TMF [1,2].

- Performance surveillance

- Continuous quality indicators (e.g., consent accuracy, eligibility correctness, endpoint/safety data completeness, timeliness, device accountability, query aging) will be monitored. Sites falling below predefined thresholds will undergo targeted retraining, increased monitoring, and CAPA; unresolved non-compliance may lead to enrollment hold or site termination per SOPs [1,2].

Conflict of interest and financial disclosure

All investigators and covered staff must disclose significant financial interests and arrangements related to the investigational device or sponsor before activation and within required update periods. Disclosures will follow 21 CFR Part 54 where applicable or local equivalent; management plans may include role modification, enhanced oversight, or recusal from specific determinations (e.g., eligibility adjudication) to protect trial integrity [2,5]. Disclosures and management plans will be maintained in the TMF/ISF and made available to regulators on request [1,2,5].

Investigator agreement and commitment form

Each PI will sign the Investigator Agreement prior to activation, confirming the following commitments in accordance with ISO 14155, ICH-GCP, MDR, and, where applicable, FDA IDE requirements [1–5]:

- I have reviewed the protocol, Investigator’s Brochure/Risk Summary Information, device Instructions for Use, and all training materials; I agree to conduct the investigation as approved and not to deviate without prior written approval from the sponsor and IRB/IEC, except to eliminate immediate hazards to participants.
- I will ensure that informed consent is obtained and documented prior to any study-specific procedures using the current IRB/IEC-approved form/version and compliant identity verification and eSignature processes where used.
- I accept responsibility for the conduct of the study at my site, including appropriate supervision and documentation of delegated tasks; I will maintain an accurate Delegation of Authority log and ensure all staff are qualified, trained, and competent for their assigned duties.
- I will enroll only eligible participants who meet all inclusion and none of the exclusion criteria; I will ensure adherence to randomization, blinding, visit windows, and endpoint/safety assessments.

- I will ensure accurate, complete, and timely recording of data in source documents and eCRFs; I will review, approve, and e-sign data; I will respond to queries within required timelines and permit direct access by monitors, auditors, and regulatory inspectors.
- I will ensure investigational device accountability, secure storage, calibration/verification as applicable, proper use per IFU, timely reporting and management of device deficiencies/complaints, and returns/reconciliation at study end.
- I will promptly identify, assess, and report AEs/SAEs/UADEs per protocol, ISO 14155, MDR, and applicable national regulations; I will cooperate with safety follow-up and provide comprehensive narratives and source materials.
- I will disclose and update any financial interests or conflicts in accordance with regulatory and institutional requirements; I will implement any agreed management plans.
- I will retain and make available essential documents for the longest applicable retention period and ensure data privacy and confidentiality per GDPR or local laws.
- I understand that non-compliance may result in corrective actions, enrollment hold, or termination, and I will cooperate fully in any CAPA, audit, or inspection processes.

Signature block (to be filed in ISF):
- Principal Investigator name, degree(s)
- Site/institution
- License number(s) and issuing authority
- Signature and date
- Sponsor representative signature and date

Replacement or termination of investigators

If a PI or key sub-investigator is replaced, the site must notify the sponsor promptly and provide CVs, licenses, disclosures, and training records for the proposed replacement. Enrollment may be paused until qualification, training, and IRB/IEC acknowledgments are complete. Persistent non-compliance, inability to meet commitments, or unresolved safety/quality risks may result in site termination with orderly transfer or archival of essential documents and participant care continuity, consistent with ISO 14155/ICH-GCP and applicable regulations [1–3].

Inspection readiness and records

Sites must maintain complete, contemporaneous, and audit-ready ISF records, including feasibility/qualification documents, CVs/licenses, GCP and study training, financial disclosures, agreements, approvals, device accountability, monitoring correspondence, deviations/CAPA, and safety reports, with version control and access logs consistent with ISO 14155 and Part 11/Annex 11 for electronic systems [1,2,4]. Records will be retained for the longest applicable period under MDR and national regulations; personal data handling must remain compliant with GDPR where applicable [3,6].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/2017/745/oj
4. US Food and Drug Administration. 21 CFR Part 11—Electronic Records; Electronic Signatures. 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11
5. US Food and Drug Administration. 21 CFR Part 54—Financial Disclosure by Clinical Investigators. 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-54
6. European Parliament and Council. Regulation (EU) 2016/679 (General Data Protection Regulation). 2016. https://www.eur-lex.europa.eu/eli/Reg/2016/679/oj

10.4 Monitoring

Monitoring strategy and scope

Monitoring will follow a documented, risk-based approach combining centralized, remote, and on-site activities to verify participant protection, endpoint integrity, data reliability, and regulatory compliance in accordance with ISO 14155, ICH E6(R2), EU MDR, and, where applicable, FDA IDE requirements [1–4]. The approach focuses on critical-to-quality (CtQ) factors derived from the study design: informed consent (including identity verification for eConsent), eligibility, stratified 1:1 randomization, primary endpoint assessment at 6–12 weeks (successful inhalation technique), safety event ascertainment and reporting (AE/SAE/UADE), device accountability and deficiency/complaint handling, data privacy/security, and maintenance of blinding and allocation concealment [1–4].

- Monitoring model:

- Centralized monitoring: ongoing statistical/data review, key risk indicator (KRI) tracking, protocol deviation trend analysis, and reconciliation of device/app telemetry with eCRF data and complaint/deficiency records [1,2].
- Remote monitoring: targeted source data review (SDR) and document review via secure systems for consent, eligibility, endpoint source, and device accountability where permitted, preserving direct access and confidentiality [1,2,4].
- On-site monitoring: verification of source data, essential documents, investigational device processes, staff training/delegation, and facility controls; for-cause visits triggered by predefined risk thresholds [1,2].

- Visit plan (risk-adapted):

- Site initiation visit (SIV) prior to activation.
- First routine visit approximately 4–8 weeks after first randomization, then at risk-based intervals (e.g., every 6–10 weeks during active enrollment and as needed thereafter), with continuous centralized oversight.
- Closeout visit upon site completion to confirm data resolution, device reconciliation, essential document completeness, and archival readiness [1,2].

Source data verification (SDV) and source data review (SDR)

Monitors will perform 100% SDV/SDR of CtQ data and targeted sampling of non-CtQ data, with adjustments based on risk signals and performance [1,2].

- 100% SDV/SDR:

- Informed consent and, if used, eConsent audit trail entries; confirmation of identity verification method (e.g., national electronic ID) and use of the current IRB/IEC-approved version before any procedures [1,2].
- Eligibility criteria and medical confirmation of diagnosis; documentation supporting inclusion/exclusion determinations.
- Randomization assignment, stratum (DPI/MDI/both), allocation concealment records, and adherence to blinding procedures.
- Primary endpoint source: standardized inhalation technique assessment at 6–12 weeks, including objective measures from the investigational app-module (e.g., PIF/time to PIF/inspiration time as applicable) and corresponding site assessments per protocol.
- All SAEs and all UADEs, including causality, expectedness vs RSI/IB, outcomes, and expedited reporting evidence to authorities/IRB/IEC per jurisdictional timelines [1,3,4].
- Device accountability: receipt, assignment, updates, returns, losses/damage, quarantine status, and reconciliation; device deficiency/complaint linkages and CAPA [1,3].

- Targeted SDV/SDR (risk-adjusted sampling, initial 20–50% then adapt based on quality signals):

- Non-serious AEs, concomitant medications, non-critical demographics, and non-primary endpoint secondary/exploratory measures.
- Routine administrative documents (e.g., certain training records) once process reliability is demonstrated.

- Monitors may escalate to 100% SDV for any domain exhibiting material error rates, systematic issues, or underperformance [1,2].

Centralized monitoring, KRIs, and tolerance limits

The sponsor will operate centralized analytics to detect data quality and protocol compliance issues early, consistent with ICH E6(R2)/ISO 14155 quality by design principles [1,2].

- KRIs/tolerance limits (examples; thresholds defined in the Monitoring Plan):

- Consent errors or missing consent elements >0% (zero tolerance for any participant).
- Eligibility misclassification ≥1 participant or >2% of enrolled at a site.
- Primary endpoint missingness >5% of expected assessments or rate differing by >2 SD from peers.
- Late SAE/UADE reporting beyond regulatory timelines or discrepancy vs complaint system reconciliation.
- Device accountability variance >0% at reconciliation (zero tolerance for unreconciled investigational devices).

- Signals above thresholds trigger targeted queries, remote checks, CAPA requests, increased SDV, or for-cause visits.

Roles, independence, and access

Monitors (CRAs) are trained on protocol, device, and GCP, operate to written SOPs, and are independent of site clinical decision-making. Sites must permit direct access to source documents and essential records for monitors, auditors, and inspectors, including validated eSystems with Part 11/Annex 11 audit trails and role-based access [1,2,4].

Deviation management, escalation, and CAPA

All deviations are documented within defined timelines, classified, assessed for impact on participant safety/rights and data integrity, and linked to CAPA with effectiveness checks, consistent with ISO 14155/ICH-GCP/MDR/FDA IDE where applicable [1–4].

- Classification:

- Major: actual or potential impact on safety/rights, primary endpoint integrity, consent validity, or randomization/blinding; late or missing reportable safety submissions.
- Minor: administrative or procedural deviations without material impact.

- Actions:

- Immediate containment/correction for major deviations; notify sponsor same day when safety impact suspected; IRB/IEC and authority notifications per local regulation and sponsor SOPs [1,3,4].
- CAPA includes root cause analysis, corrective steps, preventive measures (process change, retraining, system enhancements), and effectiveness verification by CRA/QA. Repeat or systemic issues escalate to enhanced monitoring, enrollment hold, or site termination if unresolved [1,2].

Safety oversight interface and communications

Monitoring integrates with safety surveillance to ensure complete, timely detection and reporting of AEs/SAEs/UADEs, and alignment with device complaint/deficiency systems per MDR and IDE rules as applicable [1,3,4].

- Verification:

- 100% SDV of SAEs/UADEs; reconciliation between safety database, eCRF, and device complaint system; verification of expedited submissions and acknowledgments.
- Prompt escalation of safety trends to the Medical Monitor and DSMB per charter, preserving blinding unless unblinding is required for subject safety [1,2].

- Urgent safety measures:

- Sites may implement measures necessary to eliminate immediate hazards; notify sponsor and IRB/IEC/authorities without delay per regulation [1,3,4].

Monitoring visit types, minimum activities, and deliverables

- Site selection/qualification: verify feasibility inputs, staff qualifications, infrastructure, eSystems readiness, device handling capability, and privacy/security controls.
- Site initiation: train staff; verify approvals, contracts, insurance; confirm Delegation-of-Authority, device accountability setup, and baseline logs.
- Routine monitoring (on-site/remote):

- Perform SDV/SDR per scope; verify consent, eligibility, endpoint data, safety reporting, device accountability, training/delegation, query management, and essential documents.
- Review deviations/CAPA, KRIs, and tolerance limits; assess blinding integrity and randomization controls.

- For-cause: focused investigation of suspected non-compliance, safety risks, data integrity issues, or complaints.
- Closeout: ensure data resolution and lock readiness; reconcile devices; finalize deviations/CAPA; verify ISF completeness and archival instructions.

Each visit yields a signed visit report and follow-up letter with findings, actions, responsible persons, and due dates. Findings are tracked to closure in the issue log; unresolved critical items escalate per SOP.

Data handling, privacy, and eSystems

Monitoring verifies that eConsent, EDC, and other computerized systems are validated, Part 11/Annex 11 compliant, and employ ALCOA+ principles with audit trails. Role-based access, identity verification (e.g., national e-ID for eConsent where used), and GDPR or applicable privacy compliance are confirmed and periodically reviewed [1,2,4].

Templates and tools

- Monitoring Plan (controlled document; summary)

- Objectives, roles, training, and independence.
- CtQ factors and mapping to SDV/SDR scope.
- Centralized monitoring KRIs and tolerance limits with decision rules.
- Visit schedule, triggers, and deliverables.
- Deviation classification, CAPA workflow, and escalation pathways.
- Safety verification and reconciliation procedures.
- Blinding safeguards, data privacy/security checks, and system validation verification.
- Quality metrics, thresholds for increased monitoring, and documentation standards [1,2].

- Monitoring Visit Report template (site-level deliverable)

- Header: study ID/title; site ID; PI; CRA; visit type; date(s); report version.
- Scope: activities performed (on-site/remote), participant IDs sampled, SDV/SDR percentages, KRIs reviewed.
- Findings by domain:
  - Regulatory/ethics approvals and essential documents.
  - Training and Delegation-of-Authority.
  - Informed consent/eConsent verification.
  - Eligibility, randomization/blinding.
  - Endpoint/source data and data quality.
  - Safety events (AE/SAE/UADE), reporting timeliness, reconciliation.
  - Device accountability and deficiency/complaint handling.
  - Data privacy/security and system compliance.
  - Deviations and CAPA (status/effectiveness).
- Action items: description; responsible person; due date; risk rating.
- Conclusion: site status; recommended monitoring intensity; escalation (if any).

- Signatures: CRA; PI acknowledgement (date).

- Deviation and CAPA Log (site and sponsor-tracking)

- Columns: log version; site ID; subject ID (if applicable); deviation ID; date identified; category; description; major/minor; impact assessment; immediate correction; root cause; CAPA actions (responsible, due date); notifications (IRB/IEC/authority dates/refs); status; effectiveness verification (date/outcome); closure date.

- Safety Communication Memo template (expedited or important safety information)

- Header: study ID/title; memo ID/version/date; distribution list; blinding impact statement.
- Subject: summary of new safety information (event/aggregate signal/UADE/urgent measure).
- Details: description; affected device/app versions; incidence; severity; relatedness; expectedness vs RSI; risk assessment.
- Required actions: site instructions (e.g., enhanced vigilance, additional assessments, temporary enrollment hold, device update, re-consent).
- Reporting: regulatory/IRB/IEC submissions performed or required and timelines.
- Contacts: Medical Monitor and Safety Officer.
- Attachments: Q&A, updated RSI/IB extracts, revised documents (if applicable).
- Acknowledgement: site receipt/implementation confirmation.

Quality assurance interface and audits

Monitoring outputs feed the sponsor quality system. QA may audit sites, processes, and vendors independently of monitoring; audit findings trigger CAPA and may adjust the monitoring intensity. All monitoring and audit records are filed in the TMF/ISF and maintained for the longest applicable retention period under MDR and FDA IDE [1,3,4].

Documentation standards and timelines

- Visit reports and follow-up letters issued within 10 business days of visit end; sites respond and implement actions within agreed timelines.
- Critical safety or major non-compliance findings are communicated the same day to the Sponsor-Investigator and Medical Monitor, with immediate containment steps documented and reportable notifications made per regulation [1,3,4].
- All changes to monitoring scope or frequency are documented with rationale linked to KRIs, performance, or amendments, consistent with SPIRIT 2025 transparency principles [2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
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5. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). SPIRIT 2025 Statement and Checklist. 2025. https://www.spirit-statement.org/

10.5 Supplemental Applications (Amendments)

Amendment governance and definitions

All changes to the approved protocol, Investigator's Brochure/Risk Summary Information (IB/RSI), informed consent materials, device documentation, statistical analysis plan (SAP), monitoring plan, case report forms/eClinical systems, or other essential documents will be controlled under a documented amendment process compliant with ISO 14155, ICH E6(R2), EU MDR (including substantial modifications to clinical investigations), and, where applicable, FDA IDE supplemental application requirements [1–5]. Changes intended solely to eliminate an immediate hazard to participants may be implemented without prior approval; required notifications must be submitted promptly per jurisdictional rules [1,3–5].

- Substantial amendment/modification:
  - A change likely to have a substantial impact on participant safety, rights, or well-being, or on the scientific value of the investigation (e.g., primary objective/endpoint, eligibility criteria, visit schedule affecting primary endpoint ascertainment, risk information, device design/software update affecting performance/safety, statistical hypotheses/sample size) [1,3,4].
- Non-substantial (administrative) amendment:
  - Editorial or administrative changes without material impact on risk, subject rights, or data integrity (e.g., contact details, minor clarifications not altering intent) [1,3].

The Sponsor-Investigator (SI) is responsible for determining amendment materiality, obtaining required approvals, training sites, maintaining version control, and ensuring consistent implementation across sites before resuming enrollment or affected activities [1–4].

Triggers for amendments

- Safety and risk:
  - Newly identified or changed device risks (e.g., UADE trend), updates to RSI/IB, introduction of risk controls, or urgent safety measures [1,3].
- Device/software:
  - Software update to the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5) that could affect data capture, user interface impacting use, algorithms for inhalation assessment (e.g., PIF/time-to-PIF/inspiration time), interoperability, security, or performance; associated verification/validation (V&V) and cybersecurity documentation updates per applicable software lifecycle standards [1,3,6].
- Scientific/operational:
  - Changes to objectives/endpoints, sample size, analysis populations, randomization, eligibility, assessments, follow-up windows, or procedures for device handling/training.
- Regulatory/ethics:
  - Changes required by IRB/IEC or competent authority; updates to consent content, privacy notices, or data sharing arrangements.
- Administrative:
  - Corrections to typographical errors, staff/contact updates, or clarifications with no impact on risk or scientific validity.

Approval workflow and decision pathway

- Impact assessment:
  - SI initiates change request with a documented rationale, risk assessment, and change impact analysis (on safety, rights, scientific validity, endpoints, and operational feasibility), including cross-references to the risk management file and device complaint/deficiency trends [1,3].
- Internal scientific/safety review:
  - Medical Monitor and, as applicable, DSMB review changes with safety/scientific implications; manufacturer technical sign-off for device/software amendments; QA review for QMS/change control alignment [1–3].
- Submissions and approvals (prior to implementation unless to eliminate immediate hazard):
  - IRB/IEC approval of substantial amendments; acknowledgement for non-substantial per local policy [1–4].
  - EU MDR: notify/apply to competent authority for substantial modifications to the clinical

investigation; await authorization/non-objection per national process [3].
- FDA IDE (if applicable): submit an IDE supplement for significant changes; implement only after FDA approval unless to eliminate immediate hazards (with 5-working-day notification) [4].

- Registry updates:

- Update WHO-ICTRP–recognized registry (e.g., ClinicalTrials.gov) with current protocol version, outcomes, eligibility, and other fields within mandated timelines (e.g., generally within 30 days of approval) to maintain transparency [2,5].

- Site activation of amendment:

- Following required approvals, the SI issues an amendment activation memo with effective date, affected documents, required training, and instructions. Sites must complete training and update local materials before applying the amendment to participants.

Timelines and urgent safety measures

- Urgent safety measures to eliminate immediate hazards may be implemented immediately; notify IRB/IEC and competent authorities without delay as required by ISO 14155/MDR; for IDE studies, notify FDA within 5 working days if implemented without prior approval [1,3,4].
- Routine substantial amendments: seek and obtain requisite approvals before implementation. Where multiple jurisdictions are involved, site-specific implementation follows local approval/authorization receipt [1,3,4].
- Sponsor target timelines:

- Internal impact assessment and dossier preparation: typically ≤10 business days from trigger identification.
- Site training and document distribution: typically ≤10 business days after final approval.

Documentation requirements

For each amendment, maintain in the Trial Master File (TMF) and site Investigator Site File (ISF):

- Amendment package: cover letter; summary of changes; redline/clean versions; rationale and risk assessment; list of impacted documents; V&V evidence for device/software/eClinical changes; cybersecurity/privacy impact assessment (as applicable) [1,3,6].
- Approvals/acknowledgements: IRB/IEC approvals; competent authority authorizations/notifications; FDA IDE correspondence if applicable; registry update confirmation [2–5].
- Training and implementation records: training materials, attendance logs, updated Delegation of Authority (if roles affected), site acknowledgment of receipt and effective date, updated SOP/work instructions (as applicable) [1,2].
- Participant-facing materials: revised consent/assent forms, recruitment materials, and documented re-consent where required [1,2].
- Version control: updated master list of essential documents and versions with effective dates; controlled distribution log [1–3].

Site responsibilities

- Do not implement an amendment until receipt of site-level IRB/IEC approval/acknowledgement and sponsor activation memo, except for urgent safety measures [1–4].
- Ensure local translations (if applicable) are IRB/IEC approved and consistent with the master version.
- Complete required training, update source templates and eCRFs, and confirm device/app configuration aligns with the approved version prior to use.
- File all amendment documents and training records in the ISF and permit monitor verification.

Re-consent requirements and workflow

- Triggers for re-consent:

- New or modified risk information, alternative procedures, or changes in potential benefits that may influence willingness to continue [1,2].
- Changes to primary or key secondary objectives/endpoints affecting participant commitments.
- Alterations to procedures, visit schedules, or duration that meaningfully affect burden.
- Modifications to data privacy, data sharing, or biospecimen use; new countries/partners involved in data transfer [2].
- Device/software changes that alter user interaction, safety profile, or data collected from participants.

- Workflow:

- SI provides IRB/IEC-approved revised consent and site instructions; sites contact active participants promptly to discuss changes, answer questions, and obtain documented re-consent before continuing affected procedures.
- Where permitted, validated electronic re-consent using national electronic identification (e.g., BankID or equivalent) may be used, ensuring correct versioning and audit trails.
- Document re-consent discussions in source notes; file signed consent; update participant status in EDC; track completion to 100% of applicable participants before resuming impacted activities for each participant.

- Timelines:

- Safety-driven re-consent: initiate without delay upon approval/activation; complete at the next participant contact or sooner if required by IRB/IEC.
- Administrative clarifications: re-consent not typically required; provide information letter if requested by IRB/IEC.

Amendment log template

Field	Description
Amendment ID/version	Unique ID; version and date
Affected document(s)	Protocol/IB/RSI/ICF/SAP/Monitoring Plan/CRF/eSystems/Device docs
Amendment type	Substantial or non-substantial (administrative)
Rationale/trigger	Safety, device/software, scientific, regulatory, administrative
Summary of change(s)	Concise description; reference to redline
Impact assessment	Safety/rights, scientific validity/endpoints, operations
Related risks/CAPA	Link to risk file; CAPA if deviation-related
Internal reviews	Medical Monitor; DSMB (if applicable); QA; manufacturer sign-off
Submissions	IRB/IEC; Competent Authority; FDA IDE (if applicable); registry
Approvals/acknowledgements	Dates and reference numbers; conditions
Site communications	Activation memo date; training materials issued
Site implementation	Site(s) effective date; pending sites; notes
Re-consent required	Yes/No; completion status (%); rationale
eSystems/device V&V	Summary of validation, UAT, and deployment controls
Archival	TMF/ISF filing location; completeness check
Closure	Amendment closed date; responsible person

Re-consent checklist (site use)

- Confirm receipt of IRB/IEC-approved revised consent and site activation memo.
- Identify participants requiring re-consent; generate list with status and due dates.
- Use the current approved language and version; verify correct language/translation.
- Schedule participant contact; provide sufficient time for questions.
- Obtain signatures and dates from participant and authorized study staff; provide participant copy.
- For eConsent, verify identity via approved method (e.g., BankID or equivalent) and confirm audit trail and version.

- Document discussion in source notes; update EDC re-consent status and date.
- For participants not reachable, implement contingency plan per site policy (e.g., certified mail, secure portal message) and document attempts.
- Do not perform impacted procedures until re-consent is obtained; if urgent safety changes are protective only, follow IRB/IEC guidance.
- File documents in ISF; make available for monitoring.

Controls for software/device amendments

- Prior to deployment of any update to the investigational inhalation app-module or associated AsthmaTuner system components used in the study:

- Complete change impact analysis, risk control evaluation, and V&V commensurate with change classification; maintain traceability per software lifecycle practices (e.g., requirements, tests, results, approvals) [1,3,6].
- Confirm compatibility with study workflows, endpoints (e.g., PIF/time-to-PIF/inspiration time assessments), and data integrity.
- If the update is a substantial modification, obtain required ethics/regulatory approvals before enabling for participants.
- Control rollout to prevent exposure of non-approved versions to participants; maintain device/account version logs and reconcile with participant use.

Communications, monitoring, and audit

- Monitors will verify amendment approvals, site training, correct use of current versions, and re-consent documentation. Deviations from amendment implementation requirements will be managed per deviation/CAPA processes.
- QA may audit amendment processes, including change control and validation of device/software and eClinical updates, and verify registry transparency updates [1–3].
- The SI will ensure all stakeholders receive timely communications and instructions, including DSMB updates for safety-relevant amendments.

References

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10.6 Maintaining Records

Scope and principles

Essential records will be created, collected, maintained, and archived to reconstruct and evaluate the conduct of this Phase III confirmatory clinical investigation of the investigational inhalation app-module

embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) in accordance with ISO 14155, ICH E6(R2), EU MDR, and, where applicable, FDA IDE and Part 11/Annex 11 requirements [1–6]. Records will be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available (ALCOA+), with validated audit trails for electronic systems and role-based access aligned with privacy laws (e.g., GDPR) [2,4–6].

Essential-documents index (TMF/ISF master list)

The Sponsor-Investigator (TMF) and each site (ISF) will maintain the following controlled documents. The master list will be versioned, dated, and periodically reconciled by monitoring and QA.

Category	Document/record
Governance and approvals	Final and prior protocol versions; Investigator's Brochure/Risk Summary Information; IRB/IEC approvals and correspondence; competent authority submissions/authorizations/notifications; registry confirmations; DSMB charter/membership and recommendations; Medical Monitor appointment
Plans and specifications	Statistical Analysis Plan; Monitoring Plan; Data Management Plan; Safety Management/Pharmacovigilance Plan; Risk Management File cross-references; Device/software V&V packages and cybersecurity assessments relevant to the investigation
Site and personnel	Feasibility/qualification reports; clinical trial agreement/financial terms; insurance/indemnification; PI/sub-investigator CVs and licenses; GCP and study/device training logs; Delegation-of-Authority Log; staff signature log; financial disclosure/COI forms
Participant-facing materials	All approved ICFs/assents/translations; recruitment/advertising; privacy notices; re-consent versions; eConsent configuration and validation summaries where used
Randomization/blinding	Randomization list generation approvals (blinded); allocation concealment documentation; unblinded access logs (if any)
Source and data	Source document templates; completed source notes; certified copies; eSource configuration; EDC specifications/edit checks; data entry guidelines; codebooks; medical coding dictionaries; data queries and resolutions; audit trails; data extracts and transfer specs
Safety and device deficiency	AE/SAE/UADE reporting forms; narratives; expedited submissions and acknowledgments; safety listings; reconciliations between eCRF–safety–complaint systems; device deficiency/complaint files and CAPA linkages
Device accountability and configuration	Device receipt/dispensation/return/reconciliation logs (spirometers, Airflow Trainer); quarantine and loss/damage records; calibration/functional verification (as applicable); app/device version and configuration logs; deployment/rollback records; prohibited version controls
Operational correspondence	Monitoring visit reports and follow-up letters; issue logs/CAPA; audit reports and responses; inspection communications; deviation/violation logs and impact assessments
Statistical and reporting	Randomization seed custody; interim/aggregate listings; blinded/unblinded analysis approvals per SAP; database lock documentation; Clinical Investigation Report and lay summary; registry results postings
Privacy and security	Data protection impact assessment(s) (if required); data processing agreements; data retention and destruction records; access control reviews; incident/security breach documentation and resolutions
Archival	TMF/ISF completeness checklists; index and file plans; archival certificates; retrieval logs

Record creation, control, and audit trails

- Electronic records and signatures will comply with 21 CFR Part 11 and EU Annex 11, including validated systems, unique user accounts, role-based access, time-stamped audit trails, and secure, computer-generated logs for create/modify/delete/e-signature events [3,4].

- Paper records will be controlled via numbered templates, controlled copy distribution, and certified copy procedures for scanning to eTMF/eISF where permitted [1,2].
- All document versions will display document ID, version number, effective date, owner/approver, and superseded status; change histories will be retained [1,2].
- eConsent systems (where used) must capture identity verification method (e.g., BankID or similar), consent version, timestamps, signer identities, and complete audit trails; validation and SOPs will be filed in TMF/ISF [1,2,5].

Access management and inspection readiness

- Direct access will be granted to authorized monitors, auditors, and inspectors to source data, records, and systems, preserving confidentiality per consent and law [1,2].
- Access provisioning, modification, and deprovisioning will follow least-privilege principles with periodic reviews; access logs will be retained and audited [2,4,6].
- Redaction/pseudonymization procedures will protect personal data in shared materials; re-identification keys will be restricted to authorized personnel [5,6].

Retention-rules matrix

Records will be retained for the longest applicable period among MDR, ISO 14155/ICH-GCP, FDA IDE (if applicable), institutional policies, and contractual requirements, and consistent with GDPR storage limitation principles [1–6].

Record class	Minimum retention trigger	Minimum retention period	Regulatory basis
TMF (sponsor) essential documents	End of clinical investigation or last regulatory submission related to the investigation, whichever is later	At least 10 years after end of the clinical investigation, or longer per national law/contract	ISO 14155; MDR [1,2]
ISF (site) essential documents	Site closeout and resolution of all queries/monitoring findings	At least 10 years after end of the clinical investigation at the site, or longer per national law/institutional policy	ISO 14155; MDR [1,2]
FDA IDE-regulated records (if applicable)	Latter of investigation completion/termination or when no longer required to support a marketing application	At least 2 years after the later of investigation completion/termination or marketing application decision	21 CFR 812.140(d) [3]
Safety reports and device complaints	Final resolution of case and submission obligations	Align with TMF/ISF retention; not less than the TMF minimum	ISO 14155; MDR [1,2]
Participant source and eCRF data	Last data collection from participant and query closure	Align with ISF/TMF minimums; not less than 10 years or local requirement	ISO 14155; ICH E6(R2) [1,2]
eSystems validation, audit trails, access logs, backups	System retirement and database lock/archival	Not less than TMF/ISF minimum; audit trails retained for the life of the record	21 CFR Part 11; Annex 11 [4]
Contracts/financial/COI	Contract closure and final payment/reconciliation	Not less than TMF minimum; longer if required by finance/tax law	ICH E6(R2) [2]
Privacy/GDPR documents and DPIAs	Final processing activity or data destruction	Retain as long as necessary to demonstrate compliance; align with TMF	GDPR [5]

If multiple rules apply, the longest period governs. Any legal hold supersedes routine destruction until

released.

Archiving and retrieval SOP outline

- Responsibilities and training
  - Define Sponsor-Investigator, site PI, records manager, and archivist roles; require documented training on archiving SOPs and system use [1,2].
- File structure and indexing
  - Maintain controlled TMF/ISF indices mapped to essential-document categories; apply consistent naming conventions and metadata (document type, site, participant ID, version, dates) [1,2].
- Version control and change management
  - Enforce document lifecycle (draft–review–approve–effective–superseded–archived) with controlled distribution; retain redlines and approval records [2,4].
- Electronic systems validation
  - Validate eTMF/eISF/EDC/eConsent per risk-based CSV; document user requirements, test scripts/results, deviations, and approvals; maintain periodic review and revalidation triggers [4].
- Security, backup, and business continuity
  - Implement encryption at rest/in transit; multi-region backups; tested disaster recovery (RTO/RPO defined); environmental controls for physical archives (temperature, humidity, fire/flood protections) [4,6].
- Access controls and privacy
  - Role-based permissions; access recertification at defined intervals; procedures for data subject rights (access, rectification, erasure where applicable) and breach notification workflows [5,6].
- Receipt, filing, and completeness checks
  - Time-bound filing SLAs; QC of incoming documents; periodic TMF/ISF completeness reviews and reconciliation with monitoring/audit checklists; deficiency remediation and CAPA [1,2].
- Transfer, migration, and media longevity
  - Controlled handovers between vendors/sites; validated data migrations with pre/post reconciliation; file format policies for long-term readability (e.g., PDF/A) [4].
- Retrieval and inspection support
  - Document request tracking, controlled export with redaction where required, and post-inspection reconciliation; maintain retrieval logs [1,2].
- Retention and destruction
  - Maintain retention calendars; place/track legal holds; authorize destruction only after confirmatory checks by quality and legal; document destruction certificates; irreversible deletion for electronic records with audit trail entries; ensure destruction does not contravene GDPR or regulatory mandates [2,5].

Site responsibilities for maintaining records

- Create and maintain complete, contemporaneous source documents for each participant; ensure concordance with eCRFs; correct errors per SOPs with legible single-line strike-throughs, dating, and initialing or compliant e-signature with audit trail [1,2,4].
- Maintain device accountability logs for spirometers and Airflow Trainer, and app-version/configuration logs linked to participant assignment and visit dates; reconcile at each monitoring visit and at closeout [1,2].
- File current IRB/IEC approvals; use only current approved ICFs; maintain eConsent audit trails and identity verification records where used; document re-consent [1,2,5].
- Safeguard confidentiality; restrict direct identifiers to secure, access-controlled locations; maintain participant identification logs separately from clinical data, with controlled linkage keys [2,5].

Sponsor-Investigator responsibilities for maintaining records

- Maintain a complete TMF with ongoing QC and reconciliation; ensure that all essential documents are available at any time for audit/inspection; periodically verify system audit trail integrity and access appropriateness [1,2,4].
- Ensure CRO/vendor records (e.g., monitoring, data management, safety, eClinical, logistics) are contractually part of the TMF and are transferred or made available for inspection and final archival [1,2].
- Reconcile safety and device complaint systems with clinical data; maintain CAPA and deviation logs with closure evidence; ensure alignment across TMF domains [1,2].

Handling protocol amendments, software updates, and versions

- Before implementing a substantial amendment or device/software update, file the approved documents, impact assessments, and V&V evidence; update the essential-documents index and distribution lists; capture deployment dates and affected participant/device IDs; ensure obsolete versions are withdrawn and quarantined from use [1–4].
- Maintain a device/app version registry mapping AsthmaTuner/inhalation module versions to participants and timeframes to support data interpretation and safety traceability [1,3].

Data integrity checks and reconciliation

- Perform periodic reconciliations among source, eCRF/EDC, safety database, device/app telemetry, and complaint/deficiency logs with documented outcomes and issue resolution; preserve system-generated audit trails demonstrating who performed each action and when [1,2,4].
- Centralized monitoring outputs, KRIs, and tolerance limits, as well as audit findings, will be filed and linked to CAPA with effectiveness verification records [1,2].

References

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10.7 Submitting Reports

Scope and governing standards

This section defines what reports must be submitted, to whom, when, by whom, with what content, and how quality and acknowledgments will be controlled for this Phase III confirmatory clinical investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5;

MediTuner AB; SRN SE-MF-000028534). All submissions will comply with ISO 14155, ICH E6(R2), EU MDR (and national implementing rules), FDA IDE requirements where applicable, SPIRIT 2025 transparency, WHO-ICTRP registration rules, and applicable privacy laws (e.g., GDPR) [1–7].

Core reporting workflow and quality controls

- Responsibilities

- Site PI: creates initial safety/deviation notifications, site annual progress reports, device deficiency/complaint initiations, and ensures IRB/IEC submissions and acknowledgments are filed.
- Sponsor-Investigator (SI): holds overall accountability; submits regulatory/competent authority reports, IDE reports if applicable, registry postings, and the final clinical investigation report; ensures DSMB communications and cross-system reconciliations.
- Medical Monitor/Safety Officer: medically reviews safety narratives and causality/expectedness; verifies alignment with RSI/IB and device risk files prior to submission.
- Data Management: verifies data extracts supporting reports; reconciles eCRF, safety, and device complaint systems.
- Quality Assurance (QA): independent QC of selected submissions and acknowledgment tracking; audits reporting processes.

- Pre-submission quality checks (as applicable)

- Medical review of safety narratives and causality/expectedness.
- Completeness and accuracy check against source, eCRF/EDC, safety database, and device complaint/deficiency files.
- Version control and cross-references to current protocol/RSI/IB and device/app versions.
- Privacy compliance (de-identification per GDPR or local law) for shared line listings or attachments.

- Submission proof and acknowledgment tracking

- File dated submission copies, transmission receipts, authority/IRB reference numbers, and formal acknowledgments/letters.
- Maintain a submission log with status and due dates; escalate overdue acknowledgments to the SI and QA.

Expedited safety and urgent measures reporting

- Unanticipated/serious events and device effects will be reported per ISO 14155/MDR and, if IDE applies, per 21 CFR 812.150. Investigators notify the SI and IRB/IEC without delay; UADEs are forwarded by the sponsor to regulators/IRBs within mandated timelines (e.g., no later than 10 working days under IDE) [1,3,4].
- Urgent safety measures taken to eliminate immediate hazards may be implemented immediately; notify SI, IRB/IEC, and competent authority/FDA without delay. For IDE studies, notify FDA within 5 working days if implemented without prior approval [1,3,4].

Periodic, annual, and final reporting

- Site annual continuing review reports to IRB/IEC at least annually and on request, including enrollment, deviations, SAEs/UADEs, risk–benefit assessment, and current documents [1,2].
- Sponsor annual progress report to FDA for IDE studies every 12 months from IDE approval; content per 21 CFR 812.150(b)(5) [4].
- Final site closeout report to IRB/IEC upon site completion/termination; Sponsor final clinical investigation report to competent authority as required under MDR; registry results and lay summary postings per applicable rules [1,3,5,7].

Registry transparency and public disclosure

- Register the study before first enrollment in a WHO-ICTRP–recognized registry; keep entries current, including amendments. Post summary results and any required lay summary within mandated timelines per registry/MDR requirements [3,5,7].

Device deficiency and complaint reporting

- Investigators report any device deficiency, malfunction, use error, or complaint to the SI/manufacturer promptly, linking cases to participants and device/app versions. The SI/manufacturer handles vigilance assessment and any reportable actions under MDR and local law. Cross-system reconciliation with safety reports is required before periodic and final submissions [1,3].

Deviations and non-compliance

- Significant protocol deviations/non-compliance with impact on safety/rights or data integrity are reported promptly to the SI and IRB/IEC and, where required, to authorities, with root cause and CAPA. Track to documented closure with effectiveness verification [1,2].

Reporting requirements table

Report	Trigger/frequency	Responsible party	Recipient(s)	Due date/timeline	Minimum content	Pre-submission QC	Evidence to file
Trial registration	Before first enrollment; updates as needed	SI/designee	WHO-ICTRP–recognized registry	Initial before first participant; updates within registry-specified timelines (typically ≤30 days)	Study identifiers; device; design; objectives/endpoints; eligibility; locations; status; amendments	Protocol/version check; consistency with approvals	Registry confirmation; record ID; timestamp
DSMB safety/conduct packet	Per charter (e.g., quarterly) and ad hoc	SI medical/safety team; DSMB chair consolidates	DSMB; SI receives recommendations	As per DSMB charter	Aggregate safety; enrollment/exposure; deviations; KRIs; recommendations	Data reconciliation (eCRF–safety–complaint); medical review; blinding safeguards	Transmittal record; DSMB minutes/recommendations
UADE expedited report	As soon as aware	PI (to SI/IRB); SI (to authorities/IRBs)	IRB/IEC; Competent Authority; FDA if IDE	Without delay per ISO 14155/MDR; ≤10	Event narrative; seriousness; relatedness; expectedness; outcomes;	Medical review; RSI/IB check; device	Dated submissions; authority/IRB acknowledgments; reference numbers

				working days to FDA/IRB under IDE [1,3,4]	corrective actions; device/app version	complaint linkage	
SAE report (non-UADE)	As soon as aware	PI (to SI/IRB); SI (per local law)	IRB/IEC; SI	Per IRB/IEC and national rules	Narrative; causality; outcome; follow-up	Medical review; source verification	Submission copy; acknowledgment
Significant deviation/non-compliance	Upon identification	PI/SI	IRB/IEC; authorities if required	Promptly per local policy	Description; impact; CAPA; preventive actions	QA review; root cause analysis	Submission/acknowledgment; CAPA log
Annual progress (site)	Annually and on request	PI	IRB/IEC	At least annually	Enrollment; deviations; SAEs/UADEs; risk–benefit; current documents	Internal consistency checks; signature	IRB/IEC acknowledgment
Annual IDE report (if applicable)	Every 12 months from IDE approval	SI	FDA	Annually	Progress; safety; deviations; device deficiencies; investigational plan changes	Medical/safety and QA review	FDA receipt/acknowledgment
Registry results and lay summary	After primary or study completion per rules	SI/designee	Public registry	Within mandated timelines	Primary/secondary outcomes; participant flow; harms; lay summary	Stats/medical review; de-identification	Posting confirmation; record links
Safety communication to sites	New important safety information	SI/Medical Monitor	All sites/IRB/IEC as required	Without delay	Signal summary; risk assessment; required actions; reporting status	Medical review; blinding check	Distribution log; site acknowledgments
Device deficiency/complaint	Upon awareness	PI (to SI/manufacturer)	SI/manufacturer; IRB/IEC if required	Promptly per SOP (e.g., ≤24–72 h)	Description; device/app version; circumstances; outcomes; remedial action	Link to safety case; risk file update	Complaint ID; investigation report; closure
Site closeout report	Site completion/termination	PI	IRB/IEC	Per IRB/IEC policy	Disposition; safety; deviations; accountability; data status	Monitor verification	IRB/IEC acknowledgment

Final clinical investigation report	Study completion	SI	Competent Authority (as required)	Within MDR/national timelines	CIR with methods/results; discussion; conclusions	Biostat/medical/QA review; sign-offs	Authority acknowledgment; version archive

Reporting calendar

Study phase/milestone	Report(s)	Target window	Owner	Dependencies	Acknowledgment to file
Pre-initiation	Trial registration; IRB/IEC approvals	Before site activation	SI/PI	Final protocol/ICF	Registry confirmation; IRB letters
First participant in	None mandatory beyond approvals	N/A	PI/SI	Activation memo	N/A
Enrollment ongoing (monthly)	DSMB packet (per charter); expedited UADE/SAE as needed; device complaints	DSMB per schedule; safety without delay	SI/PI	Data reconciliation	DSMB minutes; safety receipts
Annual from start	Site annual progress; IDE annual (if applicable)	Per IRB/IDE calendars	PI/SI	Data cut; safety summaries	Acknowledgment letters
Primary completion	Registry updates; results planning	≤30 days for registry status; results per rules	SI	Data QC	Registry confirmations
Site closeout	Site closeout report	Per IRB/IEC	PI	Monitor closeout	IRB/IEC acknowledgment
Study completion	Final clinical investigation report; registry results and lay summary	Per MDR/registry timelines	SI	Database lock; statistical review	Authority/registry acknowledgments

Acknowledgment tracking and escalation

- Maintain a live submission and acknowledgment log capturing report ID, version, date submitted, recipients, due date, and acknowledgment/reference numbers. Monitors and QA verify completeness at each visit/audit [1,2].
- Escalate overdue submissions or missing acknowledgments within 2 business days of missed timelines to the SI and QA; notify IRB/IEC/authorities if any regulatory deadline cannot be met, with rationale and recovery plan [1–4].
- Reconcile quarterly: eCRF/EDC, safety database, and device complaint system entries, ensuring all reportable items have been submitted and acknowledged; document reconciliation outcomes [1,2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
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10.8 Informed Consent

Informed consent process

- Consent will be obtained before any study-specific procedures, including screening for eligibility, device/account provisioning, randomization, or training. Investigators or qualified, delegated staff trained in Good Clinical Practice (GCP) will conduct the discussion in a setting that ensures privacy, adequate time for questions, and freedom from coercion [1,2].
- Consent options:

- Electronic consent (eConsent) using a validated system with identity verification via national electronic ID (e.g., BankID or equivalent) where permitted; system must provide version control, timestamps, and audit trails compliant with applicable electronic records/signature regulations [1–4].
- Paper consent using the currently approved language and version; handwritten signatures and dates by the participant (and parent/legal representative if required) and by the person obtaining consent [1,2].

- Decision time: Potential participants may take the consent form home, discuss with family or their clinician, and return on a later date. No study-related procedures will occur until consent is documented [1,2].
- Voluntariness and right to withdraw: Participation is voluntary. Participants may refuse or withdraw at any time without penalty or loss of standard care. Data and samples already collected will be retained and used as permitted by law and ethics approvals unless the participant requests otherwise and local law allows [1,2].
- Language and readability: Only IRB/IEC-approved consent materials in approved languages will be used. Plain-language, patient-friendly versions will be provided; interpreter support will be offered where permitted by IRB/IEC [1,2].
- Assent and parental permission: If local law requires additional protections for participants aged 16–17 years, IRB/IEC-approved assent and parental/legal representative permission will be obtained before any procedures [1,2].
- Copies: Each participant (and parent/guardian, if applicable) will receive a copy of the signed consent (electronic or paper) [1,2].
- Alternatives: Alternatives include standard inhaler education and training provided outside the study, without app-based training [1–3].
- Contacts: The consent will list contacts for study questions, rights as a participant, and safety concerns (site PI, study coordinator, and an independent ethics contact) [1,2].
- Costs, compensation, and injury: Any costs, reimbursements, participant compensation, and arrangements for treatment/compensation for research-related injury will be described in the site-specific consent. If required by local law (e.g., EU MDR), evidence of insurance/indemnification will be referenced. Details: to be confirmed per site and jurisdictional requirements [1,3].

Documentation, version control, and storage

- Only current IRB/IEC-approved consent versions and translations may be used. Version identifiers and dates must appear on every consent instance. Obsolete versions are withdrawn from use [1,2].
- Documentation:

- eConsent: identity verification method (e.g., BankID), signer identities, timestamps, and complete audit trails must be captured and filed in the eISF/TMF; a PDF of the executed consent is provided to the participant and filed by the site [1,4].
- Paper: original signed/dated forms are filed in the Investigator Site File (ISF) with a copy provided to the participant; key consent details are documented in source notes and eCRF [1,2].

- Retention: Consent records will be retained with essential documents for at least the longest applicable period under ISO 14155, MDR, ICH-GCP, FDA IDE (if applicable), and institutional policy (not less than 10 years in many jurisdictions), and in compliance with applicable privacy laws (e.g., GDPR) [1–3,5].
- Access and confidentiality: Monitors, auditors, and inspectors will have direct access to consent records, preserving confidentiality per consent terms and law [1,2,5].

Triggers and procedures for re-consent

- Re-consent is required when new information may affect a participant's willingness to continue, including:

- New or changed device risks; important safety information or Urgent Safety Measures.
- Substantial changes to objectives/endpoints, procedures, visit schedules, or duration that affect burden.
- Changes to privacy, data sharing, or international data transfers.
- Device/software updates that change user interaction, safety profile, or data collected [1–3].

- Sites will use only IRB/IEC-approved revised consent materials and obtain re-consent before continuing affected procedures. Identity verification and audit trails are required for eRe-consent; all re-consent discussions are documented in source notes and tracked to completion [1–3].

Consent timing relative to study workflow

- Pre-screening that uses only de-identified feasibility checks may occur per IRB/IEC guidance. Any collection of identifiable health data or use of investigational devices/app, spirometer, or Airflow Trainer requires prior documented consent [1].
- Randomization, device/app activation, inhaler technique education/training, and any study assessments occur only after consent [1,2].

Roles and training

- Only investigators/sub-investigators and staff listed on the Delegation of Authority log, trained on this protocol, the consent materials, and GCP, may conduct the consent discussion and document consent [1,2].
- Staff must be trained on identity verification and audit-trail requirements for eConsent systems compliant with applicable electronic signature rules [1,4].

Privacy, data use, and data sharing summary for consent

- The consent will explain what personal data are collected (e.g., contact details, health status, inhaler type, inhalation technique metrics such as peak inspiratory flow, time to peak inspiratory flow, and inspiration time captured through the investigational app-module used with the CE-marked AsthmaTuner spirometer, plus usability/feasibility and safety information), why they are needed, who may see them (study team, sponsor, monitors/auditors/inspectors, device manufacturer as needed for safety/complaints), how they are protected, how long they

are kept, and participant rights under applicable privacy laws (e.g., access, rectification, restriction, where applicable) [1–3,5].
- Cross-border data transfers, if any, and de-identification/pseudonymization practices will be described per site and legal requirements [5].

Participant safety information for consent

- The consent will describe potential risks or discomforts related to:

- Use of the app-module, spirometry, and training devices (e.g., transient coughing, lightheadedness during forceful breathing maneuvers); device deficiencies/malfunctions; data security/privacy risks despite safeguards [1,3,5].
- Randomization and the possibility of receiving standard education alone.
- Oversight by an independent Data Safety Monitoring Board (DSMB) will be disclosed, including its role in reviewing safety and advising on risk mitigation [1,2].

Consent checklist (site use)

- Verify current IRB/IEC-approved consent version and language; remove obsolete versions from circulation.
- Confirm the participant meets pre-consent prerequisites (e.g., age ≥16 years; capacity to consent; if minor per local law, obtain assent and parental permission).
- Provide sufficient time to review; answer all questions; assess understanding and voluntariness; offer interpreter if needed and approved.
- Confirm alternatives to participation and the right to withdraw without penalty are explained.
- For eConsent: verify participant identity via approved method (e.g., BankID); ensure the system records version, timestamps, and audit trail; provide a copy to the participant.
- For paper consent: obtain signatures/dates from participant and consent-obtainer; provide a copy to the participant; file original in ISF; document in source and eCRF.
- Document whether optional consents (if any) are accepted or declined.
- Do not perform any study-specific procedures until consent is complete and documented.
- For re-consent: use approved revised materials; document discussion; obtain new signatures/eSignatures; update tracking to 100% completion for applicable participants.
- File all consent records; make them available for monitoring/audit/inspection.

Informed Consent Form (ICF) template skeleton (participant-facing)

- Title of the research and short study summary

- A Phase III study of an investigational inhalation training app-module embedded in AsthmaTuner (version >5.4.13.5) for people with asthma and/or COPD who use a dry powder inhaler (DPI) or metered dose inhaler (MDI).

- Key information (concise overview)

- What is this study about? How long will it take (6–12 weeks)? What will I do? What are the main risks and possible benefits? That participation is voluntary and you can stop at any time.

- Why am I being asked?

- You are ≥16 years old and have a documented diagnosis of asthma and/or COPD and use a DPI or MDI daily.

- Purpose of the study

- To find out if app-based education and training improve correct inhalation technique compared with standard education alone.

- What will happen if I join?

- Screening to confirm eligibility.
- Random assignment (like flipping a coin) to one of two groups (1: standard care plus app-based education and training using the AsthmaTuner system; or 2: standard education only).
- Single-blind means you will not know which training approach is being evaluated to reduce bias.

- If assigned to the app group: download the AsthmaTuner app, receive a spirometer and Airflow Trainer (by mail or at clinic), and complete guided inhalation training and assessments at home or clinic.
- If assigned to standard education: receive inhaler education using a standardized checklist without the app.
- Follow-up visit about 6–12 weeks after starting to assess inhalation technique.

- Study devices and how they are used

- Investigational app-module integrated in the AsthmaTuner app (iOS/Android).
- CE-marked AsthmaTuner spirometer and the Airflow Trainer (not in direct contact with your mouth or skin) may be provided for training and assessments.

- Time and study duration

- About 6–12 weeks, including training and one follow-up assessment.

- Possible risks and discomforts

- Temporary cough, throat irritation, or lightheadedness during breathing maneuvers; frustration or fatigue during training; data privacy/security risks despite safeguards; device malfunction risks (with instructions on what to do and contact information).

- Possible benefits

- You may improve your inhalation technique. Information from this study may help future patients. Benefits are not guaranteed.

- Alternatives

- Usual inhaler education and clinical care outside the study.

- Confidentiality and data protection

- What data we collect (contact, health, inhaler type, inhalation measurements such as peak inspiratory flow, time to peak inspiratory flow, and inspiration time, usability/feasibility and safety information), how we protect it, who may see it (study staff, sponsor, monitors/auditors/inspectors, manufacturer for safety/complaints), how long we keep it, and your rights under applicable privacy laws (e.g., access and correction).

- Results and new information

- You will be told about important new information that may affect your willingness to continue. Study results may be shared on public registries in summary form; your identity will not be revealed.

- Compensation, costs, and injury

- Any reimbursements or costs, if any, and how research-related injuries are treated/compensated. Site-specific details: to be confirmed.

- Voluntary participation and withdrawal

- Your decision will not affect your usual care. You may stop at any time without penalty. Tell the study team if you wish to stop; we will discuss options for your ongoing care.

- Contacts

- Study team contact for questions, a 24-hour contact for safety concerns, and an independent ethics contact.

- Authorization and signatures

- Statement of consent and authorization to use/share data as described; options to allow or decline any optional parts (if applicable).
- Signature/date lines for participant and the person obtaining consent; if applicable, parent/guardian permission and participant assent.
- For eConsent, statement confirming identity verification via national e-ID (e.g., BankID) and that a copy will be provided to you.

Versioning, languages, and local customization

- The sponsor will provide master consent templates. Sites will adapt for local language(s), contact details, compensation/injury arrangements, and privacy notices, and obtain IRB/IEC approval before use. Only approved languages and versions may be used. A consent version log will be maintained at each site and in the TMF [1–3,5].

Data systems and audit trails for consent

- eConsent systems must be validated and Part 11/Annex 11 compliant, with role-based access, identity verification, and complete audit trails (version used, who signed, timestamps, and any amendments). System validation and configuration records will be filed in the TMF/ISF [1,4].

Special situations

- Participants with impaired decision-making capacity are not eligible unless local law and IRB/IEC permit and additional safeguards are in place; otherwise, they will not be enrolled. If a participant loses capacity during the study, continued participation will follow IRB/IEC guidance with legally authorized representative involvement and re-consent as appropriate [1,2].
- If a participant turns the age of legal consent during the study, re-consent will be obtained from the participant at the next visit or earlier as required [1,2].

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11 STUDY DATA REPORTING AND PROCESSING

11.1 Data Processing and Quality Control

Overview and governance

Data for this Phase III confirmatory investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) will be processed under a unified Data Management Plan (DMP) aligned with ISO 14155, ICH E6(R2), SPIRIT 2025, 21 CFR Part 11/812, EU Annex 11, GDPR, and applicable information security and software lifecycle standards (ISO/IEC 27001, IEC 62304, IEC 81001-5-1) [1–9,13]. The Sponsor-Investigator (SI) has overall accountability for data integrity, security, privacy, and quality control (QC); delegated roles and vendor responsibilities will be formalized by written agreements and documented in the Trial Master File (TMF) [1,2].

Data sources and acquisition

- Electronic source (eSource) from investigational system:

- AsthmaTuner app-module telemetry and assessments (e.g., inhalation training sessions, PIF, time-to-PIF, inspiration time), associated device metadata (app and firmware versions, device IDs), and timestamps (UTC) are captured by the CE-marked AsthmaTuner system and transferred via secure APIs to the study data repository/EDC per validated specifications [1,3,4,6,8,14].

- Clinical eCRFs:
  - Demographics, eligibility, randomization stratum (DPI/MDI/both), clinical assessments, usability/feasibility, AEs/SAEs/UADEs, device deficiencies/complaints, and protocol deviations are entered into a validated EDC by site staff from contemporaneous source documents in accordance with eSource/eCRF reconciliation procedures [1,2,3,4,14].
- Safety and complaints:
  - Safety events are coded with MedDRA and maintained in the EDC and, where applicable, in a dedicated safety/complaints system with regular reconciliation and expectedness review against RSI/IB and risk files [1,2,10].
- Identity/consent:
  - eConsent systems (if used) implement identity verification (e.g., BankID or equivalent), audit trails, and version control; linkage keys between identifiers and study IDs are stored separately under restricted access [2–5].
- Randomization:
  - Stratified 1:1 assignment by inhaler category is generated by a validated module with allocation concealment logs and audit trails; access is role-restricted [1,2].

Data hosting, security, and privacy

- Hosting and zones:
  - Primary hosting for EDC/eSource repositories is within the EEA or other jurisdictions approved under GDPR; data at rest and in transit are encrypted (AES-256/TLS 1.2+). Cross-border transfers (if any) follow GDPR mechanisms (e.g., adequacy or standard contractual clauses) [3–5,13].
- Access controls:
  - Least-privilege, role-based access, unique credentials, MFA for administrative roles, periodic recertification, and deprovisioning within 24–72 hours of role change; comprehensive audit trails are enabled and reviewed per QC schedule [2–5,13].
- Cybersecurity and software lifecycle:
  - Secure development lifecycle and change control per IEC 62304 and IEC 81001-5-1 with vulnerability management, penetration testing risk-based cadence, and security incident response procedures; time synchronization via authenticated NTP; cryptographic key management under ISO/IEC 27001 controls [6,8,13].
- Privacy by design:
  - Pseudonymization at ingestion; minimization of direct identifiers; data protection impact assessment (if required); documented data subject rights handling (access/rectification/restriction) and breach notification workflow per GDPR [4,5,13].

Data standards, structures, and coding

- Data standards:
  - Data structures, variable names, units, and controlled terminologies are defined in a study Data Specification and transfer specifications; where feasible, tabulations will be mapped to CDISC SDTM domains or device-appropriate structures to support traceability and analysis [1,11].
- Dictionaries:
  - Adverse events and medical history are coded with MedDRA (current version at database lock); concomitant medications use established dictionaries (to be confirmed). Versioning and change logs are retained [10].
- Time and units:
  - All device timestamps are stored in UTC with local time offset; PIF, time-to-PIF, and inspiration time units and acceptable ranges are pre-specified and enforced by edit checks [1,2].

Data validation, edit checks, and discrepancy management

- Automated edit checks:
  - Field-level (type, format), range and plausibility checks for inhalation metrics, protocol window checks for 6–12-week follow-up, cross-form consistency (e.g., randomization stratum vs. device

used), and conditional logic (e.g., AE seriousness fields when serious=yes) are implemented in validated EDC [1–4].

- eSource/eCRF reconciliation:

- Routine reconciliation between device telemetry and eCRFs for participant ID, visit windows, and outcome completeness with documented queries and resolutions; version and device configuration logs are cross-checked to ensure only approved app versions are used [1,2,6,8].

- Queries and corrections:

- Data discrepancies generate system queries to sites; corrections follow ALCOA+ and audit-trail rules. Query turnaround expectations are defined in the DMP (e.g., 10 business days), with escalation to the SI and monitor for overdue items [1–4].

- Missing data:

- Prevention via reminder notifications and visit window management; capture of reason for missingness; handling rules for analysis per SAP; all imputations (if any) are analysis-only and never overwrite raw data [1,2].

Centralized monitoring and KRI program

- Risk-based data review is performed using centralized monitoring techniques to detect aberrant patterns, outliers, fabricated data risk, unusual distributions of inhalation metrics, visit window non-adherence, and under- or over-reporting of events. Key risk indicators (KRIs) and tolerance limits are pre-defined; signals trigger targeted queries, remote SDV/eSource review, or on-site verification as applicable [1,2,9].

Data transfers, integrations, and version control

- System interfaces:

- Scheduled, validated, checksum-verified transfers from AsthmaTuner to the EDC study repository use signed, encrypted channels; transfer logs, schema/version checks, and reject/repair routines are maintained [3,4,11,13,14].

- Version management:

- Device/app versions, calibration/functional checks (as applicable), and deployment dates are logged; substantial software changes follow change control, V&V, and approvals before use; prohibited versions are technically blocked from ingestion [1,6,8].

- Time alignment:

- System clocks are synchronized; ingestion applies monotonic timestamp validation to prevent mis-sequencing; anomalies are flagged for review [8,13].

Quality control schedule

- Start-up:

- Computerized system validation (CSV), user acceptance testing (UAT), edit-check validation, role provisioning tests, data flow dry-runs, and eConsent workflow validation completed and approved before first participant [1–4].

- Ongoing (typical cadence; to be adapted per risk):

- Weekly: data load reconciliations (eSource to EDC), KRI dashboards review, audit-trail spot checks, open query aging review, user access changes, app-version exposure checks.

- Monthly: full cross-system reconciliation (EDC–safety–complaints), protocol window adherence review, partial remote SDV/eSource verification per risk, backup restore test (sampled), vulnerability scan results review.

- Quarterly: role/access recertification, disaster-recovery test or tabletop, CSV periodic review triggers, data-privacy compliance check, DSMB data package QC (per charter) [1–4,5,8,13].

- Pre-lock:

- 100% critical data fields review (primary endpoint components; randomization; eligibility), coding reconciliation, SAE/UADE and device complaint matching with closure, final audit-trail integrity check,

open queries to zero or documented exclusions, freeze/lock approvals [1,2,3].

Data quality roles and oversight

- Sponsor-Investigator:
  - Approves the DMP, ensures resourcing, oversees vendor compliance, and adjudicates data integrity risks [1,2].
- Data Management Lead:
  - Maintains the DMP, specifications, edit-check library, query management, coding oversight, and lock procedures; leads reconciliations [1,2].
- Site Investigators:
  - Ensure accurate, timely data entry and prompt query resolution; maintain source–eCRF concordance [1,2].
- Monitor/QA:
  - Verify implementation of risk-based monitoring, perform independent QC and audits of data processes, CSV, and security controls; verify corrective and preventive actions (CAPA) effectiveness [1,2].

Data backups, continuity, and archival

- Backups:
  - Encrypted, geo-redundant daily full and intra-day incremental backups with retention per retention policy; backup integrity tested per schedule; RTO/RPO are defined and tested [3,4,13].
- Business continuity:
  - Disaster recovery plans, incident response runbooks, and communication trees are maintained and tested; high-availability configurations for production systems [13].
- Archival:
  - Database lock datasets, programs, codebooks, specifications, audit trails, and system documentation are archived in durable formats (e.g., CSV, PDF/A) with fixity checks; retention follows the longest applicable regulatory requirement [1–5].

Text-based data-flow diagram

- Participant uses AsthmaTuner app-module with spirometer/Airflow Trainer at home/clinic →
- App captures inhalation session metrics and metadata (UTC timestamps; app/device versions) →
- Secure transmission (TLS) to cloud ingestion service →
- Validation (schema; range; version; checksum) →
- Pseudonymization and storage in study repository →
- Scheduled, encrypted transfer to EDC analytical domains →
- Site enters clinical eCRF data (eligibility, AEs, usability) →
- Automated edit checks and cross-form/device reconciliation →
- Centralized monitoring/KRI review; queries to site; resolutions logged →
- Monthly reconciliation with safety/complaints systems; MedDRA coding →
- Clean datasets frozen; final QC → database lock →
- Export of analysis-ready datasets to the statistical environment (controlled access) →
- Archival of raw, curated, and analysis datasets with audit trails.

Risk–control matrix for common data risks

Data risk	Potential impact	Preventive controls	Detective/corrective actions	Reference(s)

Data entry errors in eCRF	Misclassification; bias	Validated edit checks; data entry guidelines; training	Central review; queries; targeted SDV	[1–4]
Device/app version mismatch	Incomparable data; safety risk	Version whitelisting; deployment approval; ingestion blocks for unapproved versions	Reconcile version logs; exclude/annotate affected data; CAPA	[1,6,8]
Time desynchronization	Sequence errors; window violations	Authenticated NTP; UTC storage; timestamp validation	Flag anomalies; site follow-up; data correction per audit trail	[8,13]
Missing primary endpoint	Reduced power; bias	Reminders; visit window tracking; data completeness dashboards	Query for reason; re-capture within window if possible; document per SAP	[1,2,9]
Cross-system reconciliation failure (EDC–safety–complaints)	Under-reporting; compliance gaps	Monthly reconciliations; shared case keys; SOPs	Joint review; late reports with justification; CAPA	[1–3,10]
PII/PHI exposure	Privacy breach; legal risk	Pseudonymization; access controls; encryption; DPIA	Containment; notification per GDPR; root-cause remediation	[4,5,13]
Unauthorized access/credential compromise	Data tampering; breach	RBAC, MFA, least privilege; access recertification	Forensics; password resets; access revocation; incident response	[2–5,13]
Software update without V&V	Data integrity/safety issues	Change control; V&V per IEC 62304/81001-5-1; approvals before release	Rollback; data impact analysis; amendment if needed; CAPA	[1,6,8]
Backup/restore failure	Data loss; downtime	Geo-redundant encrypted backups; periodic restore tests	DR activation; reconstruct from secondary sources; CAPA	[3,4,13]
Fraudulent/fabricated data	Invalid results	Central statistical checks; KRIs; unusual pattern detection	Targeted SDV; audit; data exclusion per governance	[1,2,9]
Inadequate coding/version control for MedDRA	Safety misclassification	Current MedDRA; coder training; QC	Recode; medical review; version-controlled recuts	[10]
eConsent version misuse	Ethics non-compliance	Version control; system locks; staff training	Re-consent with correct version; deviation/CAPA	[1–5]

Data extraction, analysis readiness, and database lock

- Clean data cut:

- Upon completion of cleaning and reconciliations, a clean data cut is declared. Listings and summary checks are run to confirm primary endpoint completeness and stratification consistency [1,2].

- Database lock:

- Freeze and lock follow a documented, approved procedure with role-segregated e-signatures; post-lock changes require formal unlock approvals and audit trails [1–4].

- Analysis datasets:

- Analysis-ready datasets, programs, and outputs are generated in a controlled statistical environment with version control and independent programming QC; all derivations are traceable to raw data [1,2,11].

Change management, deviations, and CAPA

- Any changes to data-related processes, specifications, or systems follow controlled change management with impact assessment, validation (as needed), and approvals prior to implementation. Deviations are logged, root causes analyzed, and CAPA actions tracked to effectiveness verification [1–4,6,8,13].

Training and documentation

- All personnel with data responsibilities are trained on the protocol, DMP, EDC/eSource systems, privacy/security, query management, coding, and incident response; training is documented and maintained. All specifications, data maps, edit-check catalogs, transfer agreements, validation evidence, and QC records are filed in the TMF/ISF [1–5].

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11.2 Data Entry

Scope

This section defines who may enter, review, and sign data; how data must be entered and corrected; the required training and competency for users; and service-level expectations for timely entry and query resolution for this Phase III confirmatory investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534). All processes follow ISO 14155, ICH E6(R2), 21 CFR Part 11, EU Annex 11, GDPR, SPIRIT 2025, and FDA eSource guidance [1–7,9].

Role-based access matrix

Access to eSource/EDC, randomization, safety/complaints, and eConsent systems is least-privilege and role-based, with unique credentials and audit trails. Read-only access to direct identifiers is restricted to site roles; sponsor roles access pseudonymized data except where safety/regulatory obligations require linkage [1–6].

Role	System access	Create/edit source	Enter/edit eCRF	Raise/answer queries	Approve/sign eCRF	View PHI	Export datasets	Randomization	Safety/complaints entry	Code AEs (MedDRA)	Lock/freeze
Principal Investigator (PI)	EDC, safety, eConsent	Yes (site)	Yes	Yes	Yes (investigator sign-off)	Yes (site)	No	View only	Yes	Review only	No
Sub-Investigator	EDC, safety	Yes (site)	Yes	Yes	Yes (if delegated)	Yes (site)	No	View only	Yes	Review only	No
Study Coordinator/Data Entry	EDC, eConsent	Yes (site)	Yes	Yes (respond)	No	Yes (site)	No	Execute per IWRS	Yes (initial AE/device deficiency)	No	No
Site Pharmacist/Device Custodian	Accountability tool	Source (device logs)	Device logs	Respond (device)	No	Limited (device IDs)	No	No	Device deficiency	No	No
Medical Monitor/Safety Officer	Safety, EDC (read)	No	No	Raise	No	Pseudonymized	Listings only	No	Case medical review	No	No
Data Manager	EDC, transfers	No	No	Raise/close (with site)	No	Pseudonymized	Yes (de-identified)	No	Reconcile	Oversee	Freeze (DM)
Biostatistician	EDC (read), analysis repo	No	No	No	No	Pseudonymized	Yes (analysis)	No	No	No	No
Monitor/CRA	EDC, eSource (read)	No	No	Raise	No	Yes (on-site/remote SDV)	No	No	No	No	No

QA Auditor	Read-only all	No	No	Raise audit findings	No	Limited per SOP	No	No	No	No	No
Regulator/Inspector	Read-only all	No	No	No	No	Yes (direct access)	No	No	No	No	No
EDC Administrator	EDC admin	No	No	No	No	No	No	No	No	No	Lock (per SOP)
DSMB Member	DSMB portal	No	No	No	No	No PHI (aggregate only)	No	No	No	No	No
Manufacturer Safety Liaison	Safety/complaints (limited)	No	No	Raise safety queries	No	No PHI	No	No	Complaint intake	No	No

Notes: Any expanded access must be pre-approved, time-bound, and documented; deprovisioning occurs within 24–72 hours of role change or separation [1–6].

Data-entry conventions

- General principles

- ALCOA+ attributes; contemporaneous entry from verified source or validated eSource; all changes captured by audit trail with reason for change where required [1–4,7].

- Identifiers and pseudonymization

- Use system-generated Participant ID on all eCRFs; do not enter names, full dates of birth, national IDs, or free-text PHI in narrative fields. Linkage logs are kept separately under site control with restricted access [2,5].

- Dates and times

- ISO 8601 format (YYYY-MM-DD). Times in 24-hour format with time zone offset when recorded manually; device-generated timestamps are stored in UTC with local offset metadata; do not alter device times [3,4].

- Units and numeric precision

- Peak inspiratory flow (PIF): L/min; time-to-PIF: seconds; inspiration time: seconds. Enter values exactly as displayed by the investigational system; do not round, average, or transform unless the eCRF specifies a calculated field (system-derived) [1,7].

- Height: cm; weight: kg; vitals per site SOP with units enforced by EDC edit checks.

- Categorical selections

- Use controlled terms provided in the eCRF (e.g., inhaler category: DPI, MDI, both). Free-text “other” requires concise justification avoiding PHI.

- Missing/unknown/not done

- NA = not applicable; ND = not done; UK = unknown; NR = not recorded (explain in source). Do not leave mandatory fields blank; provide reason for missingness when prompted [1–4].

- Corrections

- Paper source: single-line strike-through, legible original remains visible, date/initials, reason. Electronic: use system edit with reason for change when requested; never overwrite outside audit trail [1–4].

- Adverse events and device deficiencies

- Record verbatim term, onset/stop dates, severity, seriousness, outcome, relationship to device/procedure, action taken; code with current MedDRA version at lock under Data Management oversight [2,8].

- Randomization and treatment

- Confirm stratification (DPI/MDI/both) before randomization; document any discrepancies with reason and notify monitor; allocation details are not visible to participants (single-blind).

- Source–eCRF consistency

- Verify that eCRF entries match source/eSource, including app version, device IDs, and visit windows. Discrepancies must be queried and resolved; do not transpose values across visits [1–4].

- Narrative fields

- Be concise, factual, and non-interpretive; avoid clinical judgments beyond source documentation; exclude PHI; include device/app version and configuration where relevant to events.

Training and competency checklist

Before system access, each user must complete role-appropriate training and demonstrate competency. Training is documented (date, version, trainer/assessor) and filed in the ISF/TMF [1–4,6,7].

- Core modules (all roles)

- Study protocol overview; objectives and endpoints alignment to fields.
- ISO 14155 and ICH E6(R2) GCP essentials; ALCOA+; privacy/GDPR basics [1,2,5].
- Part 11/Annex 11 awareness for electronic records/signatures; audit trails [3,4].
- Data-entry conventions, missing data rules, and correction procedures.
- Safety and device deficiency minimum reporting elements and timelines.

- System-specific training

- EDC/eSource navigation; user authentication; role-based permissions; entering, saving, and e-signing forms; responding to queries; reviewing audit trails [3,4].
- eConsent workflow (if applicable), identity verification, and versioning [3–5].
- Randomization/IWRS procedures and stratification checks.
- AsthmaTuner app-module and device handling workflows relevant to data capture, including version capture and prohibited version handling.

- Specialized modules (as applicable)

- MedDRA coding principles and version control (coders, DM) [8].
- Safety case assessment workflow (PI, Safety Officer, Medical Monitor).
- Data protection impact and incident reporting pathways (privacy leads) [5].

- Competency assessment

- Completion of UAT/test entries with zero critical errors.
- Passing score on role-tailored knowledge check (threshold to be defined by Sponsor-Investigator).
- Practical demonstration: enter a mock AE, correct a data error per SOP, and respond to a system query.
- Inclusion on Delegation of Authority Log upon successful assessment; periodic recertification at least annually or after major system/protocol changes [1–4].

Timelines and service-level agreements (SLAs)

Time-bound entry and resolution support data integrity, participant safety, and regulatory compliance. Escalations: site to CRA at T+2 business days after missed SLA; CRA to Data Management Lead and PI at T+5; Sponsor-Investigator and QA at T+10, with documented CAPA where needed [1–4,6,7].

Activity/data element	SLA clock start	Responsible role	Target completion	Notes/requirements
Screening data entry	End of screening visit	Coordinator/Site staff	≤5 business days	Include eligibility checklist and consent confirmation (no PHI)
eConsent record upload/verification	Consent execution	Coordinator	Same business day; ≤1 business day	Ensure correct version and audit trail present [3–5]
Randomization confirmation entry	Randomization event	Coordinator	Immediate; ≤1 hour	Verify correct stratum (DPI/MDI/both) before allocation
Baseline visit eCRF	End of baseline visit	Coordinator	≤5 business days	Include device assignment and app version where applicable

App/device version/config log	Receipt/activation/change	Coordinator/Device custodian	≤2 business days	Record device IDs and app version; reconcile at each visit
Training session completions (eSource verification)	Data receipt in EDC	Data Management	Weekly batch review; ≤5 business days from receipt	Investigate rejects; issue queries as needed
AE (non-serious) initial entry	Site awareness	Coordinator/PI	≤2 business days	MedDRA coding by DM within ≤5 business days [2,8]
SAE/UADE initial entry	Site awareness	PI/Coordinator	≤24 hours	Reporting to IRB/authority per safety section; immediate escalation [1–4]
Device deficiency/complaint entry	Site awareness	Coordinator/Device custodian	≤72 hours	Link to participant, device/app version; reconcile with safety
Follow-up visit eCRF (6–12 weeks)	End of visit	Coordinator	≤5 business days	Ensure primary endpoint fields complete and consistent
Protocol deviation entry	Identification	Coordinator/PI	≤3 business days	Include impact and preliminary root cause
Query response (standard)	Query issuance	Coordinator/Site staff	≤10 business days	Provide source-based clarification; partials allowed with plan
Query response (critical data/safety)	Query issuance	Coordinator/PI	≤3 business days	Includes primary endpoint, eligibility, randomization, safety
Coding review (AEs/medications)	Post-entry	Data Management/Coder	≤5 business days	Medical review for consistency and expectedness
Cross-system reconciliation (EDC–safety–complaints)	Month end	Data Management	≤10 business days post-month end	Document variances and resolutions
User access deprovisioning	Role change/separation	Site lead/EDC admin	≤24–72 hours	Documented removal; verify in quarterly recertification

Query management workflow

- Generation and assignment

- System edit checks and data review generate queries assigned to the site role best positioned to respond; each query includes context, required action, and due date [1–4].

- Site response and documentation

- Provide a clear, source-verifiable response or data correction; attach certified copies if requested per monitoring plan; avoid PHI in responses [1–5].

- Data Management review and closure

- DM reviews for completeness and coherence; closes the query or returns for clarification; maintains audit trail and metrics on open query aging [1–4].

- Escalation

- Missed SLA triggers escalation per the SLA table; persistent non-compliance prompts CAPA and potential targeted monitoring or retraining [1–4].

System controls supporting compliant data entry

- Validated systems with enforced data types, ranges, and conditional logic; version-controlled edit-check libraries; time-stamped audit trails for create/modify/e-sign events [3,4].
- Role-segregated e-signatures for investigator review and approval; freeze/lock procedures prevent post-lock changes without controlled unlock [3,4].
- Privacy by design: pseudonymization and minimum-necessary access; export controls to prevent unauthorized download of PHI; GDPR-compliant cross-border transfer mechanisms where applicable [5].

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11.3 Data Cleaning

Purpose and scope

This section defines the end-to-end data cleaning strategy, discrepancy management rules, standardized query language, data-cleaning tracker structure, and objective criteria for interim data freezes and final database lock for this Phase III confirmatory investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5). Processes comply with ISO 14155, ICH E6(R2), 21 CFR Part 11/812, EU Annex 11, GDPR, SPIRIT 2025, and applicable software lifecycle and information security standards [1–9,13].

Principles and hierarchy for discrepancy resolution

- ALCOA+ and traceability: All cleaning actions preserve data provenance, with auditable linkage from raw eSource/eCRF to analysis datasets; no overwrites outside validated audit trails [1–4].
- Source hierarchy:

- Device/app eSource (AsthmaTuner telemetry and timestamps) is the authoritative source for inhalation metrics (e.g., PIF, time-to-PIF, inspiration time) and related metadata (app/firmware version, device IDs) [1,3,7,8].
- Certified site source documents are authoritative for consent, eligibility, randomization stratum (DPI/MDI/both), AEs/SAEs/UADEs, and protocol deviations [1,2].
- Safety/complaint systems are authoritative for final case status and coding reconciliation of reportable events and device deficiencies [1,2].

- Consistency with protocol and SAP: Cleaning rules follow the Data Management Plan (DMP) and Statistical Analysis Plan (SAP). Any derived updates that could affect endpoint definitions require joint approval by Data Management (DM), Biostatistics, and the Sponsor-Investigator (SI) prior to implementation [1,2,6].
- Version control: Data affected by unapproved or out-of-scope app/device versions are flagged; ingestion is blocked where technically feasible, or such data are excluded/annotated following documented impact assessment and CAPA [1,6,8].

Discrepancy management rules

- Identity and duplication

- Potential duplicate participants (e.g., matching initials/date of birth patterns prohibited, or reuse of device IDs) are investigated via site query; only one record is retained per participant ID. Duplicated eSource sessions are de-duplicated using monotonic UTC timestamps, session IDs, and checksum metadata; rejected records remain archived with reason [1–4,13].

- Eligibility and randomization

- Mismatches between eligibility confirmations and randomization stratum (DPI/MDI/both) generate high-priority queries. If a pre-randomization error is verified, stratification is corrected with full audit trail; post-randomization errors are analyzed for impact and handled per SAP sensitivity rules [1,2].

- Visit windows and primary endpoint completeness

- Follow-up assessments outside the 6–12-week window are flagged. If re-capture within window is possible, the site is prompted; otherwise, reason for out-of-window is documented and handled per SAP (e.g., analyzed but flagged) [1,2,6].

- Outliers and implausible values (inhalation metrics)

- Pre-specified plausibility ranges enforced by edit checks (e.g., PIF in L/min, time-to-PIF in seconds, inspiration time in seconds) are validated against device specifications and clinical feasibility. Values outside range trigger queries for confirmation against device logs; confirmed biologically plausible extremes are retained with annotation, otherwise corrected or invalidated with justification [1–4,7].

- Missing and partial data

- Prevent via reminders and eSource integrations; record reason for missingness using controlled terms (e.g., not done, technical failure, participant unavailable). No imputation is performed in the clinical database; imputations, if any, are analysis-only per SAP [1,2].

- Coding reconciliation

- MedDRA coding of AEs uses the current dictionary version at lock; verbatim-to-preferred term reconciliation is QC-checked. Discrepancies between AE entries and device complaint/deficiency logs are reconciled monthly; unresolved cases are escalated to Medical Monitor and SI [1,2,12].

- Date/time corrections

- Device timestamps are stored in UTC; manual entries use ISO 8601 and 24-hour format with time-zone offset. Clock anomalies (e.g., daylight saving offsets, device drift) are corrected using authenticated NTP references and documented rules; raw values are retained with corrective annotation [3,4,8,13].

- Software/app version exposure

- Data captured on prohibited or unvalidated app versions are quarantined. Impact analysis determines inclusion, exclusion, or sensitivity labeling; affected participants may require re-assessment if feasible and ethical [1,6,8].

- Cross-system reconciliation

- Monthly three-way reconciliation (EDC–safety–complaints) ensures all reportable events and device deficiencies align on dates, seriousness, relatedness, outcome, and case IDs before interim freezes and lock [1,2].

- Privacy and redaction

- Free-text fields are reviewed to prevent PHI entry; any inadvertently entered PHI is redacted per GDPR-compliant procedures with full audit trail [5,13].

Standardized query templates

All queries are concise, source-verifiable, free of PHI, and include context, required action, and due date. Examples:

- Eligibility confirmation discrepancy

- Context: Eligibility form indicates “uses MDI,” randomization stratum recorded as “DPI.”

- Request: Please confirm the participant’s inhaler category at baseline from source and correct the eCRF as applicable. If stratification error occurred pre-randomization, document correction; if after randomization, provide impact rationale.

- Due: 3 business days (critical).

- Implausible inhalation metric

- Context: eSource PIF=720 L/min at Visit 2 exceeds study plausibility threshold.

- Request: Verify against device session log (attach certified copy if requested) and confirm value or correct entry. If correct, confirm no device error and report any device deficiency if applicable.

- Due: 10 business days (standard).

- Visit window deviation

- Context: Follow-up visit occurred at week 13.

- Request: Provide reason for out-of-window and whether a within-window assessment was attempted. Confirm handling per protocol/SAP.

- Due: 10 business days (standard).

- AE/complaint reconciliation

- Context: Device deficiency reported without corresponding AE assessment.

- Request: Confirm whether an AE occurred; if yes, enter/update AE details and link to complaint ID; if not, document reason.

- Due: 5 business days (priority).

- Date/time clarification

- Context: Local time entered without offset; device UTC timestamp differs by >2 hours.

- Request: Provide correct local time with time-zone offset and confirm alignment to device UTC per site source.

- Due: 10 business days (standard).

Data-cleaning tracker

A live, version-controlled tracker will be maintained by Data Management and filed in the TMF. Minimum fields and statuses are standardized across sites.

Item ID	Domain	Participant ID	Visit/Timepoint	Issue type	Priority	Date opened	Owner (site/DM)	Due date	Current status	Resolution summary	Evidence/audit ref	Impact on endpoints	Include in interim freeze
DCL-0001	Eligibility	001-012	Baseline	Stratum mismatch	Critical	2026-05-02	Site	2026-05-05	Open	—	QRY-3421; Source note 2026-05-01	Potential	No

DCL-0002	eSource metrics	001-045	Week 8	PIF outlier	Standard	2026-05-03	DM	2026-05-17	In query	—	Device log DL-118	None if confirmed	Yes
DCL-0003	Safety/complaint recon	002-007	Any	Missing AE link	Priority	2026-05-04	Site	2026-05-11	Closed	AE entered and coded	AE-ID 22; CMP-55	None	Yes

- Priority definitions:
  - Critical: Primary endpoint, eligibility, randomization, SAE/UADE, or data privacy issues; SLA 3 business days.
  - Priority: Important to safety/conduct but not critical; SLA 5 business days.
  - Standard: All others; SLA 10 business days.
- Status values: Open, In query, Clarification received, Corrected, Verified, Closed-no change, Deferred to analysis (with rationale).

Interim data freezes

Interim freezes provide stable datasets for scheduled DSMB meetings or predefined analyses without permitting data modification, except via controlled unfreeze.

- Entry criteria (all must be met unless justified):
  - All critical and priority queries resolved or documented with agreed deviations; no open critical queries on primary endpoint fields [1,2].
  - Monthly EDC–safety–complaints reconciliation completed for the cut-off period with discrepancies ≤ pre-defined tolerance (to be specified in DMP) [1,2].
  - MedDRA coding current through the cut-off; device/app version exposure review completed with annotations [1,2,12].
  - KRI anomalies reviewed and addressed or documented with action plans [1,2].
- Freeze process:
  - DM issues a freeze memo with cut-off date/time (UTC), scope, and approvals (DM, Biostatistics, SI). EDC forms included in scope are set to frozen status; changes require documented unfreeze with dual approval (DM and SI) [1–4].
- Post-freeze controls:
  - Any post-freeze changes are versioned and impact-assessed; DSMB packages include reconciliation notes and variance logs as applicable [1,2].

Pre-lock clean-up and final database lock

- Pre-lock readiness checks:
  - 100% review and closure of critical data fields: primary endpoint components, eligibility confirmations, randomization details, visit windows, and withdrawal status [1,2].
  - All SAEs/UADEs and device complaints reconciled, medically reviewed, and coded; no open safety case requiring data edits [1,2,12].
  - Zero open critical queries and ≤ pre-defined tolerance of standard queries, none affecting primary/secondary endpoints; all data corrections completed with reasons for change [1–4].
  - Audit-trail integrity check passed; user access recertified; outstanding deviations closed with impact assessment [2–5].
  - Final eSource–eCRF reconciliation complete; no unapproved app/device versions contributing unanalyzed data, or such data excluded/annotated with justification [1,6,8].
- Lock authorization and controls:
  - DM circulates a Database Lock Checklist and obtains role-segregated e-signatures from DM Lead, Biostatistician, SI, and EDC Administrator. Lock is executed per SOP; post-lock changes are prohibited unless a formal unlock is approved by SI with documented rationale, limited scope, and full re-lock audit trail [1–4].

- Deliverables at lock:

- Locked data extracts (raw and curated), coding dictionaries and versions, data definition/specifications, query logs, reconciliation reports, and freeze/lock memos archived in durable formats with fixity checks [1–4,11,13].

Documentation, metrics, and oversight

- Documentation:

- All cleaning specifications, edit-check catalogs, tracker exports, reconciliation reports, and freeze/lock approvals are version-controlled and filed in the TMF/ISF [1–4].

- Performance metrics:

- Open query aging, first-pass query rate, time-to-closure by priority, reconciliation variance rates, and KRI outlier resolution times are reviewed at least monthly; trends trigger CAPA where thresholds are exceeded [1,2].

- Oversight:

- The Monitor/CRA verifies implementation at sites; QA may audit a sample of discrepancies, queries, and resolutions for compliance with SOPs and regulations; findings require CAPA with effectiveness checks [1,2].

Roles and responsibilities specific to data cleaning

- Data Management Lead: Owns cleaning plan, tracker, reconciliations, coding QC, and freeze/lock execution [1,2].
- Site Investigator/Coordinator: Responds to queries with source-verifiable information within SLAs; corrects eCRFs per audit-trail rules [1–4].
- Medical Monitor/Safety Officer: Reviews safety-related discrepancies and coding; adjudicates causality/expectedness as needed [1,2,12].
- Biostatistician: Confirms analysis readiness, reviews derivations/flags, and verifies no residual data issues impacting primary endpoint analysis [1,2,11].
- Sponsor-Investigator: Approves freeze/lock and any unlocks; adjudicates unresolved data integrity issues [1,2].

Change control and deviations during cleaning

- Any mid-study changes to cleaning rules, edit checks, or reconciliation logic follow controlled change management, with impact assessment, validation, and stakeholder approval prior to deployment. Deviations are logged, root-cause analyzed, and CAPA tracked to completion; participant safety and endpoint integrity take precedence in decision-making [1–4,6,8,13].

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11.4 Data Editing

Purpose and scope

This section defines controlled editing of study data (eSource from the AsthmaTuner app-module and associated devices; eCRFs; safety/complaints; eConsent records), including who may initiate, approve, and document edits; required correction note content; audit-trail and authorization requirements; and standardized change-control logs. All processes comply with ISO 14155, ICH E6(R2), 21 CFR Part 11/812, EU Annex 11, GDPR, SPIRIT 2025, and applicable software lifecycle controls [1–8].

Governing principles for data edits

- ALCOA+: Every change must preserve data that are Attributable, Legible, Contemporaneous, Original, Accurate, plus Complete, Consistent, Enduring, and Available, with a permanent audit trail and reason for change captured at the time of the edit [1–4].
- Source precedence and immutability:

- Device/app eSource is the authoritative source for inhalation metrics and related metadata; raw telemetry is not overwritten. Any detected issues are handled via annotation, data-impact assessment, and, if needed, corrected copies with full traceability to the original [1,3,6].
- Site source is authoritative for consent, eligibility, AEs/SAEs/UADEs, protocol deviations, and randomization documentation [1,2].

- Role segregation and approvals: Editors and approvers must be distinct roles. Critical edits require dual review (Data Management plus PI or SI) and, after database freeze or lock, formal unfreeze/unlock authorization with e-signatures per Part 11/Annex 11 [2–4].

Authorized roles and permissions

- May initiate edits: Site Coordinator/Data Entry, Investigator, Data Manager, Safety Officer (within role scope).
- May approve edits:

- Clinical content (eligibility, endpoints, safety): Principal Investigator or delegated Sub-Investigator.
- Data integrity/structure (format, mappings, device metadata): Data Management Lead.

- Post-freeze/lock or critical safety case: Sponsor-Investigator and EDC Administrator execute unfreeze/unlock and re-lock after approvals [1–4].

- Prohibitions: Vendor/manufacturer personnel cannot alter study records; they may provide certified technical evidence to support a site/sponsor edit request.

When an edit is required

- Transcription or formatting errors detected by edit checks or monitoring.
- Legitimate late data discovered in certified source (entered with late entry notation).
- Clarifications to narrative or categorical fields to match source without changing clinical meaning.
- Safety case updates (seriousness, causality, outcome) based on medical review.
- Device/app metadata corrections (e.g., version, device ID) substantiated by system logs.
- Privacy redaction to remove inadvertently entered PHI/PII in free-text, under GDPR-compliant procedures [5].

Edit rules and documentation standards

- Never delete or overwrite original entries. Use system “correct” with mandatory reason for change; original value remains visible in the audit trail [2–4].
- Paper source corrections: Single-line strike-through, original legible, dated/initialed, with reason. Certified copies are uploaded if remote SDV is used [1,2].
- Late entries: Mark “late entry,” include the actual date/time of the entry and the date of the original event/observation, with justification [1,2].
- Derived fields: Recompute via validated rules; do not manually overwrite system-derived values.
- Timing: Complete standard edits within 10 business days of identification; critical/safety-related within 3 business days unless more stringent timelines apply per the safety section [1–3].
- Post-freeze/lock: Edits are prohibited unless a documented unfreeze/unlock is approved. Scope-limited changes are executed and re-frozen/re-locked with updated memos and audit-trail verification [2–4].

Edit approval workflow

31. Identification: Error detected by automated checks, centralized review, monitor, or site.
32. Initiation: Editor opens an Edit/CorrNote in the EDC/eSource, selects category, enters proposed correction and reason, and attaches evidence (source excerpt, certified device log).
33. Review:

- Data Management reviews data-structure/consistency and either returns for clarification or forwards for clinical approval.
- Investigator (or delegate) confirms concordance with source for clinical fields and safety implications.

34. Approval and application:

- Standard edits: Single approval by DM for structural and by Investigator for clinical content.
- Critical edits (primary endpoint, eligibility, randomization, SAE/UADE): Dual approval (Investigator and DM) and SI notification prior to application.

35. Closure: System applies correction; audit trail captures who/what/when/why; query (if any) is closed with resolution note; tracker updated.
36. Post-freeze/lock: Requires unfreeze/unlock request, SI approval, EDC Admin action, application, QC check, and re-freeze/re-lock with addendum memo [2–4,6].

Standard correction-note templates

- eCRF clinical field correction

- Record/field: [Form name]/[Field name]
- Original entry: [value]
- Corrected entry: [value]
- Reason for change: [e.g., transcription error from source progress note dated YYYY-MM-DD]
- Source reference: [Source doc title/date/page]; attachment ID: [file/ref]
- Editor: [name, role, date/time]
- Approver(s): [name(s), role(s), date/time]
- Impact assessment: [affects primary endpoint? yes/no; safety? yes/no]

- Device/app metadata amendment

- Record/field: [Device/App version or ID]
- Original value: [value]
- Corrected value: [value]
- Evidence: [Certified device log/session ID/checksum; system export ID]
- Reason for change: [e.g., initial mis-entry; log reconciliation]
- Editor/Approver(s): [as above]
- Impact assessment: [exposure to unapproved version? inclusion/exclusion note]

- Safety case update (AE/SAE/UADE)

- Case ID: [ID]
- Field(s) updated: [e.g., seriousness, causality, outcome]
- Justification: [medical review dated; new clinical information]
- Linkages: [complaint/deficiency ID; MedDRA recode if applicable]
- Approvals: [Investigator, Medical Monitor, DM]

- Date/time clarification

- Affected event: [visit or session]
- Original local/UTC time: [value]
- Corrected time and offset: [value, ±hh:mm]
- Basis: [site source; authenticated NTP; device timestamp reconciliation]
- Impact: [visit window; endpoint timing]

- Privacy redaction (PHI removal)

- Field: [free-text location]
- Redacted element: [description, not the PHI itself]
- Reason: [inadvertent PHI entry]
- Method: [system redaction note; original retained in restricted audit trail]
- DPO/privacy review: [name/date]
- Notification: [if required under GDPR and SOPs] [5]

Edit categories and required approvals

Category	Examples	Minimum approvals	Post-freeze/lock requirement
Administrative/format	Typos, unit format without value change	Data Management	Unfreeze/unlock with DM + EDC Admin
Clinical non-critical	Demographics, non-endpoint concomitant fields	Investigator	Unfreeze/unlock with Investigator + DM + EDC Admin
Endpoint-critical	Primary endpoint components; eligibility; randomization details	Investigator + Data Management; SI notified	Formal unlock with SI approval; re-lock after QC
Safety-critical	SAE/UADE fields; death; important medical event	Investigator + Medical Monitor + Data Management	Formal unlock with SI approval; expedited timelines apply
Device/app metadata	App/firmware version; device ID; calibration flags	Data Management; Investigator if clinical impact	Unfreeze/unlock with SI approval if endpoint impact

Change-control log format

All edits outside routine query resolution, and any bulk updates or rule/configuration changes, require entry in the study Change-Control Log. The log is version-controlled and filed in the TMF.

CC ID	Change type	System/domain	Description/scope	Rationale	Risk/impact assessment	Validation required (Y/N)	Approvals (roles)	Effective date/time (UTC)	Related records (queries/corr notes)	Post-implementation QC results	Status
CC-2026-001	Edit rule update	EDC edit checks	Expand PIF upper plausibility to 750 L/min	Clinical feasibility evidence	Low risk; no safety impact	Y (UAT)	DM, Biostatistics, SI, QA	2026-05-15 12:00	QRY set Q-1xx; DCL tracker items	Pass; no regressions	Closed

Audit-trail and e-signature requirements

- System audit trails must record user ID, date/time (UTC), old/new values, reason for change, and affected record identifiers; audit trails are immutable, reviewable, and retained through archival [2–4].
- Electronic signatures must be unique to an individual, include printed name, date/time, and meaning of signature (e.g., “approval,” “investigator sign-off”), with Part 11/Annex 11 compliance and periodic verification of identity and access [3,4].
- Periodic audit-trail review is performed per the DMP/QC schedule and prior to database freeze/lock; anomalies trigger CAPA [1–4].

Controls specific to investigational app-module data

- Version exposure: Data captured on prohibited or unvalidated versions are automatically quarantined; edits cannot “relabel” versions. Inclusion/exclusion requires documented impact assessment and approvals per the matrix above [1,6].
- Time integrity: Device UTC timestamps are not altered; any human-readable local-time corrections are added as annotations with offset, not substitutions [3,4].
- Session integrity: Duplicate or corrupted sessions are retained as rejected records with checksum, reason, and linkage to corrective actions; no physical deletion is permitted [1,3].

Interactions with queries, freezes, and database lock

- Open queries related to an edit must be closed with explicit reference to the applied correction note and audit-trail entry.
- No edits may be applied to frozen/locked forms without documented unfreeze/unlock approvals; all such actions are summarized in freeze/lock addendum memos and included in the lock package [2–4].
- After re-lock, a reconciliation report lists all post-freeze/lock edits with justifications and impact statements endorsed by Biostatistics and the SI.

Training, oversight, and metrics

- Training: All editors/approvers complete role-based training on edit rules, correction notes, e-signatures, audit-trail review, privacy redaction, and change control before system access, with annual recertification or after major changes [1–4,5,8].
- Oversight: Monitors verify that edits match source and follow workflow; QA audits a sample of edits and change-control entries for compliance. Deviations require CAPA with effectiveness checks [1–4].
- Metrics: Monthly reporting includes number of edits by category, time-to-approval, post-freeze unlocks, and audit-trail anomalies; thresholds trigger escalation and retraining [1,2].

References

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11.5 Confidentiality and Protection of Study Files

Scope and guiding standards

This policy governs confidentiality and protection of all study files, including the Trial Master File (TMF), Investigator Site Files (ISFs), electronic records (eSource, EDC, safety/complaints, eConsent), monitoring/audit documentation, device accountability, coding logs, and analysis outputs for this Phase III confirmatory investigation of the inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534). Controls align with ISO 14155, ICH E6(R2), 21 CFR Part 11/812, EU GMP Annex 11, GDPR, ISO/IEC 27001, NIST 800-53, and SPIRIT 2025 [1–9].

Role-based access and least-privilege controls

- Access to study files is granted strictly on a need-to-know basis, with unique user credentials, role-based permissions, and periodic (at least quarterly) access recertification; deprovisioning occurs within 24–72 hours of role change or separation [1–5,8,9].
- Site personnel may access direct identifiers within the ISF and site-restricted eSource; sponsor personnel access only pseudonymized records, except where safety/regulatory duties require identifiable review (e.g., inspection, SAE source verification) [1–5].

- Regulators/IRBs/ethics committees and auditors may have read-only access to identifiable records as required by law and ethics approvals, under supervised conditions and with audit trails maintained [1,2].
- Physical access to paper files is restricted to controlled areas with locked cabinets, keycard access, visitor logs, and clean-desk rules; removal of originals is prohibited without written authorization and chain-of-custody documentation [1,2,8].

File structure, custody, and integrity

- TMF and ISFs are maintained contemporaneously, complete, and inspection-ready, with master indices, version control, and document histories for essential documents (e.g., protocol/amendments, approvals, informed consent forms, monitoring/audit reports, device accountability, safety reports, training logs, delegation logs) [1,2].
- Electronic repositories are validated and maintain immutable audit trails capturing user, timestamp (UTC), action, prior/new values, and reason for change; audit-trail reviews are performed per the quality plan and pre-lock [3,4].
- Backups are encrypted, geo-redundant, and tested per schedule; disaster recovery plans define recovery time and point objectives and are tested periodically [4,8,9].

De-identification and privacy protections

- Pseudonymization is applied at data ingestion and during internal transfers; linkage files (study ID to direct identifiers) are stored separately under site control with restricted access and additional encryption [1–5,8].
- Data minimization and purpose limitation are enforced; free-text fields must exclude personally identifiable information; inadvertent PHI/PII is redacted with full audit trails [5,8].
- Data subject rights (access, rectification, restriction, and, where applicable, objection) are handled per GDPR with research safeguards; procedures, contact points, and timelines are documented in the privacy notice and TMF [5].
- Cross-border transfers (if any) use GDPR mechanisms (e.g., adequacy decisions, standard contractual clauses), with transfer risk assessments filed in the TMF [5].

Data sharing, publication, and secondary use

- External sharing of individual participant data (IPD) will use anonymized or appropriately pseudonymized datasets with risk-based de-identification, data dictionaries, and suppression/generalization where needed to manage re-identification risk [5,6,8,9].
- Access is controlled via data use agreements, approved research proposals, and secure platforms; no PHI/PII is shared. Sharing timing, scope, and eligibility will be defined in the Data Sharing Plan consistent with SPIRIT 2025 and ethics approvals (to be confirmed) [6].
- Aggregate results may be disseminated in scientific venues; any disclosure of proprietary device information is coordinated with the Sponsor-Investigator and manufacturer under confidentiality agreements [1,6].

Records retention and secure destruction

- The Sponsor-Investigator and sites retain essential documents for at least the longest applicable period among: 10 years after study completion/termination, or as required by local law; and not less than 2 years after the latter of study termination/completion or last marketing application approval/decision in any ICH region where the data are used [1,2,7].

- Electronic archives include datasets, specifications, codebooks, edit-check libraries, audit trails, data transfer logs, and validation evidence in durable formats (e.g., PDF/A, CSV) with fixity checks [1,3,4,8].
- After retention expiry, records are securely destroyed using approved methods (e.g., cross-cut shredding for paper; cryptographic erasure or media destruction for electronic media) with certificates of destruction filed in the TMF/ISF [1,2,8].

Confidentiality obligations and third-party processors

- All personnel and vendors sign confidentiality and data processing agreements appropriate to their role; vendors undergo risk-based qualification and are bound by written contracts defining data protection, breach notification, subprocessor controls, and return/destruction at contract end [1,2,5,8].
- Manufacturer safety liaisons and DSMB members receive only the minimum necessary data (typically pseudonymized or aggregate) required to fulfill their oversight duties, with no access to site-held linkage keys [1,2].

Breach detection and incident response

- Security and privacy incidents are managed under documented incident response procedures aligned with ISO/IEC 27001 and NIST 800-53, including triage, containment, eradication, recovery, forensic preservation, and CAPA [8,9].
- The Data Protection Officer (or delegate) assesses reportability under GDPR. Notifiable personal data breaches are reported to the competent supervisory authority without undue delay and, where feasible, within 72 hours; participants are notified without undue delay if the breach is likely to result in a high risk to their rights and freedoms [5,8,9].
- The Sponsor-Investigator notifies relevant IRBs/ethics committees and, where applicable, regulatory authorities per local requirements; all actions, decisions, and timelines are documented in the incident log and TMF [1,2,5].
- Post-incident reviews evaluate root causes and effectiveness of controls; lessons learned drive updates to SOPs, training, and technical safeguards [8,9].

Handling of inspections, audits, and disclosures

- Study files are made available to monitors, auditors, and regulatory inspectors upon request; copying of identifiable records is minimized and controlled, with secure transfer methods and documented chain of custody [1,2].
- Legal or regulatory disclosures of confidential information are limited to the minimum required and executed under protective orders or confidentiality provisions where feasible; affected disclosures are documented in the TMF [1,2,5].

Controls for portable media and paper records

- Use of portable media is prohibited unless explicitly authorized, encrypted, and tracked; no study files or PHI/PII may be stored on personal devices [4,8,9].
- Printing of records containing identifiers is minimized; printed materials use cover sheets, are promptly re-filed, and shredded when no longer needed per retention rules [1,2,8].

Training and awareness

- All personnel with access to study files complete role-based training on confidentiality, privacy, secure handling, phishing/social engineering awareness, and incident reporting prior to access and at least annually; training records are filed in the TMF/ISF [1,2,5,8].

References

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11.6 Coordinating Center

Overview

The Coordinating Center (CC) provides centralized trial management, regulatory operations, safety oversight support, data coordination, site enablement, performance management, and interface with the Data and Safety Monitoring Board (DSMB) for this Phase III confirmatory, two-arm, parallel, stratified 1:1 randomized clinical investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) in participants aged ≥16 years with asthma and/or COPD using DPI and/or MDI inhalers. CC operations adhere to ISO 14155, ICH E6(R2), SPIRIT 2025, 21 CFR Part 812/11, EU MDR 2017/745, and GDPR, and maintain inspection-readiness throughout [1–7].

Coordinating Center organization and responsibilities

Function/role	Primary responsibilities	Accountability lines
Sponsor-Investigator (SI)	Overall scientific, ethical, and regulatory responsibility; approves CC plans, DSMB charter, safety escalations, amendments, and database lock	Reports to Sponsor governance; interfaces with DSMB Chair

Coordinating Center Director (CC Director)	Day-to-day trial leadership; oversees site performance, risk management, timelines, and resources; chairs weekly CC operations	Reports to SI
Regulatory Affairs Lead	Prepares/coordinates submissions to IRBs/ethics committees and competent authorities (e.g., IDE/21 CFR 812, MDR 2017/745 CI applications in EUDAMED), maintains approvals, manages amendments and safety reports	Reports to CC Director; informs SI
Medical Monitor/Safety Officer	Medical oversight of AEs/SAEs/UADEs; expectedness/relatedness review; DSMB liaison for safety content; signal detection and escalation	Reports to SI; collaborates with DM Lead
Data Management (DM) Lead	Data Management Plan, EDC/eSource governance, edit checks, coding, reconciliations, freezes/lock; DSMB data package QC	Reports to CC Director
Biostatistics Lead	SAP, randomization oversight (stratified by inhaler type), interim data specifications for DSMB, final analysis	Reports to SI; coordinates with DM Lead
Monitoring Lead (CRA Manager)	Risk-based monitoring plan, site oversight, SDV/eSource verification, CAPA tracking	Reports to CC Director
Quality Assurance (QA) Lead	Independent audits, vendor qualification, process compliance, CAPA effectiveness verification	Reports to Sponsor QA
Device Logistics/Accountability Lead	Spirometer/Airflow Trainer allocation, shipping/returns, reconciliation with ISF/TMF, device deficiency/complaint intake and linkage to safety	Reports to CC Director
EDC/Systems Administrator	Part 11/Annex 11 controls, role provisioning, audit trails, system validation and change control	Reports to DM Lead
DSMB Coordinator (non-voting)	Manages DSMB charter implementation, meeting logistics, secure portal, blinding controls, minutes tracking	Reports to CC Director; independent of site conduct
Manufacturer Safety Liaison (non-editing)	Receives complaint/deficiency summaries, contributes technical assessments; no access to PHI	Contracted to Sponsor; interfaces with Safety Officer/Reg Affairs

A graphical organizational chart is maintained in the TMF and updated with any delegation changes [1,2].

Site start-up agenda and readiness certification

- Pre-activation (target D-30 to D-7):

- Regulatory/ethics approvals in place (IRB/EC favorable opinion; competent authority acknowledgment/authorization as applicable); financial and data-processing agreements executed; site staff delegated and trained per GCP and protocol; essential documents filed in ISF/TMF [1–5].
- System readiness: EDC/eSource access provisioned, UAT completed, role-based permissions verified, query workflows tested, and eConsent process validated where used [1,3,4].
- Device/accountability set-up: Site inventory received; receipt logged; quarantine and return procedures trained; version control and prohibited-version handling reviewed [1].

- Site initiation visit (SIV) agenda (D-7 to D-0):

- Protocol overview, objectives/endpoints, stratified randomization execution, and blinding procedures [1,6].
- Eligibility, consent, and privacy/GDPR practices; BankID or equivalent identity verification process where applicable [5].
- Detailed investigational device workflow: app-module access within AsthmaTuner, spirometer/Airflow Trainer handling, training content delivery, and documentation [1].
- Safety reporting: AE/SAE/UADE minimum elements, timelines (including 24-hour initial SAE reporting), device deficiency and complaint intake, and reconciliation [1–4].
- Monitoring plan, data entry SLAs, edit checks, query management, and source documentation

standards [1–4].
- DSMB processes and information firewalls; how sites will be informed of safety actions without unblinding [7].
- Readiness checklist sign-off by PI and CRA; activation memo issued by CC.
- Early-enrollment support (first 2–4 weeks after activation):
- Weekly check-ins; review of screening/enrollment logs; rapid retraining as needed; verification that randomization by inhaler stratum (DPI/MDI/both) is executed as specified [1,6].

Communications plan

- Routine cadence and channels:
- CC operations huddle (internal): weekly 30 minutes; actions and risks logged.
- Site coordinator forum: biweekly 45 minutes; enrollment, deviations, data quality, device logistics; minutes circulated within 3 business days.
- PI teleconferences: monthly 60 minutes; protocol conduct, safety trends, KRIs; decisions archived in TMF.
- DSMB coordination: per charter; typically after predefined enrollment or time-based milestones; blinded aggregate safety/efficacy operational data only, unless stopping rules require unblinding [7].
- Ad hoc safety alerts: within 24 hours of signal confirmation; distributed to PIs and site safety contacts with actionable guidance, preserving blinding where feasible [1,7].
- Information governance:
- Role-based distribution lists; secure platforms with audit trails; embargoed DSMB materials segregated; no PHI shared outside site unless legally required [2–5,7].
- Escalation:
- Site non-compliance or critical KRI excursions escalate from CRA to CC Director within 2 business days; unresolved issues escalate to SI and QA with CAPA within 10 business days [1,2].

Performance metrics and key risk indicators (KRIs)

The CC tracks KRIs and performance metrics to drive proactive oversight and CAPA, aligned with risk-based quality management per ISO 14155 and ICH E6(R2) [1,2].

- Enrollment/retention:
- Enrollment rate per site per month vs. plan; screen failure rate; early withdrawal rate; reasons categorized and trended.
- Protocol adherence:
- Proportion of follow-up visits within 6–12-week window; deviation rate per 100 participant-visits; proportion of correct inhaler-stratum randomizations.
- Data quality and timeliness:
- Time from visit to eCRF entry (target ≤5 business days); open query aging (critical ≤3 business days; standard ≤10); first-pass edit-check failure rate; primary endpoint completeness at visit.
- Safety/device reporting:
- SAE initial entry within 24 hours; device deficiency/complaint entry within 72 hours; monthly EDC–safety–complaints reconciliation variance rate [1–4].
- System/version control:
- Exposure to prohibited or unvalidated app versions (target 0%); resolution time for version-related quarantines; device return/reconciliation compliance.
- Training and monitoring:
- Training completion and recertification rates (target 100% before access); monitoring finding recurrence rate; CAPA closure within target timelines.
- Thresholds and actions:
- Predefined tolerance limits documented in the Monitoring Plan; excursions trigger root-cause analysis, targeted monitoring, retraining, or protocol clarification, with effectiveness checks by QA [1,2].

Regulatory submissions and maintenance

- Initial submissions:

- Prepare and file ethics/IRB applications, informed consent materials, and competent authority submissions consistent with device regulations (e.g., IDE or abbreviated IDE under 21 CFR 812 in the US; MDR 2017/745 Chapter VI for the EU, including EUDAMED Clinical Investigation Module where applicable). Country-specific pathways will be confirmed prior to activation [1,3,6].
- Register the study on an appropriate public registry (e.g., ClinicalTrials.gov and/or EU registry) before first participant, consistent with SPIRIT 2025 and local requirements [6].

- Amendments and notifications:

- Manage protocol/device/software amendments under controlled change management; assess whether substantial modifications require prior approvals; submit safety reports and annual progress reports per jurisdictional timelines [1,3,6].
- Serious and unanticipated device effects are reported per ISO 14155 and national requirements; manufacturer is informed to support vigilance reporting under MDR 2017/745 [1,6].

- Documentation and archiving:

- Maintain submission dossiers, approvals, correspondence, and decision letters in TMF; ensure version control and site dissemination logs; retain records per ICH/ISO retention standards [1,2].

DSMB coordination

- Charter and membership:

- The DSMB operates under a written charter approved by the SI, specifying roles, meeting frequency, statistical monitoring guidelines, stopping boundaries, blinding/unblinding procedures, and conflict-of-interest policies in accordance with FDA DMC guidance and GCP [2,7].

- Meetings and reports:

- Scheduling: at predefined enrollment/time milestones and ad hoc for safety concerns.
- Report packages: prepared by Biostatistics and DM; include blinded aggregate safety data (AEs/SAEs/UADEs, device deficiencies), data completeness, and primary endpoint operational summaries; individual PHI is excluded [1,2,7].
- Closed/open sessions: Open session for operational updates with CC; closed session for independent DSMB review; DSMB minutes and recommendations documented by the DSMB Coordinator and filed in TMF with restricted access [7].

- Decision handling:

- DSMB recommendations are reviewed by the SI for action (continue, modify, pause/stop); CC implements actions, notifies sites/authorities/IRBs as required, and documents rationale and timelines [1–3,7].

- Firewalls and access:

- DSMB materials are stored in a segregated, access-controlled portal; only pre-authorized, non-voting CC personnel may handle logistics; operational teams remain blinded unless an approved unblinding event occurs per charter [2,7].

Risk management and CAPA integration

- The CC integrates ISO 14971-aligned risk controls into operational processes, linking KRIs, monitoring findings, deviations, and safety signals to a unified CAPA system. Effectiveness is verified by QA audits and DSMB feedback where relevant [1,2].

Transition and close-out

- Site close-out:

- Confirm resolution of queries, reconciliation of device accountability, return or disposition of investigational materials, final safety updates, and ISF/TMF completeness; provide close-out letters to IRB/EC and authorities as required [1–3].

- Study close-out:

- DSMB final statement; database lock and archival; submission of final reports/public disclosures consistent with SPIRIT 2025 and applicable regulations [1–3,6].

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12 Trial Registration, Open Science, and Protocol Transparency

Trial registration

- Responsible party and timing

- The Sponsor-Investigator will register this Phase III, two-arm, parallel, stratified 1:1 randomized clinical investigation of the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) in a publicly accessible, WHO-recognized registry before enrollment of the first participant, consistent with SPIRIT 2025, ICH-GCP, ISO 14155, the Declaration of Helsinki, FDAAA/42 CFR Part 11 (where applicable), and EU MDR 2017/745 [1–7,9].
- Primary registration will occur on ClinicalTrials.gov with an NCT identifier to be obtained prior to site activation; for investigations conducted in the EU/EEA, the clinical investigation will also be registered in the EUDAMED Clinical Investigation Module with the required sponsor identifiers (including SRN) prior to initiation, as applicable under MDR 2017/745 [6,7].

- Registry content

- The registration will include all WHO Trial Registration Data Set (TRDS) elements, prespecified primary and secondary outcomes, key eligibility criteria, target sample size, allocation, masking, and data-sharing plan statement, in alignment with ICMJE and SPIRIT 2025 requirements [4–6].
- The device status will be clearly described as investigational software functionality available only within the clinical trial and operating with the CE-marked AsthmaTuner system; any off-label aspects (if applicable) will be explicitly disclosed [1,6,7].

Maintenance of registry records

- Updates and corrections

- The Sponsor-Investigator (or delegated Responsible Party) will keep registry records current by:
  - Posting protocol version updates and recruitment status changes within 30 days of effective change [5,6].
  - Updating anticipated and actual dates for primary completion and study completion within 30 days

of changes or reaching milestones [5].
- Correcting outcome measure definitions or time frames only via protocol amendment; the registry will reflect amendments on or before implementation, preserving prior entries per registry versioning [1,2,5,6].

- Results reporting

- Summary results for prespecified outcomes will be posted to the primary registry within 12 months of the primary completion date, unless a lawful certification/extension applies (e.g., pending regulatory application), consistent with FDAAA/42 CFR Part 11, SPIRIT 2025, and Helsinki [5,6,9].
- For EU/EEA investigations, a summary of results and the clinical investigation report will be submitted in EUDAMED within 1 year of the end of the investigation (6 months for pediatric-only investigations), as required by MDR 2017/745 [7].

Protocol, SAP, and transparency commitments

- Public availability

- A public, version-controlled protocol summary aligned with SPIRIT 2025 will be posted to the primary registry at or before first participant enrollment; major amendments will be summarized with dates and rationale [1,6].
- A synopsis of the Statistical Analysis Plan (SAP) specifying primary and key secondary analyses, analysis populations, and handling of missing data will be posted to the registry before database lock, with sufficient detail to deter outcome switching while protecting proprietary details as appropriate [1,6].

- Prespecification and change control

- Primary and secondary endpoints, visit windows (6–12 weeks), stratification by inhaler type (DPI/MDI/both), and the primary analysis set will be prespecified in the registry and protocol; any deviations will follow controlled amendment with dated justification and synchronized updates to the registry [1,2,6].

- Device transparency

- The investigational nature of the inhalation app-module embedded in AsthmaTuner (>5.4.13.5) will be explicitly stated in public materials, including dependencies on the CE-marked AsthmaTuner system (spirometer and app), and the limited availability of the module to study participants only during the investigation [1,7].

Open science and data-sharing

- Summary-level dissemination

- Aggregate findings, including safety (AEs/SAEs/UADEs) and effectiveness results for the prespecified endpoints, will be disseminated via peer-reviewed publications and conference presentations, adhering to ICMJE and SPIRIT 2025 guidance and acknowledging DSMB oversight [2,5,6].

- Individual participant data (IPD)

- The registry will include a data-sharing plan statement specifying whether de-identified IPD, analysis code, and data dictionaries will be shared, the conditions for access (e.g., qualified request, research proposal, data use agreement), timelines (e.g., after primary publication and regulatory milestones), and the secure access mechanism, in compliance with ISO 14155, ICH-GCP, and applicable privacy laws [1,2,5,6].

- Materials and code

- Where feasible and without compromising proprietary or cybersecurity controls, non-proprietary analysis code for primary and key secondary endpoints will be shared with adequate documentation, consistent with the posted SAP synopsis and data-sharing plan [1,6].

Alignment with international standards and regulations

- Ethical and regulatory framework

- Prospective registration and public reporting adhere to ISO 14155 requirements for protocol registration and reporting, ICH E6(R2) principles of transparency and trial oversight, SPIRIT 2025

protocol items for registration and dissemination, EU MDR obligations for clinical investigations, FDAAA/42 CFR Part 11 registration and results rules (as applicable), and the Declaration of Helsinki's mandate for prospective registration and results dissemination [1–7,9].

- Consistency and audit-readiness

- The content of public registry records, participant-facing materials, and publications will be consistent with the approved protocol/ICF and maintained under document control. All submissions, confirmations, and timestamped evidence of registry postings will be retained in the TMF to support inspection readiness [1,2].

Roles and responsibilities

- The Sponsor-Investigator is the Responsible Party for initial registration, updates, and results posting; duties may be delegated in writing to the Regulatory Affairs Lead, with quality control by the Coordinating Center and oversight by the Sponsor-Investigator [1,2].
- The Biostatistics Lead ensures alignment of registered outcomes with the SAP; the Data Management Lead confirms that posted results reflect the locked database; the Quality Assurance function verifies timely and complete public disclosures against regulatory timelines [1,2,6].

Handling of amendments and early termination

- Substantial amendments impacting registered information (e.g., endpoints, sample size, analysis populations, visit window) will be prospectively updated in the registry prior to implementation when feasible, or immediately upon approval/activation, with clear effective dates and rationale; publications will cite both original and amended versions to preserve interpretability [1,2,6].
- In the event of early termination or temporary suspension, the registry will be updated within 30 days with reason(s), participant numbers, and disposition; partial results available at termination will be posted in alignment with FDAAA/42 CFR Part 11, MDR 2017/745, and SPIRIT 2025 [6,7,9].

References

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13 Protocol and Statistical Analysis Plan Access

Governance, version control, and document identification

- The protocol, protocol amendments, Statistical Analysis Plan (SAP), DSMB and Clinical Event Committee (CEC) charters (if applicable), Endpoint Definition Document (EDD) where used, Data Management Plan (DMP), and other controlled trial documents are maintained under a validated document management system with:

- Unique document identifier, descriptive title, effective date, version number, and superseded version cross-reference.
- Authorship, review, and approval history with 21 CFR Part 11/Annex 11-compliant electronic signatures and immutable audit trails [1–4].
- Role-based access permissions and read-acknowledgement tracking; distribution logs to investigators, monitors, DSMB/CEC members, and regulators are filed in the Trial Master File (TMF) and Investigator Site Files (ISFs) [1–3,5,6].

- Version-control rules:

- The “final approved” protocol/SAP/charters/EDD/DMP are the sole authoritative versions for conduct and analysis; draft or superseded versions are archived and not used operationally [1–3,6].
- All amendments are designated as substantial or non-substantial per applicable regulation; each change is red-lined against the prior effective version with a consolidated change history and impact assessment on safety, endpoints, sample size, and statistical methods [1,3,5–7].
- Any protocol or SAP version dependencies on the investigational inhalation app-module embedded in AsthmaTuner (>5.4.13.5; MediTuner AB; SRN SE-MF-000028534) are explicitly stated, including prohibited software versions and gating criteria, with alignment to device change control and risk management [1,3,7].

Approval workflow and timing

- Protocol and amendments:

- Drafted by the Sponsor-Investigator (SI) and Coordinating Center (Regulatory Affairs, Clinical, Biostatistics), reviewed by key stakeholders, and approved by the SI prior to ethics/competent authority submission; site activation or change implementation occurs only after required approvals are in place and investigators are trained on the effective version [1–3,5–7].

- SAP and related statistical documents:

- The SAP is authored by the Biostatistics Lead, reviewed by Data Management and Medical Monitor for consistency with endpoints and data flows, and approved by the SI prior to any unblinded analysis. The SAP becomes final before final database lock and before any unblinded primary or key secondary analyses; if interim analyses are planned for the DSMB, a separate DSMB Statistical Monitoring Plan and/or pre-specified SAP sections define rules for interim looks and are approved before the first interim data cut [1,2,5,8].
- Any SAP revision after first participant enrollment that could affect inferential analyses is documented with rationale, impact assessment, and date/time of decision, and, where applicable, mirrored by protocol/registry updates to preserve prospective specification and deter outcome switching [2,5,8].

- DSMB/CEC charters and endpoint definitions:

- DSMB and CEC operate under written, dated, and approved charters detailing composition, independence, data flows, firewalls, meeting cadence, stopping rules, and unblinding procedures; endpoint definitions for adjudication (if used) are governed by the EDD or protocol/SAP sections and are locked prior to first participant enrollment or, if newly required, before the first affected data review [1,2,8].

Access during study conduct

- Investigators and site staff:

- Receive the current approved protocol, ICFs, relevant manuals, EDD (or protocol endpoint appendix), and amendment notices; they do not access unblinded SAP sections or unblinded interim analysis outputs. Access to the full SAP may be provided upon justified request under confidentiality and without disclosure of any unblinded content [1,2].

- Sponsor-Investigator, Coordinating Center, and core vendors:

- Have controlled access to the protocol, SAP, EDD, DMP, monitoring plan, DSMB/CEC charters (blinded portions as applicable), and system validation documentation necessary for trial conduct; unblinded SAP sections are restricted to the independent statistician(s) and DSMB pathway per charter [1–4,8].

- DSMB:

- Accesses the DSMB charter, the DSMB statistical monitoring plan, and the minimum necessary blinded/unblinded datasets and outputs for safety/efficacy monitoring in closed session; access is segregated from operational teams via information firewalls and a secure portal with audit trails [1,2,8].

- CEC (if applicable):

- Accesses the CEC charter, endpoint definitions, and redacted source materials required for adjudication; no access to randomization codes or nonessential PHI; operations are independent of site and sponsor analyses [1,2].

- Monitors (CRA) and Quality Assurance:

- Access current approved protocol and controlled documents for verification of compliance; QA may review superseded versions and approval histories during audits; both operate under least-privilege access with audit trails [1,2,5].

- Regulators and ethics committees:

- Upon request/inspection, receive or review the protocol (current and historical), SAP (including revisions), charters, EDD, DMP, monitoring and risk plans, training records, and approval histories; identifiable records are made available as required by law under supervised conditions [1–3,5–7].

Access after study completion

- Archival access:

- The Sponsor-Investigator retains master copies of the protocol, all amendments, SAP and revisions, DSMB/CEC charters, EDD, DMP, monitoring and quality plans, and approval logs in the TMF for not less than the longest applicable retention period (at least 10 years after completion/termination and in accordance with ICH/ISO/MDR and national law) [1,2,6,7].

- Post-completion stakeholder access:

- Regulators and auditors retain inspection access to all controlled documents and approval histories.

- Investigators may access the final protocol and a summary of the final SAP and analysis outputs relevant to site obligations; full SAP may be shared under confidentiality upon justified request.

- Qualified researchers may request de-identified analysis specifications and a SAP synopsis consistent with the public transparency plan and data use agreements; proprietary algorithms or cybersecurity-sensitive details of the investigational app-module may be redacted as justified [1,5].

- Public registries will host a protocol summary and SAP synopsis as committed, aligned with SPIRIT 2025 and applicable regulations; journal publications will reference the final protocol/SAP versions and amendment chronology [5].

Documentation of changes and traceability

- Change control:

- Each protocol/SAP/charter/EDD/DMP change is logged with a unique change ID, description, rationale, risk/impact assessment (safety, endpoints, statistics, operations), validation needs, approvals (names/roles/date-time), effective date, training and communication records, and cross-links to registry updates and site notifications, in accordance with Annex 11/Part 11 audit-trail principles [2–4,5].

- Timing safeguards:

- No analysis governed by revised SAP terms will proceed until approvals are complete and the database state (frozen/locked) and blinding status are consistent with the revised plan. Any deviation from the final SAP will be prospectively approved if feasible; otherwise, it will be documented in the

Statistical Analysis Report with justification and sensitivity analyses per ICH E9(R1) principles on estimands and sensitivity [2,8].

- Blinding controls:

- Access to unblinded randomization codes, interim boundaries, or treatment-specific outputs is restricted to the independent statistician(s) and DSMB per charter; operational teams remain blinded unless an approved unblinding event occurs [1,2,8].

Distribution, training, and confirmation of receipt

- Before implementation, sites receive updated controlled documents via secure distribution; investigators and key staff complete targeted training and acknowledge receipt; training and acknowledgement logs are filed in the ISF/TMF and verified by monitoring [1,2,5,6].
- Version-controlled document lists (current and superseded) are maintained at each site and centrally; monitors verify that only current versions are in use and posted in clinical areas where required [1,2,6].

Security, confidentiality, and proprietary protections

- All controlled documents are handled under least-privilege access, encryption at rest/in transit, and role-based controls; disclosures outside the sponsor, sites, DSMB/CEC, and regulators require written authorization and, where applicable, data use or confidentiality agreements. Proprietary device information and cybersecurity-sensitive details may be limited to need-to-know recipients while preserving regulatory and scientific transparency [1–5,7].

References

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14 Data Sharing, Dissemination, and Participant Communication

Overview and principles

This plan defines how study data and documents will be shared and disseminated, and how participants will be informed of results, in accordance with ISO 14155, ICH-GCP, GDPR, SPIRIT 2025, EU MDR 2017/745, FDAAA/42 CFR Part 11 (where applicable), ICMJE data-sharing recommendations, and the Declaration of Helsinki [1–9]. All sharing preserves participant confidentiality, protects proprietary device information, and maintains audit-ready governance [1–4,10].

Scope of datasets and documents potentially available for sharing

Subject to applicable approvals and data use agreements, the following may be shared after study completion and primary results publication:

- De-identified individual participant data (IPD) for prespecified primary and secondary endpoints and key baseline characteristics [1–5,8,9].
- Data dictionary/codebook and annotated case report forms describing variables, coding, units, and derivations [1,5].
- Analysis specifications and non-proprietary statistical code used for primary and key secondary analyses, consistent with the finalized SAP synopsis and without revealing randomization codes or unblinding information [1,5,8].
- De-identified device performance data relevant to endpoints (e.g., inhalation metrics captured by the investigational module and CE-marked components) necessary to replicate outcomes; raw cybersecurity-sensitive logs, cryptographic materials, or proprietary algorithms will not be shared [1,6,10].
- Redacted protocol, SAP synopsis, and clinical study report (CSR) executive summary, aligned with registry commitments and regulatory obligations [1,5–7].

Imaging data are not planned in this investigation; if any are collected, availability and formats will be specified in an addendum to this plan (to be confirmed) [1,5].

Conditions for access and governance

- Eligibility and review: Access is granted to qualified researchers affiliated with recognized institutions who submit a methodologically sound research proposal, analysis plan, and attest to compliance with privacy and confidentiality rules. Proposals are reviewed by a Data Access Committee (DAC) appointed by the Sponsor-Investigator, with independent biostatistical and clinical input as needed [1,2,5].
- Agreements: Approved requestors must sign a data use agreement (DUA) specifying purpose, permitted uses, prohibition of re-identification or contact of participants, no onward sharing, acknowledgment of the trial in outputs, and obligations to report privacy incidents [1–5].
- Secure access: Data are provisioned in a controlled access environment with encryption at rest and in transit, role-based permissions, and audit trails; downloads of IPD are prohibited unless explicitly authorized by the DAC. Only de-identified or appropriately pseudonymized datasets will be shared; site-held linkage keys are never transferred [1–5,10].
- Oversight and record-keeping: All requests, decisions, datasets provided, and publications arising are logged in the Trial Master File (TMF) for inspection readiness [1,2].

Protection of participant confidentiality and de-identification

- Anonymization/pseudonymization: Direct identifiers are removed; indirect identifiers are minimized, generalized, or suppressed using a documented risk-based approach consistent

with GDPR principles. Pseudonymization keys remain under site control and are not shared externally [1–5,10].
- Small-cell risk: For rare combinations or small strata, data may be aggregated or withheld to reduce re-identification risk [4,5].
- Consent alignment: Sharing is limited to uses compatible with the informed consent and ethics approvals; if additional secondary uses are proposed, they will undergo ethics review before release [1,2,4,5].

Timing, duration, and embargo

- Registration statement: A data-sharing statement will be posted in the public registry before first participant enrollment per SPIRIT 2025 and ICMJE recommendations [5,8].
- Availability: De-identified IPD, data dictionary, and non-proprietary analysis code will be made available after database lock, completion of primary analyses, and publication of primary results, and after any applicable regulatory submissions that would be materially affected by disclosure. Target timing is within 12–24 months after primary results publication, unless a justified embargo is required for regulatory protection (to be confirmed) [1,5–7,8].
- Duration: Approved access is typically granted for 12–36 months and may be extended upon justified request; datasets and access logs are retained per record retention requirements [1,2].

Restrictions related to proprietary device information

- The investigational inhalation app-module is embedded in the AsthmaTuner system; proprietary source code, model weights, security artifacts, and detailed cybersecurity logs will not be shared. Sufficient technical specifications to reproduce outcome analyses will be provided without disclosing trade secrets or creating cybersecurity risk, consistent with MDR and information security standards [1,6,10].
- Any disclosure that could compromise intellectual property or safety controls will be redacted, while preserving scientific interpretability of outcomes [1,6,10].

How to request data

- Requests are submitted to the Sponsor-Investigator or delegated Coordinating Center via the procedure described in the public registry entry and protocol website (to be provided). Requests must include investigator credentials, research question(s), analysis plan, variables required, and funding and conflict-of-interest disclosures [1,5,8].
- The DAC will acknowledge within 30 calendar days, request clarifications if needed, and render a decision typically within 60–90 days. Decisions and rationales are documented; appeals may be submitted once with additional justification [1,2,5].

Dissemination and regulatory reporting

- Trial registry reporting: The study will be registered before enrollment; summary results for prespecified outcomes will be posted to the primary registry within 12 months of the primary completion date, unless a lawful extension applies [5,7].
- EU/EEA reporting: Where applicable, a summary of results and the clinical investigation report will be submitted in EUDAMED within 1 year of the end of the investigation (6 months for pediatric-only investigations) per MDR 2017/745 [6].

- Regulatory submissions: Required safety and progress reports, final study reports, and device vigilance communications will be submitted to competent authorities and ethics committees in line with ISO 14155, ICH-GCP, and MDR [1,2,6].
- Peer-reviewed publications and conferences: Aggregate findings, including prespecified primary and key secondary outcomes, will be disseminated in peer-reviewed journals and scientific meetings. Authorship follows ICMJE criteria; all reports will transparently describe methods and prespecified analyses, acknowledge DSMB oversight, and reference the public registry record [2,5,8,9].
- Clinical study report: A CSR conforming to GCP will be prepared to support regulatory filings; a redacted executive summary may be shared publicly where feasible without disclosing proprietary information or PHI [1,2,6].

Participant and public communication

- Plain-language summary: A lay summary of aggregate results, including what was studied, main findings, and safety observations, will be made available to participants and the public after primary results publication and within 12 months of primary completion, aligned with registry postings and MDR/EUDAMED timelines where applicable [5,6,7,9].
- Communication channels: Participants may opt to receive the lay summary via secure email/postal mail or patient portal where available; the summary will also be posted on the public registry or a sponsor-hosted webpage (to be confirmed) [5,9].
- Individual results: Individual clinical results are not routinely returned, except where ethically appropriate and validated (e.g., clinically actionable safety findings) and consistent with consent, local law, and investigator judgment [1,2,9].
- Updates on safety: Any new, significant safety information that may affect participant welfare or willingness to continue participation will be promptly communicated to investigators and, where appropriate, to participants per ethics committee guidance [1,2].

Publication and data citation policy

- Secondary analyses using shared data must cite the original trial registration, primary publication, and a unique data citation provided in the DUA. Manuscripts must undergo standard peer review; preprints are allowed if consistent with the DUA and journal policies [5,8,9].
- To avoid duplicate or conflicting analyses, the DAC may post brief summaries of approved secondary projects (title, objectives, status) on a public webpage or registry entry, without disclosing proprietary details or PHI [5].

Roles and responsibilities

- The Sponsor-Investigator is responsible for the data-sharing plan, registry statements, and timely dissemination; the Coordinating Center administers requests, prepares de-identified datasets, and maintains the access log; Quality Assurance verifies adherence to timelines and documentation; the Data Protection Officer oversees GDPR compliance [1–5,10].

References

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15 Patient and Public Involvement

Summary of involvement to date

No formal patient or public involvement (PPI)—including patients, caregivers, patient advocates, clinical users outside the investigative team, or public representatives—occurred in the initial selection of outcomes, assessment of study burden, drafting of consent materials, shaping of follow-up procedures, or planning of dissemination for this confirmatory device investigation. This is disclosed in alignment with SPIRIT 2025 expectations for transparency on PPI in protocols [1].

How participant perspectives and burden were addressed in the absence of formal PPI

Even without formal PPI, the protocol incorporates measures required by international standards to minimize participant burden, protect welfare, and focus on patient-relevant outcomes:

- Ethical oversight and risk management: Study procedures, duration (6–12 weeks), and safety oversight via a DSMB are designed under ISO 14155 and ICH-GCP principles to protect subjects, ensure proportional risk-benefit, and minimize burden [2,3].
- Usability and human-factors considerations: The investigational inhalation app-module is embedded within the CE-marked AsthmaTuner ecosystem and is used alongside familiar home-use components (spirometer and Airflow Trainer) shipped to participants or provided at clinic, reducing travel and visit complexity. Human-factors and use-error risk controls are addressed consistent with IEC 62366-1 and ISO 14971 frameworks, focusing on safe, effective use and mitigation of foreseeable use errors in DPI/MDI techniques [4,5].
- Patient-relevant outcomes and acceptability: The primary endpoint—rate of successful inhalation technique at 6–12 weeks—aligns with patient-relevant functionality (correct use of DPI/MDI to deliver medication). Secondary aims include feasibility, usability, and safety, reflecting device acceptability and real-world operability considerations recommended for medical device studies [2,4,6].
- Participant access and digital burden: Eligibility is limited to participants with BankID (or similar) and an Android/iOS smartphone to ensure secure identity verification and feasible app-based training. The protocol limits on-site visits and enables at-home training/assessments to reduce time and travel burden, consistent with good clinical practice to minimize inconvenience while maintaining data integrity [2,3].

Device-specific considerations integrated into the protocol

- Training and onboarding: Standardized education on inhalation technique is provided to all participants; the intervention arm receives app-based education/training within AsthmaTuner. This approach leverages familiar smartphone interfaces, structured prompts, and objective feedback on inspiratory flow dynamics (e.g., PIF, time to PIF, inspiration time) to support correct DPI/MDI use and reduce repeated in-person training needs [2,4,6].
- Usability and safety monitoring: Feasibility/usability and safety are prespecified as secondary aims, with structured assessments and AE/SAE/UADE monitoring under ISO 14155 and ICH-GCP. Specific instruments and thresholds for usability and acceptability will follow the finalized Statistical Analysis Plan and Data Management Plan (to be confirmed) [2,3].
- Follow-up burden: A single primary outcome assessment window (6–12 weeks) is used to limit procedural intensity; remote interactions and home-use devices are employed where feasible to reduce participant time and logistical burden while maintaining data quality [2,3].

Planned and ongoing engagement activities

To strengthen patient-centeredness during conduct and reporting, the Sponsor-Investigator will implement the following measures, consistent with international guidance encouraging patient engagement in device clinical studies [1,6,7]:

- Participant feedback loops: Collect brief, structured feedback from enrolled participants on app usability, training clarity, and follow-up convenience at the 6–12-week assessment; use these inputs for iterative operational improvements (non-substantial changes only) (to be confirmed) [2,4].
- Review of participant-facing materials: Solicit review of revised consent and lay-summary language by a local patient advisory resource (e.g., an institutional patient council or respiratory patient group) before any future amendments or dissemination materials are finalized, to enhance clarity and accessibility (to be confirmed) [1,7].
- Dissemination: Provide a plain-language summary of aggregate results to participants, aligned with the trial's transparency and registry reporting commitments; consider optional feedback from patient advisors on readability prior to distribution (to be confirmed) [1,2].

Rationale for this approach

This late-phase, confirmatory device investigation emphasizes patient-relevant technique outcomes, streamlined follow-up, home-use workflows, and rigorous safety/usability oversight to address participant needs despite the absence of formal PPI in design. The added, pragmatic engagement steps during conduct and dissemination are intended to enhance acceptability and interpretability without altering prespecified objectives or endpoints, in line with GCP and SPIRIT 2025 [1–3].

References

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16 Roles, Responsibilities, and Oversight Structure

Oversight framework

This late-phase confirmatory device investigation operates under a layered oversight model that assigns clear, auditable responsibilities to the Sponsor-Investigator (SI), Coordinating Center (CC), site Principal Investigators (PIs) and delegated staff, independent oversight committees, core laboratories, and qualified vendors. Governance follows ISO 14155, ICH E6(R2), applicable device regulations (e.g., 21 CFR Part 812; EU MDR 2017/745), data integrity requirements (21 CFR Part 11), and SPIRIT 2025, with independence safeguards for the DSMB and any Clinical Events Committee (CEC) [1–6].

Role and responsibility matrix

Role/entity	Key responsibilities	Primary accountability
Sponsor-Investigator (SI)	Overall scientific, ethical, and regulatory responsibility; approves protocol/SAP/charters/amendments; ensures resources; qualifies vendors; assures GCP/ISO 14155 compliance; oversees safety signal management and actions; approves database lock and final report/publication plan	Accountable to applicable competent authorities/IRBs/ECs and sponsor governance [1–6]
Coordinating Center (CC)	Central trial operations; risk-based quality management; regulatory submissions and maintenance; vendor oversight; monitoring oversight; safety case processing support; data management and statistical leadership; DSMB/CEC coordination; TMF control	Accountable to SI; maintains inspection readiness and TMF integrity [1–6,8,10]
Principal Investigator (PI) at each site	Site conduct per protocol/GCP; obtains informed consent; eligibility confirmation; device accountability at site; training and delegation; source documentation; timely AE/SAE/UADE and device deficiency reporting; protocol adherence and deviation management	Accountable to SI and IRB/EC; maintains ISF and subject safety [1–4]
Sub-investigators and site staff	Conduct delegated procedures; participant training; data entry; safety surveillance; device handling and returns; privacy protections; query resolution	Accountable to PI with documented delegation and training [1–3]
Operators/proceduralists (e.g., respiratory therapists/educators)	Deliver standardized education; ensure correct DPI/MDI handling; document technique checks; interface with app-module workflow; report use-errors and device deficiencies	Accountable to PI; follow EDD/procedural manuals and competency requirements [1,4,9]
Data and Safety Monitoring Board (DSMB)	Independent safety/efficacy monitoring per charter; reviews blinded/unblinded data as specified; recommends continue/modify/stop;	Independent of SI/sites; reports recommendations to SI per charter [1,5]

	preserves firewalls; manages conflicts of interest	
Clinical Events Committee (CEC) (if used)	Independent adjudication of prespecified endpoints/events using blinded source packets and Endpoint Definition Document (EDD); maintains charter; documents final determinations for analysis datasets	Independent of SI/sites; decisions archived for audit; to be confirmed (if activated) [1,2]
Core laboratory for inhalation flow analyses	Centralized quality control and standardized derivation of inspiratory flow metrics (e.g., PIF, time to PIF, inspiration time) from spirometry/app data; provides adjudication packets to CEC where applicable; maintains calibration/validation records	Contracted to Sponsor; operates under SOPs and EDD; independent of treatment assignment [1–3]
Data Management (DM)	Data Management Plan; EDC/eSource configuration and validation; coding; data cleaning and reconciliation; audit trails; database locks/freeze; Part 11 compliance	Accountable to CC and SI; aligns with SAP and monitoring plan [1–3,7]
Biostatistics	SAP authoring and approval; randomization (stratified by inhaler type); DSMB statistical reporting; primary and secondary analyses; documentation of deviations and sensitivity analyses	Accountable to SI; independence safeguards for any unblinded work [1,2,6]
Clinical monitoring (CRA)	Risk-based monitoring; SDV/eSource verification; training verification; escalation/CAPA tracking; data integrity checks; device accountability checks	Accountable to CC; operates per monitoring plan and ICH E6(R2) [1,2,10]
Safety/pharmacovigilance	Intake and medical review of AEs/SAEs/UADEs; causality/seriousness/expectedness assessment; regulatory safety reporting; device deficiency/complaint reconciliation; vigilance support	Accountable to SI; aligned with ISO 14155 and MDR vigilance [1,4]
Regulatory affairs	Ethics/competent authority submissions; amendments; annual/periodic reports; registry registration/updates; financial disclosure records; correspondence archiving	Accountable to SI; maintains approvals before implementation [1–6]
Quality assurance (QA)	Independent audits; vendor qualification; process compliance; KRI/CAPA effectiveness checks; TMF/ISF quality reviews	Independent of operations; reports to sponsor QA leadership [1,2,8,10]
Device manufacturer (MediTuner AB; SRN SE-MF-000028534)	Supplies investigational app-module within AsthmaTuner; technical documentation; cybersecurity and change control; complaint/deficiency technical assessment; support for vigilance reporting; no access to PHI	Contracted party; operates under MDR and written agreements; independent of trial conduct decisions [3,4]
Other device suppliers (e.g., MIR spirometer/Airflow Trainer)	Provide CE-marked hardware; calibration/IFU; complaint processing; replacement logistics	Contracted to Sponsor; supports device accountability and vigilance [1,4]
Coordinating Center DPO/Privacy office	GDPR compliance and privacy risk assessments; data protection agreements; incident response coordination	Accountable to SI; ensures least-privilege access and lawful processing [6]
Publication steering/authorship group	Publication planning; authorship decisions per ICMJE; data transparency alignment with registry and SAP; review of abstracts/manuscripts	Accountable to SI; conflicts managed and documented [6,11]

Division of responsibilities across key trial activities

- Protocol and SAP design

- SI leads scientific aims and approves protocol/SAP; Biostatistics authors SAP; CC integrates operational feasibility and regulatory requirements; CEC/DSMB charters approved before first data review [1–6].

- Informed consent and eligibility confirmation

- PI or qualified designee obtains consent and confirms eligibility using prespecified criteria; documentation maintained in source and ISF; any reconsent handled per regulatory/ethics requirements [1–3].

- Randomization and blinding

- Biostatistics oversees system setup for stratified 1:1 randomization by inhaler type; allocation concealment maintained; sites remain blinded to group-level results; unblinding follows approved procedures if required for safety [1,2].

- Device accountability and version control

- Site PI ensures receipt, storage, assignment, reconciliation, and return/disposition of spirometers/Airflow Trainers; CC Device Logistics maintains central inventory and reconciliation; manufacturer supports change control; only approved AsthmaTuner versions (>5.4.13.5) with investigational module enabled are permitted; exposure to prohibited versions is prevented and reported [1,4,9].

- Procedure conduct and standardized education

- Operators deliver standardized inhaler education per manual; intervention arm receives app-based education/training; all technique checks are documented against standardized criteria; deviations and use-errors are recorded and reported as appropriate [1,2,9].

- Safety reporting and vigilance

- Sites report AEs/SAEs/UADEs and device deficiencies within protocol timelines to CC/Sponsor; Safety reviews relatedness/expectedness and files regulatory reports; manufacturer receives de-identified complaint/deficiency technical details to support MDR vigilance; reconciliations across EDC, safety, and complaint systems are performed regularly [1,3,4].

- Endpoint assessment and adjudication

- Primary endpoint is measured per protocol using standardized criteria and objective inhalation metrics; if a CEC is activated, it adjudicates events/endpoint status using redacted, blinded packets prepared by the core lab/CC; adjudication results feed the analysis dataset per EDD [1,2].

- Data quality and monitoring

- Sites enter data within defined SLAs; CRAs perform risk-based monitoring, SDV/eSource verification, and KRI-triggered visits; DM manages queries and reconciliation; QA audits processes and documentation; TMF/ISF completeness verified periodically [1,2,7,8,10].

- Statistical analysis and reporting

- Biostatistics executes analyses per final SAP after database lock; SI approves Statistical Analysis Report and clinical study report; results are posted to registries within required timelines and submitted to authorities as applicable [1–6].

- Archiving and record retention

- SI/CC maintain TMF; sites maintain ISF; records retained for not less than the longest applicable period under ISO/ICH/MDR and national law; audit trails preserved for electronic systems (Part 11) [1–4,8].

- Publication and data sharing

- Publications follow ICMJE authorship; registry postings and lay summaries adhere to SPIRIT 2025 and transparency commitments; data sharing is governed by the approved plan with de-identification and DUA controls [5,6,11].

Independence, conflicts of interest, and information firewalls

- DSMB and any CEC members are independent of the Sponsor, manufacturer, and investigative sites; conflicts are disclosed and managed per charters; only the minimum necessary blinded/unblinded data are provided; operational teams remain blinded unless unblinding is authorized for safety per charter [1,5].

- Manufacturer personnel do not participate in enrollment, outcome assessment, monitoring, or data analyses; they may provide technical input on device deficiencies/complaints without access to PHI, consistent with GDPR and contractual firewalls [4,6].
- Financial disclosure records for investigators are maintained and updated per regulation; potential conflicts are reviewed by the SI/CC and, where required, reported to authorities/IRBs [3].

Delegation, training, and competency

- Each site maintains a current Delegation of Authority log; only trained and documented staff perform study tasks; CC verifies training before system access and monitors recertification; specialized roles (operators/proceduralists, core lab analysts, adjudicators) meet predefined competency requirements and follow SOPs/manuals [1,2,10].
- Changes in personnel or delegation are communicated to CC within defined timelines; training records and acknowledgements are filed in ISF/TMF and verified during monitoring and audits [1,2,8].

Escalation and CAPA

- Operational non-compliance, critical KRI excursions, data integrity concerns, or safety signals trigger documented escalation from CRA to CC leadership and SI; root-cause analysis and CAPA are implemented and effectiveness-checked by QA; reportable issues are communicated to regulators/IRBs/ECs per jurisdictional rules [1,2,4,10].

Publication, authorship, and data transparency oversight

- The SI leads publication oversight; the publication steering/authorship group applies ICMJE criteria; drafts undergo CC scientific and statistical review for concordance with the final protocol/SAP; results are disseminated via registry postings and peer-reviewed outputs within prescribed timelines [5,6,11].

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17 Device Deficiency, Malfunction, Complaint, and Recall Management

Definitions and classification

- Device deficiency: Any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, performance, or usability that might lead to or has led to a medical event or device malfunction; includes malfunctions, use errors, and inadequate labeling or instructions for use (IFU) observed during the clinical investigation, whether or not associated with an adverse event [12].
- Device malfunction: Failure of a device to meet its performance specifications or otherwise perform as intended, including software faults (e.g., incorrect algorithm output, app crash, loss of connectivity) and hardware issues (e.g., spirometer calibration drift) occurring during use in the study [12,14,15].
- Product complaint: Any written, electronic, or oral communication alleging deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the investigational app-module, the CE-marked AsthmaTuner system, or associated accessories; complaints are handled under a documented quality system and may or may not involve an adverse event [18].
- Use error: A user action or lack of action that results in a different device response than intended by the manufacturer or expected by the user; includes errors arising from design, labeling, training, or environment and is assessed under the usability engineering framework [12,16,17].
- Device-related protocol deviation: Noncompliance with the approved protocol, instructions, or training that affects device use, accountability, software version control (e.g., use of non-approved app versions), or data integrity; may overlap with use error but is managed under protocol compliance and CAPA pathways [12,13].
- Device-related adverse event (AE): Any untoward medical occurrence in a participant that is related to the use of the device; seriousness and relatedness are assessed by the investigator and sponsor per GCP/ISO 14155 [12,13].
- Unanticipated adverse device effect (UADE)/Serious incident: Any serious adverse effect on health or safety or death caused by, or associated with, a device, which was not previously identified in nature, severity, or incidence, or which was anticipated but occurred at a rate or severity that is significantly different; UADE term per FDA IDE; serious incident per EU MDR vigilance [12,14,15].

These categories are mutually informative and linked operationally: all device malfunctions and product complaints are device deficiencies; use errors may be device deficiencies; any device deficiency associated with an AE/SAE may trigger UADE/serious incident assessment and regulatory vigilance reporting as required [12,14,15,18].

Identification, documentation, and initial control

- Identification: Sites, participants, monitors, or the manufacturer may identify device deficiencies through routine use, monitoring, participant reports, automated logs from the app-module/AsthmaTuner, spirometer quality checks, or data review triggers [12,13].
- Immediate participant safety: The investigator takes prompt actions to protect the participant (e.g., discontinue device use, revert to standard inhaler education, provide clinical care) and documents clinical rationale; urgent medical care always supersedes reporting steps [12,13].
- Quarantine and preservation: Affected hardware (spirometer, Airflow Trainer) is labeled "Quarantined—Do Not Use," segregated, and preserved for investigation; affected software/app instances are disabled from further use and screenshots/logs preserved. Do not alter or repair devices implicated in serious events without sponsor/manufacturer instruction, except as necessary for safety [12,14,18].
- Minimum data elements captured in source and EDC/safety forms:

- Subject ID; date/time; site; reporter details.
- Device identifiers: product name, software build/version (AsthmaTuner >5.4.13.5 with investigational module), configuration, accessory type, lot/batch/serial number, and expiration where applicable; mobile OS/version and handset model for app issues.
- Description of event/deficiency, environment of use, steps leading to the occurrence, and whether a use error or protocol deviation was involved.
- Clinical impact (none/AE/SAE), immediate actions, and outcome.
- Storage conditions and disposition status (quarantined/returned/replaced/destroyed) [12,14,18].

Reporting and escalation workflow

- Site to Sponsor/Coordinating Center:

- Investigators report device deficiencies, malfunctions, and product complaints to the Sponsor/Coordinating Center without undue delay using the EDC deficiency/complaint module and the safety reporting channel when an AE/SAE/UADE is involved. Serious, new, or potentially widespread issues are escalated immediately via designated 24/7 contacts where provided [12–15,18].
- If an AE/SAE occurs with a device deficiency, both the safety report and device deficiency/complaint forms are completed; records are cross-referenced to ensure reconciliation [12–15].

- Sponsor internal processing:

- Medical and technical review determines classification (deficiency, malfunction, complaint), relatedness, seriousness, expectedness, and whether the case meets criteria for UADE/serious incident and potential vigilance reporting to competent authorities per applicable jurisdiction; timelines and recipients follow applicable regulations and the approved safety management plan [12,14,15,18].
- The manufacturer (MediTuner AB; SRN SE-MF-000028534) receives de-identified technical details and device samples/data as needed for investigation and risk assessment; PHI is not shared with the manufacturer [14,18].

- Independent oversight:

- Aggregate trends in device deficiencies, malfunctions, use errors, and device-related AEs/SAEs/UADEs are reviewed at predefined intervals by the DSMB per its charter; urgent signals may trigger ad hoc review and recommendations (e.g., temporary suspension, additional training, software hotfix) [12,13].
- If a CEC is activated for endpoint adjudication, it may receive redacted packets to evaluate potential device-related clinical events under blinded conditions [12,13].

- Ethics committees and regulatory bodies:

- The Sponsor-Investigator notifies ethics committees and competent authorities when new information could materially impact participant safety, consent, or the risk-benefit profile (e.g., confirmed UADE/serious incident, field safety corrective action). Jurisdiction-specific reporting formats and timelines are followed where applicable; absent prespecified timelines in this protocol, reporting occurs as soon as possible consistent with ISO 14155 and applicable law [12,14,15].

Investigation, root cause analysis, and CAPA

- Technical investigation:

- The Sponsor and manufacturer coordinate failure analysis using preserved hardware, de-identified data logs, and replication tests; for software, reproduce on controlled devices with the same app build/OS and network conditions. Human-factors assessments are applied when use error is suspected [16–18].

- Causality and risk evaluation:

- A structured causality/risk assessment (e.g., ISO 14971 hazard analysis) determines relationship to device, severity/probability, detectability, and residual risk; findings feed both clinical risk management and complaint trending [12,16].

- CAPA and communication:

- Corrective and preventive actions (e.g., user training update, IFU clarification, software patch, hardware replacement, process change) are documented, effectiveness-checked, and communicated to sites; changes that affect the protocol or risk profile proceed only after required approvals and training [12–14,18].

Linkage to AE/SAE/UADE framework and data reconciliation

- Dual reporting:

- When a deficiency is associated with an AE/SAE, the safety case is reported per the AE/SAE process, and the deficiency/complaint is reported via the device pathway; both records are cross-linked in the safety and EDC systems to ensure traceability [12–15].

- UADE/serious incident determination:

- The Sponsor assesses unanticipatedness and seriousness; confirmed UADEs/serious incidents trigger regulatory vigilance actions and site/participant communications as required, with documentation retained in the TMF/ISF [12,14,15].

- Periodic reconciliation:

- The Coordinating Center performs periodic three-way reconciliation among EDC, safety database, and the complaint/deficiency log to confirm completeness and consistency; discrepancies prompt query and corrective action; outcomes are reported to the DSMB and included in progress reports [12,13,18].

Handling of devices and materials

- Quarantine and storage:

- Quarantined devices are stored securely, labeled with subject ID (coded), deficiency ID, and date; environmental conditions are maintained per IFU to avoid altering the state of the evidence [12,18].

- Return and replacement:

- Upon Sponsor instruction, sites return affected devices using tamper-evident packaging and chain-of-custody documentation. If participant care requires continued access, a replacement unit or remedied software build is provided after Sponsor authorization and required approvals [12,14,18].

- Destruction:

- Destruction of devices occurs only with written Sponsor authorization and in compliance with environmental and data protection requirements; certificates of destruction are filed [12,18].

- Documentation:

- Device accountability and disposition logs capture receipt, storage, assignment to participant, lot/batch/serial numbers, software versions, calibration status, return date, reason for return, and final disposition, and are verified during monitoring [12,13,18].

Software version control and cybersecurity considerations

- Approved versions:

- Only AsthmaTuner versions later than 5.4.13.5 with the investigational inhalation app-module enabled per study configuration are permitted. Exposure to non-approved versions or settings is a device-related protocol deviation and is documented, investigated, and reported as a device deficiency if safety or performance may be affected [12–14].

- Log preservation:

- For software issues, preserve application and system logs, error codes, timestamps, handset/OS versions, and network status; screenshots or screen recordings should be captured when feasible without exposing PHI [12,18].

- Security events:

- Suspected security/privacy incidents related to the app-module are escalated via the data protection incident process in parallel with device deficiency handling; technical forensics proceed under least-privilege and audit-trail controls [12–14,18].

Field safety notices, corrective actions, and recalls

- Triggers:

- Confirmed device issues that pose or could pose a risk may necessitate a field safety corrective action (FSCA), field safety notice (FSN), correction or removal/recall, or software patch; the Sponsor coordinates with the manufacturer under applicable vigilance and recall regulations [14,18–20].

- Study conduct during FSCA/recall:

- Enrollment/use may be paused or restricted pending risk assessment; sites follow Sponsor instructions to quarantine affected units or disable specific software builds; alternative procedures (e.g., standard education only) may be used to maintain participant care where permitted [12,14,15].

- Notifications:

- Sites and affected participants are informed promptly in clear language about the issue, interim risk mitigations, and any required actions. Reconsent is obtained when new safety information may affect willingness to continue. Ethics committees and competent authorities are notified per applicable requirements [12–15,18–20].

- Documentation and closure:

- All communications, decisions, and actions (including completion of recalls/corrections at each site) are documented; effectiveness checks are performed and filed in TMF/ISF. Any protocol amendments needed to implement lasting changes are submitted and approved before implementation [12–15,18–20].

Training, monitoring, and quality assurance

- Training:

- Investigators and site staff are trained on identification, documentation, and escalation of device deficiencies, malfunctions, use errors, and complaints; competency is documented and refreshed after relevant amendments or FSNs [12,13,17,18].

- Monitoring:

- Monitors verify source documentation, device accountability, quarantine/return records, and consistency between safety and complaint systems; key risk indicators (e.g., repeated app crashes, calibration drifts, high use-error rates) trigger focused review and CAPA [12,13,16,18].

- Audit and inspection readiness:

- The Sponsor maintains auditable records of complaints, investigations, risk assessments, CAPA, and regulatory correspondence; systems used for reporting and tracking maintain immutable audit trails consistent with quality system and GCP requirements [12,13,18].

Participant communication and consent alignment

- Participant notifications:

- When a device deficiency affects participant safety or study procedures, the site informs the participant as soon as feasible, documents the discussion, and provides written instructions if needed (e.g., discontinue app use until update installed). Reconsent is performed when warranted by changes in risk or procedures [12–14].

- Consistency with consent and privacy:

- Complaint handling and data sharing with the manufacturer use coded data only, consistent with informed consent and data protection obligations; any new data uses undergo ethics review prior to implementation [12–14,18].

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18 Appendices and Supplementary Materials

Overview

The following controlled appendices and supplementary materials support standardized, compliant implementation of this Phase III confirmatory clinical investigation of the inhalation app-module embedded in AsthmaTuner (version later than 5.4.13.5; MediTuner AB; SRN SE-MF-000028534) in subjects aged ≥16 years with asthma and/or COPD using DPI and/or MDI. All appendices are version-controlled, approved prior to use, and maintained in the sponsor's Trial Master File (TMF) and each site's Investigator Site File (ISF). Only current effective versions may be used operationally; superseded versions are archived with complete change histories and distribution logs in accordance with ISO 14155, ICH-GCP, SPIRIT 2025, EU MDR, 21 CFR Part 812/Part 11, and TMF guidance [1–6].

Schedule of Assessments (SoA)

The SoA specifies timing, windows, and responsibilities for eligibility, randomization, device training, endpoint assessments, safety monitoring, and data collection. Details below are representative; site-level calendars with exact visit windows and assessment responsibilities are provided in the Procedure Manual and SAP/DMP. Any updates follow controlled amendment processes [1–6].

Study period	Screening/Baseline	Randomization (Day 0)	Intervention/Control Period (Weeks 0–12)	Follow-up (Week 6–12)	Early Termination
Informed consent	XX				X

Eligibility confirmation and stratification by inhaler type (DPI/MDI/both)	XX				
Allocation (1:1)Allocation (1:1)		XX			
Standardized inhaler education (both arms)Standardized inhaler education (both arms)		XX			
App-based education and training (intervention arm only)App-based education and training (intervention arm only)		X	X (as per IFU)X (as per IFU)		
Device/accountability (spirometer, Airflow Trainer)	X	X	X (check)	X (reconcile)	X (reconcile)
Primary endpoint: rate of successful inhalation techniquePrimary endpoint: rate of successful inhalation technique				X	X (if applicable)
Usability/feasibility assessments (prespecified instruments)Usability/feasibility assessments (prespecified instruments)			X (per plan)	XX	
Safety assessments (AE/SAE/UADE; device deficiency)	X (baseline)	X	X (continuous)	X	X
Data entry, query resolution, and monitoring	X	X	X	X	X

Note: Detailed assessment definitions, instruments, windows, and allowable remote procedures are specified in the Endpoint Definition Document (EDD), Procedure Manual, and SAP/DMP (to be used together) [1–5].

Eligibility Checklist

- Operational checklist for inclusion/exclusion verification, including:

- Age ≥16 years; documented asthma and/or COPD; daily DPI and/or MDI use; access to BankID (or similar) and an Android/iOS smartphone; ability to independently handle and inhale through DPI/MDI; no planned discontinuation of DPI/MDI within 6–12 weeks.
- Exclusions operationalized with objective source verification requirements.

- Signature fields for investigator/designee, date/time, and source data location references.
- Versioned and aligned with the protocol and ICH-GCP source documentation principles [1–3,5].

Informed Consent Form (ICF) Template

- Patient-friendly consent and HIPAA/GDPR-aligned privacy notices, consistent with protocol risks, procedures, data uses, and data sharing/lay summary plans; includes withdrawal, alternatives, compensation/expenses, and contacts.
- Translations and readability verification records (where applicable).
- Version control and IRB/EC approval history maintained in ISF/TMF [1–5,7].

Procedure Manual (Operations Manual)

- End-to-end workflow: screening, consent, stratified randomization by inhaler type, standardized education, app-module onboarding, remote/home procedures, endpoint assessments, and visit conduct.
- Source documentation requirements and minimum essential data elements.
- Risk-based operational controls (e.g., triggers for additional training) per ISO 14155 and ICH-GCP [1,2,5].

Device Instructions and Application/Deployment SOP

- Investigational app-module use within AsthmaTuner (>5.4.13.5) and configuration requirements; prohibited versions; gating criteria; handset/OS compatibility checks; user onboarding steps; troubleshooting.
- Airflow Trainer and CE-marked spirometer handling, care, calibration/verification per manufacturer IFU; chain-of-custody and return procedures.
- Screen captures and step checklists; safety precautions; escalation pathways [1,4,8,9].

Operator Training and Credentialing Materials

- Competency-based curricula for investigators, respiratory educators/therapists, and coordinators, covering:

- Standardized DPI/MDI technique education and use-error mitigation (IEC 62366-1).
- App-module onboarding, data capture, and privacy practices.
- Device deficiency/complaint recognition and reporting; UADE/serious incident awareness.

- Training assessments, checklists, and retraining triggers; training logs for ISF/TMF [1,2,8,9].

DSMB Charter and Statistical Monitoring Plan

- Composition, independence, meeting cadence, data flows, closed/open session procedures, stopping guidelines, unblinding safeguards, confidentiality, and conflict-of-interest management.
- Interim data scope (if any), shells for safety/efficacy monitoring, communication and recommendation pathways to Sponsor-Investigator [1,2,6,10].

Clinical Event Committee (CEC) Charter and Endpoint Definition Document (EDD) (if activated)

- Prespecified endpoint definitions and adjudication rules for successful inhalation technique and any clinically relevant events; blinding procedures; voting and tie-break rules; quality control.
- Source packet composition guidelines and timelines; audit trail expectations [1,2,5].

Core Laboratory Manual (Inhalation Flow Metrics)

- Standardized processing of inspiratory flow signals (e.g., PIF, time to PIF, inspiration time) from spirometer/app data; calibration and validation records; data transfer formats; quality checks; derivations aligned with SAP.
- Independence from treatment assignment; issue management and reprocessing rules [1–3].

Specimen Collection and Shipping Manual

- Not applicable for routine biospecimens in this trial; placeholder maintained should any biosample collection be introduced via approved amendment (to be confirmed) [1,5].

Data Management Plan (DMP)

- EDC/eSource configuration, edit checks, coding frameworks, role-based access, data entry timelines, discrepancy management, external data transfers, audit trails (21 CFR Part 11 compliance), and database lock procedures.
- Data listings, derivations, and reconciliation rules (e.g., safety, complaint, and EDC synchronization) [1–3,6].

Statistical Analysis Plan (SAP)

- Prespecified analyses for primary and secondary endpoints; analysis populations; handling of multiplicity, missing data, intercurrent events, and sensitivity analyses per ICH E9(R1).
- Randomization schema (1:1) with stratification by inhaler type; shells for TLFs; deviations from plan handling; amendments governance [2,5,11].

Risk-Based Monitoring Plan

- Centralized and on-site/remote monitoring strategy; key risk indicators; SDV/eSource verification scope; eligibility verification; endpoint data quality checks; device accountability verification; CAPA processes; escalation pathways.
- Frequency and triggers for targeted reviews; documentation standards [1,2,6].

Device Accountability and Version Control Forms

- Logs for receipt, storage, assignment, calibration/verification (where applicable), software version/build, handset/OS pairings, returns, quarantine, disposition, and reconciliation across inventory and EDC.
- Chain-of-custody for returns and quarantined devices; certificates of destruction templates [1,4].

CRF Completion Guidelines and Annotated CRFs

- Variable definitions, coding dictionaries, units, time windows, allowable values, query rules; endpoints mapped to CRF fields; linkage to EDD and SAP.
- Part 11-aligned guidance on eSignatures and audit trails; timing expectations for entry and correction [1–3].

AE/SAE/UADE Reporting Forms and Guidance

- Harmonized forms and user guides for medical events, device-related events, device deficiencies/malfunctions, product complaints, and unanticipated adverse device effects/serious incidents.
- Assessment of seriousness, relatedness, expectedness; reporting timelines and recipients per jurisdiction; IMDRF coding references; cross-linkage to complaint logs [1,2,4,12–14].

Device Deficiency/Complaint/Recall Management Tools

- Intake and triage forms; technical investigation worksheets; root-cause analysis templates; ISO 14971 risk evaluation and benefit-risk documentation; CAPA records; FSCA/recall tracking and site completion logs [1,4,8,13].

Data Privacy and Security Appendix

- GDPR-aligned data processing records, role-based access matrices, data retention schedule, pseudonymization/anonymization procedures, small-cell risk controls, and incident response workflows; ISO/IEC 27001-aligned controls for data in transit/at rest [1,5,7,15].

Data Sharing and Transparency Materials

- Public registry data-sharing statement; data request procedures; Data Access Committee SOP; DUA template; dataset de-identification specifications; analysis code sharing parameters; lay summary templates for participants [1,5].

Participant-Facing Result Communication Materials

- Plain-language results summary templates and FAQs; options for delivery (secure email/portal/post); site cover letters; documentation of distribution and opt-in preferences [1,5].

Training Records and Delegation Tools

- Delegation of authority logs; initial and refresher training checklists; role-specific competency attestations; read-and-understand acknowledgement forms; amendment-triggered retraining logs [1,2].

Quality Management and Audit Tools

- Internal audit plans, checklists, and reports; vendor qualification records; TMF/ISF completeness checklists; KRI dashboards; CAPA plan templates; inspection readiness packages [1–6].

Publication and Dissemination Appendix

- Publication steering procedures; authorship criteria acknowledgement; abstract/manuscript approval workflow; registry posting checklist; citation requirements for protocol/SAP versions [5].

Version Control and Document Governance

- Each appendix bears a unique identifier, version number, effective date, author/reviewer/approver signatures, and superseded version link. Distribution logs and read-acknowledgements are maintained. Changes undergo documented impact assessment and approvals before implementation. Current versions are posted at sites and in the secure portal; monitors verify currency during visits [1–6].

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19 PROTOCOL SUMMARY

Overview

This late-phase, confirmatory, two-arm, parallel-group clinical investigation will evaluate the safety and effectiveness of an investigational inhalation app-module embedded in the AsthmaTuner system (version later than 5.4.13.5; MediTuner AB; SRN SE-MF-000028534) for improving inhalation technique in adolescents and adults with asthma and/or COPD who use dry powder inhalers (DPI) and/or metered dose inhalers (MDI). The study will be conducted in accordance with ISO 14155, ICH-GCP, applicable device regulations (e.g., 21 CFR Part 812; EU MDR 2017/745), and SPIRIT 2025 recommendations [23–27].

Hypothesis

Among participants with asthma and/or COPD using DPI and/or MDI, app-based education and training delivered via the investigational module will increase the rate of successful inhalation technique at 6–12 weeks compared with standardized, non-app-based inhaler education alone (superiority hypothesis) [23–27,30–33].

Objectives and endpoints

- Primary objective: To determine whether app-based education and training improves the rate of successful inhalation technique at the 6–12-week follow-up compared with control (standardized education only). Primary endpoint: proportion of participants achieving successful inhalation technique per prespecified, standardized criteria at 6–12 weeks (assessor-blinded) [23,27,30–33].
- Secondary objectives:

- To assess feasibility and usability of the investigational module during the study period using prespecified instruments and usage metrics (e.g., completion rates, user feedback) [23,27].
- To evaluate safety, including device-related adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs), and device deficiencies/malfunctions [23,26].

- Exploratory objectives:

- To explore changes in objective inspiratory flow dynamics (e.g., peak inspiratory flow [PIF], time to PIF, inspiration time) collected via the integrated system and their association with successful technique across DPI/MDI strata [23,30,31].
- To describe differential effectiveness by inhaler type (DPI vs MDI vs both), age group, and baseline technique [23,27,30].

Study design

- Design: Prospective, randomized, controlled, two-arm, parallel-group, individual, assessor-blinded trial with 1:1 allocation to:

- Intervention: Standardized inhaler education plus investigational app-based education/training.
- Control: Standardized inhaler education without app-based components.

- Randomization: Centralized, concealed 1:1 assignment, stratified by inhaler type at baseline (DPI only, MDI only, both DPI and MDI) to address technique-specific differences and inspiratory flow dependencies relevant to DPIs [23,27,30,31].
- Blinding: Outcome assessors are blinded to treatment allocation; participants and site personnel delivering education cannot be blinded due to the nature of the intervention [23,27].
- Duration: Each participant is followed for 6–12 weeks; the primary endpoint is assessed once within that window [23,27].

Population

- Target population: Participants aged ≥16 years with documented asthma and/or COPD who use a DPI and/or MDI daily, can independently handle and inhale through these devices, have access to BankID (or similar) and a compatible Android or iOS smartphone, and are not planning to stop DPI/MDI use in the 6–12 weeks after inclusion.
- Key exclusions: Age <16 years; no access to secure electronic personal identification; no compatible smartphone; planned discontinuation of DPI/MDI within 6–12 weeks from inclusion; inability to independently handle and inhale through DPI/MDI [23–27,28,29,31].

Rationale: Inhaler technique errors are common and clinically meaningful in asthma/COPD; DPIs are particularly dependent on adequate inspiratory flow (e.g., PIF) for effective drug delivery, underscoring the need for targeted training and objective assessment [28–31].

Interventions and device use

- Investigational device: Inhalation app-module integrated in AsthmaTuner (>5.4.13.5), available on iOS/Android exclusively for study participants. The module provides structured, app-based education/training and objective technique assessments leveraging the AsthmaTuner spirometer and Airflow Trainer (MIR) provided to participants at home or clinic [23,26,31].
- Control procedure: Standardized inhalation technique education delivered per a prespecified checklist and criteria without app-based components [23,27].
- Usability and human-factors: Training and use follow usability engineering and risk-management principles; objective metrics (e.g., PIF, time to PIF, inspiration time) supplement standardized criteria not easily quantified in routine care [23,26,31].

Assessments and follow-up

- Baseline: Eligibility, demographics, medical history, inhaler type/usage, baseline technique assessment, and device onboarding/accountability [23,27].
- Intervention period (to 6–12 weeks): App-based training per IFU (intervention arm), ongoing safety surveillance, and feasibility/usability data collection [23].
- Primary follow-up (6–12 weeks): Assessor-blinded inhalation technique evaluation per standardized criteria; usability/feasibility instruments; reconciliation of device accountability; safety assessments [23,27].
- Early termination visit: If applicable, perform primary assessments where feasible and complete safety reporting [23].

Safety monitoring and reporting

- Oversight: An independent Data and Safety Monitoring Board (DSMB) provides ongoing oversight per a preapproved charter; the Sponsor-Investigator retains overall responsibility for safety monitoring [23,26,36].
- Reporting: AEs/SAEs/UADEs and device deficiencies/malfunctions are collected systematically and reported to the Sponsor and, when required, to regulatory authorities and ethics committees per ISO 14155 and MDR/IDE requirements and timelines [23,25,26].
- Risk mitigations: Quarantine/return procedures for implicated devices, software version control, and field safety/corrective actions are managed under a documented quality system and vigilance framework [23,25,26].

Statistical considerations

- Primary analysis: Superiority comparison of the proportion with successful inhalation technique at 6–12 weeks between intervention and control, analyzed in the intent-to-treat population using a stratified test (e.g., Cochran-Mantel-Haenszel) by inhaler-type strata; risk difference and 95% confidence interval will be reported. Sensitivity analyses will address missing data and protocol deviations per a finalized Statistical Analysis Plan aligned with ICH E9(R1) [23,27,35].
- Secondary analyses: Feasibility/usability endpoints summarized descriptively and compared between arms as appropriate; safety summarized by incidence, severity, and relatedness; exploratory modeling of inspiratory flow metrics and technique success will be prespecified [23,27,31,35].
- Multiplicity: Control of type I error for key secondary endpoints will be prespecified in the SAP (to be confirmed) [27,35].

Sample size rationale

The sample size targets superiority on the primary endpoint (successful technique at 6–12 weeks). Assumptions for planning (to be confirmed before first patient in):

- Control success rate: 55% based on literature showing frequent inhaler technique errors despite standard education [30,33].
- Intervention success rate: 70% (absolute improvement of 15 percentage points), reflecting expected benefit of structured, app-based training and objective feedback [31–33].
- Power and alpha: 90% power, two-sided alpha 0.05.
- Allocation and stratification: 1:1 allocation; stratified by inhaler type (DPI/MDI/both).
- Dropout/missing primary endpoint: 10% anticipated.

Under these assumptions, approximately 242 evaluable participants per arm are required for a two-group comparison of proportions. Inflating by 10% for attrition yields a total sample size of about 538 participants (269 per arm). Final numbers will be recalculated with the finalized assumptions and verified using validated software; rationale and methods follow standard texts for proportions with stratification considered in design and analysis [27,34,35].

Data quality and integrity

- Randomization, allocation concealment, and assessor blinding are enforced through validated systems and procedures.
- Data capture uses validated EDC/eSource with audit trails compliant with 21 CFR Part 11 and GCP; monitoring follows a risk-based plan; all activities are inspection-ready [23,25,27].

Ethics, registration, and dissemination

- Ethics: Written informed consent is obtained before any study procedure; the protocol and consent are approved by relevant IRBs/ECs and conducted per the Declaration of Helsinki, ISO 14155, and ICH-GCP [23,24,27].
- Registration and transparency: The study will be prospectively registered in a public registry; summary results and a lay summary will be posted within required timelines; data-sharing statements and conditions follow SPIRIT/ICMJE guidance (to be detailed in the registry entry) [25–27].

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19.1 Design

This is a prospective, multicenter, two-arm, parallel-group, individually randomized, assessor-blinded, controlled clinical investigation with centralized, concealed 1:1 allocation stratified by baseline inhaler type (DPI only, MDI only, or both). The primary purpose is to confirm the effectiveness and safety of the investigational inhalation app-module (embedded in AsthmaTuner, version later than 5.4.13.5) compared with standardized, non-app-based inhaler education. Approximately 538 participants (about 269 per arm) are planned to provide ≥90% power at a two-sided alpha of 0.05 to detect a clinically meaningful absolute improvement of roughly 15 percentage points in the primary endpoint, allowing for about 10% attrition. Each participant is followed for 6–12 weeks, with the primary outcome (proportion achieving successful inhalation technique per prespecified criteria) assessed once within the protocol-defined 6–12-week window by assessors blinded to treatment assignment; safety is monitored throughout with oversight by an independent DSMB.

19.2 Study Objectives

Primary effectiveness objective

- To determine whether app-based education and training delivered via the investigational inhalation app-module increases the proportion of participants achieving successful inhalation technique at the assessor-blinded 6–12-week follow-up, compared with standardized, non-app-based education alone [23,27,30–33].

Safety objective

- To characterize the safety of the investigational device by assessing the incidence, severity, and relatedness of adverse events (AEs), serious adverse events (SAEs), unanticipated adverse device effects (UADEs), and device deficiencies/malfunctions throughout the study period, with DSMB oversight per charter [23,26,36].

Feasibility and usability objective

- To evaluate feasibility and usability of the investigational module during the study period using prespecified instruments and usage metrics, including participant completion and engagement measures collected during the intervention phase and at the 6–12-week follow-up window [23,27].

Device performance and exploratory effectiveness objective

- To explore device performance and effectiveness signals by describing objective inspiratory flow dynamics (e.g., peak inspiratory flow, time to peak inspiratory flow, inspiration time) captured by the integrated system during training and at the 6–12-week assessment, and examining their association with successful inhalation technique across inhaler-type strata (DPI, MDI, both) [23,27,31].

19.3 Primary Endpoints

Primary procedural and early safety endpoint

Composite of procedural/device success without unacceptable safety signals associated with use of the investigational inhalation app-module embedded in AsthmaTuner. A participant meets the composite when all of the following are observed from device deployment through the primary endpoint assessment window, as operationalized in the Endpoint Definition Document and SAP:

- Successful onboarding and configuration of the approved AsthmaTuner version with investigational module per IFU, with completion of required user training steps and confirmation of device accountability.
- Acquisition of at least one valid inhalation assessment by the integrated system that meets pre-specified quality and usability criteria for signal integrity and task completion, enabling feedback/training as intended.
- No device-related serious adverse event or unanticipated adverse device effect, and no device malfunction/deficiency requiring permanent discontinuation, device replacement without successful remediation, or urgent field corrective measures for the participant.
- No clinically significant use error attributable to the device design, labeling, or user interface that results in medical intervention or interrupts completion of assigned education/training.
- No confirmed cybersecurity or data integrity incident related to the investigational module that materially impacts participant safety, privacy, or endpoint interpretability.

This composite reflects established expectations for late-phase device evaluations to demonstrate safe, effective deployment and absence of unacceptable device-related risks under ISO 14155, MDR/IDE vigilance principles, and usability/risk-management frameworks [1,9–12].

Primary clinical efficacy endpoint

Proportion of participants achieving successful inhalation technique at the assessor-blinded follow-up

within the protocol-defined 6–12-week window. Success is a responder classification determined using prespecified, standardized criteria appropriate to the participant's inhaler type (DPI, MDI, or both), integrating structured observation and, where applicable, objective inspiratory flow metrics derived from the AsthmaTuner spirometer (e.g., peak inspiratory flow, time to peak inspiratory flow, inspiration time) processed per the Core Laboratory Manual. Endpoint ascertainment, adjudication rules, and handling of intercurrent events and missing data are detailed in the Endpoint Definition Document and SAP, aligned with ICH E9(R1) and SPIRIT guidance. This endpoint targets clinically meaningful improvements in inhaler technique associated with better asthma/COPD management and drug delivery, and is suitable for confirmatory evaluation of the investigational device versus standardized education alone [1–8,2,3].

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19.4 Study Population

The study will enroll adolescents and adults (aged ≥16 years) with physician-documented asthma and/or COPD who use a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI) daily and can independently handle and inhale through their device(s). Participants may span a range of disease severity and symptomatic control typical of treated asthma/COPD populations, including individuals with persistent inhaler-technique challenges or limited access to frequent in-clinic training, reflecting an unmet need for scalable, home-based technique support. The population includes users of DPI, MDI, or both, acknowledging technique-specific considerations (e.g., the importance of adequate inspiratory effort for some DPIs) that justify stratification by inhaler type and targeted training. Eligibility requires protocol-defined confirmatory diagnostic methods and source documentation to verify the underlying diagnosis and current inhaler use, with successful completion of standardized, assessor-blinded technique evaluations as specified elsewhere in the protocol.

19.5 Phase

This clinical investigation is a Phase III (pivotal), late-phase, confirmatory, randomized, controlled, assessor-blinded, parallel-group medical device study designed to generate substantial evidence of safety and effectiveness for the investigational inhalation app-module integrated with AsthmaTuner in adolescents and adults with asthma and/or COPD, conducted in accordance with ISO 14155, ICH-GCP, EU MDR 2017/745, and 21 CFR Part 812, and aligned with SPIRIT 2025 recommendations for late-phase device trials [37–41].

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19.6 Clinical Sites

This investigation will be conducted at multiple clinical sites with experience in asthma and/or COPD management and inhaler technique education, including secondary and tertiary care respiratory clinics and qualified primary care centers. Sites must demonstrate the operational capacity to enroll participants aged 16 years and older who are daily users of dry powder inhalers (DPI), metered dose inhalers (MDI), or both; conduct standardized, assessor-blinded inhalation technique evaluations; support the investigational device workflow (AsthmaTuner application with investigational inhalation app-module, compatible spirometer, and Airflow Trainer logistics); and ensure use of an appropriate electronic personal identification service for participant authentication as specified in the protocol.

A designated Coordinating Center, as defined elsewhere in this protocol, will provide overall study coordination, including site initiation, training on the protocol and device use per the Instructions for Use, centralized randomization setup, data management oversight, core laboratory coordination for objective inspiratory flow metrics (where applicable), safety oversight facilitation in alignment with the independent DSMB, and harmonization of operational procedures across sites. The Coordinating Center will also support risk-based monitoring, quality management, and communications with participating sites and the sponsor/investigator according to the finalized monitoring and data management plans.

Each participating site will be led by a site principal investigator (PI) who is a qualified physician or equivalent healthcare professional with expertise in respiratory diseases and clinical research. Site PIs are responsible for:

- Ensuring local ethical approvals and regulatory authorizations are in place before enrollment and maintained throughout the study.
- Overseeing site personnel training on the approved protocol, Good Clinical Practice, and device accountability procedures, including assessor blinding safeguards and standardized endpoint ascertainment.
- Confirming participant eligibility; obtaining informed consent; ensuring appropriate randomization; and maintaining the blind for endpoint assessors.
- Supervising investigational device deployment, user onboarding, and troubleshooting; managing device inventory, tracking, and returns; and ensuring accurate source documentation and case report form completion.
- Ensuring timely reporting of safety events, device deficiencies, malfunctions, and complaints; supporting corrective and preventive actions when required; and facilitating DSMB requests as applicable.
- Cooperating with monitoring, audits, and inspections; implementing corrective actions; and ensuring data quality, confidentiality, and protocol adherence.

If the study is conducted across more than one country, all sites will follow the same master protocol, with country-specific operational adaptations limited to approved regulatory and ethics requirements. Site activation, enrollment targets, and any staggered initiation will be documented in the project plan and site activation materials. The final list of participating countries, institutions, and departments, including the Coordinating or lead center, will be maintained in the Trial Master File and communicated to stakeholders upon activation.

19.7 Regulatory Statement

The inhalation app-module embedded in AsthmaTuner (version later than 5.4.13.5; manufacturer: MediTuner AB; SRN: SE-MF-000028534) is used for investigational purposes in this Phase III study, which will be conducted under applicable regulatory and ethics oversight with all required sponsor-held approvals or notifications obtained before initiation and maintained throughout the investigation.

19.8 Study Duration

Overall study timeline

- The planned overall study duration extends from first participant enrollment (first participant randomized) until completion of the last participant's final follow-up assessment within the protocol-defined window, followed by data verification, database lock, and reporting activities.
- The total calendar time required will depend on site activation and accrual rates and will conclude once the target sample size has been enrolled, all participants have completed their final protocol-required assessments, and all data have been cleaned and locked. The projected enrollment period and lock/reporting timelines will be documented in the project plan and may be updated operationally without altering participant follow-up requirements.

Per-participant duration

- Each participant's active study participation begins at informed consent and includes screening/baseline procedures, randomization, intervention or control education as assigned, and follow-up.
- The primary clinical efficacy endpoint is assessed at a single assessor-blinded follow-up visit occurring within the protocol-defined 6–12-week window after randomization.
- Participants who discontinue the investigational intervention or control education prematurely will be encouraged to complete the assessor-blinded follow-up visit within the same 6–12-week window or, if not feasible, at an early termination visit aligned to that window to support primary endpoint ascertainment.
- Additional safety or administrative contacts, if needed to resolve outstanding data or device accountability, do not extend the primary follow-up window and will be completed as soon as practicable.

End of study

- The study will be considered complete when the last participant has completed the final follow-up visit within the 6–12-week window (or an aligned early termination visit), all protocol-specified device accountability and data reconciliation are finalized, and the database is locked.

19.9 Sponsor and Oversight

Sponsor model

This investigation is conducted under a sponsor–investigator model. The sponsor–investigator holds overall responsibility for trial design, regulatory submissions and notifications, financing, trial management, risk-based monitoring, safety reporting, quality management, and ensuring compliance with ISO 14155, ICH-GCP, EU MDR 2017/745, and 21 CFR Part 812 throughout the study lifecycle [1–4]. Sponsor duties include establishing and maintaining the Trial Master File, approving and controlling protocol amendments, ensuring that monitoring and data management are performed per the approved plans, and overseeing timely reporting of serious and unanticipated adverse events/effects to competent authorities, ethics committees, and investigators as required [1–4].

Principal Investigator role and site oversight

At each participating site, the Principal Investigator (PI) is accountable for day-to-day conduct and oversight, including:

- Ensuring prior ethics approval and regulatory authorization are in place and maintained before participant enrollment and device use [1–4].
- Confirming staff training on the protocol, device Instructions for Use, safety reporting, data protection, and maintaining assessor blinding for endpoint evaluations, consistent with SPIRIT 2025 recommendations for role clarity and oversight documentation [5].
- Verifying eligibility; obtaining and documenting informed consent; executing randomization; preserving assessor blinding; and ensuring protocol adherence and data integrity [1,2,5].
- Managing investigational device accountability and traceability, including deployment, returns, and documentation of device deficiencies, malfunctions, and complaints, with prompt reporting to the sponsor and per applicable regulations [1,3].
- Conducting timely identification, documentation, and reporting of AEs, SAEs, UADEs, and other safety findings according to regulatory and ethics requirements and sponsor instructions [1–4].
- Cooperating with monitoring, audits, and inspections; implementing corrective and preventive actions; and safeguarding participant rights, safety, and well-being in accordance with GCP [1,2].

Independent safety oversight

An independent Data and Safety Monitoring Board (DSMB) is established by the sponsor–investigator to provide external safety oversight in accordance with ISO 14155, ICH-GCP, and recognized DSMB guidance [1,2,6]. The DSMB operates under a sponsor-approved charter that prespecifies its composition, independence, meeting procedures, safety data to be reviewed, decision rules, and communication pathways [1,6].

Scope of review:

- Ongoing review of participant safety, including AEs, SAEs, UADEs, device deficiencies/malfunctions with potential for harm, withdrawals due to adverse events, and safety-relevant protocol deviations [1,6].
- Periodic evaluation of enrollment, data completeness, protocol adherence, and risk–benefit balance; and recommendations regarding study continuation, modification, or termination based on predefined considerations in the charter [1,6].
- Review of unblinded safety data when necessary to fulfill its mandate, with procedures to maintain assessor blinding at sites and to limit operational bias [1,6].

Meeting frequency and reporting:

- The DSMB will meet at regular intervals appropriate to the risk profile and enrollment/follow-up tempo of this late-phase device study, anticipated at least quarterly, with ad hoc meetings convened for emerging safety concerns or upon DSMB Chair request. Meeting cadence and interim looks will follow the DSMB charter [1,6].

- Written DSMB recommendations will be provided to the sponsor–investigator, who is responsible for implementing actions and notifying investigators, regulators, and ethics committees as required [1–4,6].

The sponsor–investigator retains ultimate responsibility for participant safety and study conduct. Site PIs must promptly implement DSMB-endorsed safety actions and any associated protocol or consent updates once approved by the sponsor and relevant authorities/ethics committees, consistent with applicable regulations and SPIRIT 2025 guidance on oversight and communication pathways [1–5].

54. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
55. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
56. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
57. US Food and Drug Administration. 21 CFR Part 812—Investigational Device Exemptions. 2024. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812
58. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). SPIRIT 2025 Statement and Checklist. 2025. https://www.spirit-statement.org/
59. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees

19.10 Device and Manufacturer

The investigational device is the inhalation app-module embedded within the AsthmaTuner mobile application (version later than 5.4.13.5), used in this study to guide, train, and assess participants' inhalation technique for dry powder inhalers (DPI) and/or metered dose inhalers (MDI), targeting the inspiratory maneuver relevant to upper and lower airways. The device is manufactured by MediTuner AB (SRN: SE-MF-000028534).

Investigational device description and use in the study

- Device type: Software as a Medical Device (SaMD) module integrated in AsthmaTuner (iOS and Android).
- Intended use in this investigation: To provide app-based education and training for correct DPI/MDI inhalation technique and to support objective assessment of inhalation performance as part of the study's endpoints and usability/feasibility evaluations.
- Target population and anatomy: Adolescents and adults (≥16 years) with asthma and/or COPD who use DPI and/or MDI; training focuses on inspiratory flow generation and timing during inhalation through the participant's own inhaler type(s).
- Operating environment and accessories: The module functions within the CE-marked AsthmaTuner system and is used together with a compatible spirometer and an Airflow Trainer to enable objective measures (e.g., peak inspiratory flow, time to peak, and inspiration time). The Airflow Trainer is made of the same type of plastic as the spirometer by the same manufacturer (MIR) and is not in direct contact with the participant's mouth or skin during testing. The spirometer and Airflow Trainer are provided to participants by shipment to home or handout at clinic, per site workflow.
- Access and availability: The AsthmaTuner app is obtained via the App Store or Google Play; the investigational inhalation app-module is activated only for enrolled study participants.
- Compatibility and prerequisites: Use requires a supported smartphone (Android or iPhone) and access to an approved electronic personal identification service (e.g., BankID or equivalent) as specified in the protocol.

19.11 Key Follow-up Assessments

Overview

The key follow-up assessments are designed to support blinded ascertainment of the primary endpoint within the protocol-defined 6–12-week window after randomization, with additional feasibility, usability, and safety evaluations collected in parallel as specified in the finalized visit schedule. Where an early termination visit is required, the same assessments will be attempted within the 6–12-week primary assessment window to preserve endpoint integrity and minimize missing data, consistent with best-practice trial guidance on aligning assessments to outcomes and analysis plans [9].

Primary endpoint ascertainment (assessor-blinded; 6–12-week window)

- Standardized inhalation technique evaluation by a trained, assessor-blinded evaluator using the protocol-defined criteria for each participant's inhaler type(s) (DPI, MDI, or both), recorded as success/failure and error domains per the finalized endpoint definitions. This assessment provides the primary outcome at the single follow-up visit [7–9].
- For participants using more than one inhaler type, technique is evaluated separately for each applicable device category per the protocol to ensure consistent, stratified endpoint assessment [7–9].

Objective inhalation performance measures (co-assessed within the 6–12-week window)

- Physiological measures of inspiratory maneuver performance obtained with the protocol-specified compatible spirometer and Airflow Trainer to corroborate technique domains relevant to DPI and MDI use (e.g., inspiratory flow generation and timing), with results processed according to the core laboratory or centralized procedure where applicable. These data support secondary and exploratory analyses of performance characteristics associated with successful technique [7,8,10,11].

Usability and feasibility assessments (6–12-week window)

- Participant-reported usability and feasibility of the assigned education/training approach collected using protocol-specified questionnaires or structured feedback tools appropriate to the study design, without unblinding the endpoint assessor [9].
- For the investigational arm, device utilization metrics (e.g., training session completion and interaction logs) captured via the application to quantify exposure to the intervention and feasibility of at-home use; for the control arm, documentation of delivery and receipt of standardized non–app-based education as per site procedures [9].

Safety and device-related assessments (through 6–12 weeks and at the follow-up visit)

- Systematic assessment of adverse events, serious adverse events, unanticipated adverse device effects, and device deficiencies/malfunctions, including onset date, severity, relationship, actions taken, and outcomes, per protocol and regulatory requirements.
- Review of any changes in inhaler regimen, clinically significant exacerbations, or healthcare utilization that may affect risk–benefit interpretation during the study period, documented without altering the primary endpoint assessment process [7–9].

Operational safeguards and data integrity (applies to all above assessments)

- Maintenance of assessor blinding for the primary endpoint evaluation; endpoint-related assessments are completed before any discussion that could reveal treatment allocation, and any additional contacts (e.g., for safety, device accountability, or data clarification) do not substitute for, nor extend beyond, the 6–12-week primary assessment window [9].
- If a participant discontinues assigned education/training prior to the scheduled visit, efforts will be made to complete the blinded endpoint and associated follow-up assessments within the same 6–12-week window or at an aligned early termination visit, to minimize missing primary outcome data and support the prespecified analysis population [9].

60. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2024 update. https://ginasthma.org
61. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD. 2024 report. https://goldcopd.org
62. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). SPIRIT 2025 Statement and Checklist. 2025. https://www.spirit-statement.org/
63. Usmani OS, Lavorini F, Marshall J, Dunlop WCN, Heron L, Farrington E, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. Respir Res. 2018;19(1):10. doi:10.1186/s12931-017-0710-y
64. Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal inspiratory flow rates with commonly prescribed dry powder inhalers in COPD patients. J Aerosol Med Pulm Drug Deliv. 2017;30(6):424–432. doi:10.1089/jamp.2016.1336

19.12 Feasibility Metrics

Overview

Feasibility metrics will characterize procedural practicality and implementation of the investigational inhalation app-module within the study workflow (home and clinic) and will be summarized descriptively. Metrics will be derived from application utilization logs, device logistics records, and case report forms (CRFs) without hypothesis testing or predefined success thresholds. Summaries will be presented overall and, where informative, by site and by inhaler stratum (DPI, MDI, both).

Defined feasibility metrics

- Device access, setup, and initial training

- Proportion of randomized participants in the investigational arm who: download and access the AsthmaTuner app; complete identity verification; activate the inhalation app-module; pair/connect the spirometer and Airflow Trainer; and complete at least one guided training session after randomization.
- Time from randomization to first completed guided training session (minutes or days), and number of support contacts (emails/calls/app messages) required to achieve initial activation and first training.
- Documented device logistics completion (shipment or handout confirmed; functioning equipment on first use; need for replacement).

- At-home use and measurement feasibility

- Proportion of investigational-arm participants with at least one valid app-recorded inhalation performance session during the study period, and proportion completing the protocol-specified measurement session(s) without in-person assistance.
- Descriptive utilization patterns captured by the app (e.g., number of training sessions per participant and per week; distribution of session duration; proportion of sessions auto-completed vs user-terminated).
- Data completeness for objective inhalation measures (evaluable sessions/expected sessions) and reasons for unevaluable sessions (e.g., connectivity issues, user cancellation, sensor not detected), as documented in CRFs or app logs.

- Follow-up and assessment operability

- Proportion of all randomized participants who complete the assessor-blinded endpoint visit within the 6–12-week window (or aligned early termination visit), and reasons for outside-window assessments or missed visits.
- Duration of the blinded endpoint visit (check-in to completion of inhalation technique assessment) and any need for repeat attempts due to operational factors (e.g., equipment readiness, environment).
- Occurrence of events that could jeopardize blinding during endpoint ascertainment (yes/no with description), and whether mitigation procedures preserved assessor blinding.

Analysis and handling

- Feasibility outcomes will be summarized using counts and percentages for categorical variables and medians with interquartile ranges for continuous variables. No formal hypothesis tests are planned.
- Where applicable, descriptive summaries will be stratified by inhaler category (DPI, MDI, both) and by site to inform operational learnings and potential learning-curve effects.
- Missing feasibility data will be reported as such; no imputation is planned.

19.13 Data Handling

Overview and principles

Data will be collected, processed, and stored in accordance with ISO 14155, ICH-GCP, EU MDR, 21 CFR Part 812, and applicable data protection regulations, using validated, access-controlled systems with complete audit trails to ensure data integrity per ALCOA+ principles [1–6]. Electronic systems used for data capture and management will be validated and Part 11–compliant; system validation, user access provisioning, and change control will be documented in the Data Management Plan (DMP) and system qualification records [2,5].

Data sources and capture

- Source data: medical records, site worksheets, assessor-blinded inhalation technique evaluations, device accountability logs, training/education documentation, and participant-reported information.
- Electronic data capture (EDC): case report forms (CRFs) and observational entries will be captured in a validated EDC system with role-based access, time-stamped audit trails, and query workflows [2,5].
- Device-generated data: the AsthmaTuner inhalation app-module and connected accessories will generate utilization logs and objective performance files (e.g., PIF, time-to-PIF, inspiration time) transmitted via encrypted channels to the study database or designated secure repository; data elements ingested to the analysis dataset will be prespecified in the DMP [1,5].
- Safety data: adverse events/effects, device deficiencies/malfunctions, and related actions will be entered into the EDC and coded using MedDRA; concomitant medications will be coded with the WHO Drug Dictionary [2,7,8].
- Metadata: timestamps, software version (later than 5.4.13.5), device identifiers, and site/assessor identifiers will be captured to support traceability, auditability, and analysis stratification [1,2].

Data flow, encryption, and security

- All electronic transfers will use industry-standard encryption; data at rest will be stored on secure, access-controlled servers with routine backups and disaster recovery procedures aligned to the sponsor’s information security framework (e.g., ISO/IEC 27001 controls) [5,9].
- Role-based access will restrict users to the minimum necessary privileges; training and authorization will be documented prior to granting access [2,5].
- System audit trails will record creation, modification, and deletion events for data and metadata, including user, timestamp, and reason for change; audit trails are read-only and reviewable [2,5].

Pseudonymization, privacy, and data protection

- Participants will be assigned unique study IDs; direct identifiers will remain at sites unless explicit consent and lawful basis permit transfer, and any crosswalk linking codes to identities will be stored separately with restricted access [1,3,6].
- Processing of personal data will comply with applicable law, including GDPR where relevant; data processing and transfer agreements will define roles and responsibilities of controllers/processors, cross-border transfer safeguards, and data subject rights handling [3,6].
- Any U.S. sites, if applicable, will ensure compliance with local privacy and security requirements in addition to GCP [2].

Data quality control and query management

- Data entry checks, programmed edit checks, range validations, and missing/consistency checks will be implemented in EDC; system-generated queries will be resolved by sites with documented investigator confirmation where medical judgment is required [1,2,5].
- Source data verification and risk-based monitoring will be performed per the Monitoring Plan to ensure accuracy, completeness, and concordance between source documents and CRFs [1,2].
- Protocol deviations impacting data integrity will be documented, categorized, and assessed for impact on analysis populations per the Statistical Analysis Plan (SAP) [1,2].

Coding, standards, and datasets

- Medical history, AEs/SAEs/UADEs will be coded with MedDRA; concomitant medications with WHO Drug Dictionary; device deficiencies will be categorized using standardized device taxonomy where available; dictionary versions will be fixed prior to database lock [2,7,8].
- Tabulation and analysis datasets will be structured to recognized clinical data standards (e.g., CDISC SDTM/ADaM or equivalent fit-for-purpose specifications) to support traceability from raw data to analysis results; dataset specifications and derivations will be defined in the DMP and SAP [5,10].

Handling of missing, out-of-range, and implausible values

- The DMP/SAP will prespecify rules for outlier flagging, implausible value reconciliation, and hierarchy of data sources when multiple records exist for the same variable; unresolved discrepancies will be retained but flagged, and sensitivity analyses will be described in the SAP as applicable [1,2,5].
- No post hoc imputation will be performed outside SAP-defined methods; all imputations, if any, will be fully documented with rationale and programming specifications [5].

Blinding and access controls

- Assessor blinding for the primary endpoint will be operationalized by segregating endpoint assessments from intervention utilization data; individuals with access to unblinded data (e.g., DSMB support staff, unblinded statisticians) will be independent of clinical operations and endpoint assessors, with access limited to the minimum necessary [1,2].
- DSMB reviews may include unblinded safety data per the DSMB charter; outputs to the sponsor-investigator will be structured to preserve site-level and assessor blinding unless necessary for safety actions [1,2].

Centralized review

Objective inhalation performance files from the app-connected spirometer/Airflow Trainer will undergo centralized quality control and algorithmic verification by the sponsor's core analytics team; no independent endpoint adjudication committee is planned.

Database lock, archival, and retention

- Database lock will occur after resolution of all outstanding queries, coding finalization, quality control checks, and sign-offs per the DMP; any post-lock changes will require controlled unlock procedures and documentation [2,5].
- Essential documents and records, including the electronic trial master file, will be archived securely for at least 10 years after the end of the clinical investigation or longer where required (e.g., until two years after the latter of investigation termination or approval/withdrawal of approval in the United States), applying the longest applicable retention period across jurisdictions [1,3,4].
- Upon archival, datasets, programs, and documentation sufficient to reproduce results (including data standards, derivation specifications, and audit trails) will be retained in read-only formats with validated checksum or equivalent integrity verification [2,5].

Data sharing and transparency

Any sharing of de-identified datasets, dictionaries, and analysis code will follow the protocol's data sharing framework, participant consent, and legal/ethical approvals; only pseudonymized data will be shared externally with appropriate governance and protection measures, consistent with SPIRIT recommendations and data protection law [3,5,6].

Contingency and business continuity

- Backups will be performed at defined intervals with periodic restoration testing; disaster recovery objectives (RPO/RTO) for critical systems will be defined and tested per the sponsor's business continuity plan [5,9].
- Incidents (e.g., suspected data breaches, significant data loss, cybersecurity events) will be managed under documented incident response procedures, including timely notification to applicable authorities/ethics committees as required by law and GCP [1–3,6].

Responsibilities and oversight

- The sponsor–investigator is responsible for establishing and maintaining the DMP, ensuring system validation, and overseeing data quality, security, and compliance; site investigators are responsible for timely, accurate, and complete data entry and source documentation [1,2].
- Audits and regulatory inspections will be facilitated with full access to requested data, audit trails, and system validation documentation; corrective and preventive actions will be implemented and tracked where findings are identified [1,2].

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20 Synopsis

Overview

This is a Phase III, confirmatory, two-arm, parallel-group, individually randomized, single-blind, stratified controlled clinical investigation evaluating the effectiveness, usability/feasibility, and safety of the inhalation app-module embedded within the AsthmaTuner mobile application (version later than 5.4.13.5; MediTuner AB, SRN: SE-MF-000028534) for training and assessment of inhalation technique in adolescents and adults with asthma and/or COPD who use a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI). The trial is designed and conducted in accordance with ISO 14155, ICH-GCP, EU MDR, and 21 CFR Part 812, and reported per SPIRIT 2025 recommendations [1–5].

Rationale

Correct inhaler technique is essential for optimal asthma and COPD management and is emphasized in international guidelines [6,7]. Critical inhaler errors are common and associated with worse clinical outcomes, and DPI use is particularly sensitive to inspiratory flow capability, which may be suboptimal in subsets of patients [8,9]. App-based, at-home, structured education with objective feedback on inspiratory performance may reduce technique errors and improve rates of successful technique compared with standard education delivered without app-based support.

Study design

- Design: Two-arm, parallel, individually randomized (1:1), assessor-blinded, superiority trial with stratification by inhaler category at randomization (DPI, MDI, or both DPI+MDI).
- Arms:

- Investigational: Standard education of inhalation technique plus app-based education and training using the inhalation app-module within AsthmaTuner.
- Control: Standardized, non–app-based education of inhalation technique using a protocolized checklist.

- Blinding: Endpoint assessors are blinded to treatment allocation; participants and trainers are unblinded due to the nature of the intervention.
- Follow-up: Single primary endpoint assessment at 6–12 weeks post-randomization; safety, usability, feasibility, and objective inhalation performance are co-assessed within the same window.
- Oversight: Sponsor–investigator model with an independent Data and Safety Monitoring Board (DSMB) operating under a charter [1–3,5,10].

Study population

- Target population: Participants aged ≥16 years with a documented diagnosis of asthma and/or COPD who are daily users of DPI and/or MDI.
- Setting: Multicenter clinical investigation at sites experienced in the management of asthma/COPD and inhaler education.

Key eligibility criteria

- Inclusion highlights: Age ≥16 years; documented asthma and/or COPD; daily use of DPI and/or MDI; ability and willingness to provide informed consent and complete study procedures; access to a compatible smartphone and an approved electronic personal identification service.
- Exclusion highlights: Age <16 years; no access to BankID or equivalent electronic personal identification; no compatible Android/iPhone smartphone; planned discontinuation of DPI/MDI within 6–12 weeks; inability to independently handle and inhale through DPI or MDI. Full criteria apply at screening and randomization per protocol and GCP [1,2].

Investigational device and workflow

- Device: Inhalation app-module integrated in AsthmaTuner (iOS/Android), enabled only for enrolled participants; device use requires the CE-marked AsthmaTuner system with a compatible spirometer and an Airflow Trainer accessory to support objective inspiratory maneuver measurements (e.g., peak inspiratory flow [PIF], time-to-PIF, inspiration time).
- Access/logistics: App downloaded from public app stores; spirometer and Airflow Trainer shipped to participant's home or provided at clinic; activation and training supported per protocolized procedures.
- Comparator: Standard education of inhalation technique based on a standardized criteria checklist without app-based training.

Primary hypothesis and endpoint

- Primary hypothesis: App-based education and training using the inhalation app-module, when added to standard education, will increase the proportion of participants with successful inhalation technique at the blinded 6–12-week assessment compared with standard education alone.
- Primary endpoint: Assessor-blinded success/failure of inhalation technique at 6–12 weeks using protocol-defined, inhaler-specific standardized criteria; for participants using both DPI and MDI, technique is evaluated separately for each inhaler category.

Secondary and exploratory objectives/endpoints

- Usability/feasibility: Participant-reported usability and feasibility of the assigned education/training; app utilization metrics (e.g., number and duration of training sessions, completion rates); operability of the endpoint visit within window; data completeness for objective performance measures.
- Objective performance: Inspiratory maneuver characteristics (e.g., PIF, time-to-PIF, inspiration time) acquired using the connected spirometer/Airflow Trainer to explore correlations with technique success and to characterize performance by inhaler category.
- Safety: Incidence, nature, and relatedness of adverse events (AEs), serious AEs (SAEs), unanticipated adverse device effects (UADEs), and device deficiencies/malfunctions throughout the study period, coded and reported per regulatory requirements [1–4].

Assessments and schedule

- Baseline: Eligibility confirmation; informed consent; collection of demographics, diagnosis, inhaler type(s), and baseline technique per protocol; randomization stratified by inhaler category.

- Follow-up (6–12 weeks): Assessor-blinded inhalation technique evaluation (primary endpoint) for each applicable inhaler category; objective inspiratory performance measures; usability/feasibility questionnaires; systematic safety assessment. If early termination occurs, efforts will be made to obtain primary endpoint and key assessments within the 6–12-week window to minimize missing data [5–7].

Safety monitoring and oversight

- DSMB: Independent DSMB reviews accumulating safety data, protocol adherence, risk–benefit, and makes recommendations regarding continuation, modification, or termination; unblinded safety review may occur under chartered procedures [1–3,10].
- Site/sponsor responsibilities: AEs/SAEs/UADEs and device deficiencies are collected and reported per ISO 14155, ICH-GCP, MDR, and 21 CFR Part 812 [1–4].

Blinding, data quality, and adjudication

- Blinding: Endpoint assessors remain blinded; operational safeguards prevent disclosure of allocation during endpoint visits.
- Centralized review: Objective inhalation performance files undergo centralized quality control/verification; no independent endpoint adjudication committee is planned. Data capture and management follow validated, access-controlled, audit-trailed systems per GCP and SPIRIT guidance [2,5].

Sample size and statistical considerations

- Primary analysis: Superiority comparison of proportions with successful inhalation technique at 6–12 weeks between arms in the intention-to-treat population, accounting for inhaler stratification; sensitivity analyses may include per-protocol populations consistent with late-phase device studies [1,2,5].
- Effect size and power: The assumed control success rate, expected absolute improvement with the app-based intervention, two-sided alpha, power, anticipated dropout, and analysis methods are specified in the Statistical Analysis Plan. The final sample size and allocation ratio reflect these assumptions and late-phase confirmatory objectives; if any assumption requires revision, a blinded sample size re-assessment without unblinding treatment effects may be considered per SAP and DSMB oversight [1,2,5]. Final target enrollment: to be confirmed (TBC) based on finalized assumptions consistent with the approved SAP.

Data sharing and dissemination

Results will be registered and reported in a public trials registry and disseminated in peer-reviewed venues. De-identified datasets and analysis code may be shared under controlled conditions consistent with participant consent, data protection laws, and SPIRIT guidance [3,5].

Benefit–risk assessment

Potential benefits include improved accessibility to inhalation training, objective inspiratory performance feedback, and higher rates of correct technique, which are expected to align with better disease control when combined with usual care [6–9]. Anticipated risks are minimal and relate primarily to data privacy, device malfunctions/deficiencies, or transient discomfort during spirometry-like assessments; these are mitigated through validated systems, training, monitoring, and DSMB oversight per GCP and device regulations [1–4].

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21 ICF

Why you are being asked to take part

You are being invited because you are 16 years or older, have asthma and/or COPD, and use a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI) every day. The purpose of this study is to find out if app-based education and training with the inhalation app-module inside the AsthmaTuner mobile application can improve correct inhaler technique compared with standard education alone after about 6–12 weeks [6,7].

About the study device

- The investigational device is the inhalation app-module integrated in the AsthmaTuner app (version later than 5.4.13.5). It is made by MediTuner AB (SRN: SE-MF-000028534).
- The module provides step-by-step education and guided training for inhaler use and can record objective inhalation performance (for example, peak inspiratory flow, time to peak, and inspiration time) when used with a compatible spirometer and an accessory called an Airflow Trainer.
- The Airflow Trainer is made of the same type of plastic as the spirometer (from MIR). It is not in direct contact with your mouth or skin during testing.
- The investigational module is enabled only for participants in this study. The AsthmaTuner app can be downloaded from the App Store or Google Play, and you will activate the inhalation training module after you join the study.

What will happen if you join

- Screening and consent: We will confirm you meet the study requirements. You will be asked to sign this consent form. If you are under the legal age of consent in your country, a parent/guardian will also need to consent, and you will need to agree (assent) if applicable by local law [1,2].
- Randomization: You will be randomly assigned (like flipping a coin) to one of two groups (1:1):

- Investigational group: standard education plus app-based education and training using the inhalation app-module.
- Control group: standard education using a checklist and non–app-based training.

- Blinding: The person who evaluates your inhaler technique at follow-up will not know which group you are in.
- Study activities and timeline:

- You will continue your usual asthma/COPD care.
- If you are in the investigational group, you will download AsthmaTuner, verify your identity (for example, using BankID or a similar approved service), activate the inhalation app-module, and pair it

with the provided spirometer/Airflow Trainer. You will use the module for education and guided training at home during the study period.

- If you are in the control group, you will receive structured, standardized education without the app.
- About 6–12 weeks after randomization, you will attend one follow-up visit for:
  - A blinded assessment of your inhalation technique for each type of inhaler you use (DPI, MDI, or both).
  - Objective inhalation performance measurements using the spirometer/Airflow Trainer.
  - Short questionnaires about usability/feasibility.
  - A safety check for any medical problems or device issues since joining the study.
- Equipment logistics: The spirometer and Airflow Trainer will be shipped to your home or given to you at the clinic. If a problem is found with the equipment, we will help troubleshoot or replace it.
- Total duration: About 6–12 weeks from randomization.

Who can take part

- You can join if you:

- Are 16 years or older.
- Have a confirmed diagnosis of asthma and/or COPD.
- Use a DPI and/or MDI daily.
- Can give informed consent and complete study tasks.
- Have a compatible Android or iPhone smartphone and can use BankID (or a similar approved identity service).

- You cannot join if you:

- Are younger than 16 years.
- Do not have access to BankID (or similar) or do not have a compatible smartphone.
- Plan to stop using your DPI and/or MDI in the 6–12 weeks after joining.
- Cannot independently handle and inhale through a DPI or MDI.

Your responsibilities

- Use your inhalers as directed by your usual care team.
- If in the investigational group, follow the in-app instructions for education/training and try to complete the suggested sessions.
- Attend the follow-up visit within 6–12 weeks.
- Tell the study team about any health changes, device issues, or concerns.

Possible benefits

- You may learn and practice correct inhaler technique more easily, with at-home access to guided training and objective feedback. Correct technique is linked to better asthma/COPD control when combined with usual care [6,7].
- You may not directly benefit from taking part. What we learn could help improve education for other patients who use inhalers.

Possible risks and discomforts

- Breathing assessments: You may feel short of breath, lightheaded, cough, or tired briefly during spirometry-like measurements. These effects usually pass quickly.
- Device issues: Software or equipment may not work as expected. If that happens, we will help you and may replace equipment. If we identify a safety issue, we may ask you to stop using the investigational module.
- Privacy and data security: As with any digital system, there is a small risk of unauthorized access to data. We use strong security, access controls, and encryption to protect your information [1–3,8].
- Other: There are no blood draws, radiation, or invasive procedures planned in this study. The Airflow Trainer does not contact your mouth or skin.

Alternatives to participating

You do not have to join this study to receive inhaler education. Alternatives include receiving inhaler training and usual care from your clinic without using the investigational app-module.

New findings

We will tell you about any new information that might affect your willingness to remain in the study.

Safety monitoring and oversight

An independent Data and Safety Monitoring Board (DSMB) will regularly review study safety information and may recommend changes or stopping the study for safety reasons [1,2,9]. All adverse events, serious adverse events, unanticipated adverse device effects, and device deficiencies will be collected and reported according to clinical investigation regulations [1–4].

If you are injured

If you are harmed as a result of taking part in this study, medical care will be available. Who pays for that care depends on local laws, institutional policies, and any study-specific insurance. Details for your site will be provided here: [local injury/compensation policy and contacts to be completed].

Confidentiality and how your data will be used

- Your personal data will be protected and handled under Good Clinical Practice and applicable data protection laws (for example, GDPR in the EU/EEA). Only authorized study staff, monitors, auditors, ethics committees, and regulators may review your records to make sure the study is done correctly and safely [1–3,8].
- Your data will be assigned a unique study code. Direct identifiers will remain at the site unless you explicitly allow their transfer under applicable law. Data sent to the sponsor will be coded/pseudonymized.
- Electronic data (including app/device-generated data) will be encrypted during transfer and stored on secure servers with access controls and audit trails [1–3].
- We plan to keep study records for at least 10 years or longer if required by law. After this period, data will be archived or securely destroyed as required [1,3].
- Results from this study may be published or shared in research registries. Your identity will not be revealed in any report, presentation, or publication.

Data sharing and future use

- De-identified study data and analysis code may be shared with other researchers under controlled conditions, if allowed by law and this consent. Any such sharing will remove direct identifiers and use safeguards to protect your privacy [5,8].
- Your data will not be used for commercial marketing to you.
- You may withdraw permission for future use of your data at any time by contacting the study team; this will not affect data already used in analyses or reports, as permitted by law.

Costs and payments

- There is no cost to use the investigational app-module. You will continue to pay your usual healthcare costs outside the study.
- Reimbursement for reasonable travel or time may be offered where allowed. Details for your site: [reimbursement/compensation details to be completed].

Voluntary participation and right to withdraw

Taking part is voluntary. You can decide not to join, or you can leave the study at any time without penalty or loss of benefits to which you are otherwise entitled. Your usual medical care will not be affected. If you withdraw, we may ask to collect information at a final visit, but this is your choice.

When the study doctor may stop your participation

The study doctor may stop your participation if:

- It is in your best medical interest.
- You do not meet or no longer meet the study requirements.

- You do not follow study instructions.
- The study is stopped by the sponsor, DSMB, regulators, or ethics committee.

Device problems, complaints, and recalls

If you notice a problem with the app, spirometer, or Airflow Trainer (for example, the app crashes or the device does not record properly), contact the study team right away. We will help you troubleshoot, replace equipment if needed, and report the issue. If a recall or important safety update occurs, we will contact you with instructions.

What happens to your usual care and medications

Continue your prescribed inhalers and other treatments as directed by your own healthcare providers. This study does not replace your regular medical care.

Access to study results

When the study is finished, a summary of results will be shared in a public registry and may be published in scientific journals. You may request a lay summary from the study team.

Contact information

- Study doctor/investigator: [name, phone, email]
- 24-hour medical contact for urgent issues: [phone]
- Study coordinator: [name, phone, email]
- Independent ethics committee/IRB: [name, phone/email]
- Data protection contact (if applicable): [contact]

What you are agreeing to

By signing the consent form you will receive, you confirm that:

- You understand the study and have had your questions answered.
- You meet the study requirements and agree to take part.
- You allow collection and use of your health and device data for this study, under the protections described.
- You understand you can withdraw at any time without affecting your care.

Additional notes for participants aged 16–17 years

If you are 16–17 years old, local laws may require both your assent and your parent/guardian's consent before you can take part. Please speak with the study team if you have questions [1,2].

Technology and access requirements

To join, you will need:

- A compatible Android or iPhone smartphone.
- Access to BankID or a similar approved electronic personal identification service to activate the study module.

If you do not have these, you cannot take part.

Summary of your study pathway

Step	What happens	When
1	Consent and eligibility check	Before joining
2	Randomization to investigational or control group	After eligibility
3	App activation and device setup (investigational group only); standard education (both groups)	Shortly after joining
4	At-home education/training (investigational group) or standard education (control)	Throughout 6–12 weeks
5	Blinded inhaler technique assessment, objective measurements, questionnaires, safety review	At 6–12 weeks

If you have questions

Please contact the study team at any time. You will receive a copy of the signed consent form.

Consent

You will be asked to sign and date a separate signature page that confirms your consent to participate, and, if applicable, your consent for future de-identified data use.

References

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7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD. 2024 report. https://goldcopd.org
8. European Parliament and Council. Regulation (EU) 2016/679 (General Data Protection Regulation). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj
9. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees

21.1 Study Title and Purpose

Study title

- Full scientific title: Phase III, randomized, assessor-blinded, parallel-group clinical investigation of the AsthmaTuner inhalation app-module (version >5.4.13.5) to improve inhalation technique in adolescents and adults with asthma and/or COPD using dry powder and/or metered dose inhalers
- Short lay title: App-based inhaler training to improve how people use their inhalers

What this study is about

This is a Phase III clinical study of a Class II or Class III medical device. The device is the inhalation app-module embedded in the AsthmaTuner mobile application (version later than 5.4.13.5), made by MediTuner AB (SRN: SE-MF-000028534). The study will compare two groups: standard education alone versus standard education plus app-based education and training over about 6–12 weeks. The person who checks your inhaler technique at follow-up will not know which group you are in.

Main aim

The main aim is to find out whether adding app-based education and guided training to standard education increases the proportion of participants who use their inhalers correctly at the 6–12-week follow-up visit, compared with standard education alone.

Who can take part

People aged 16 years or older with a confirmed diagnosis of asthma and/or COPD who use a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI) every day may be invited to join. You need to have a compatible Android or iPhone smartphone and access to an approved electronic personal identification service (such as BankID).

Important notes about your choice

Taking part is voluntary. This is research, not routine medical care. You can choose not to join, or you can leave the study at any time, without penalty and without affecting the care you receive from your usual healthcare providers [1–3].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials). SPIRIT 2025 Statement and Checklist. 2025. https://www.spirit-statement.org/

21.2 Background About the Disease and Current Treatments

What condition is being studied

This study focuses on asthma and chronic obstructive pulmonary disease (COPD). Both are long-term lung conditions that make it harder to move air in and out of the lungs. Asthma is usually caused by airway inflammation and tightening that can vary over time. COPD (which includes chronic bronchitis and emphysema) is generally progressive, meaning it can slowly worsen over years, especially after long-term exposure to irritants such as tobacco smoke [1,2].

How these conditions affect people over time

- Asthma often causes episodes of breathlessness, wheeze, chest tightness, and cough that can flare up (“exacerbations”). With the right treatment and correct inhaler use, most people can keep symptoms under control and reduce exacerbations [1].
- COPD typically causes persistent breathlessness, cough, and phlegm, and is linked to a gradual decline in lung function and quality of life. Many people experience exacerbations that can lead to hospital visits and faster disease progression [2].
- For both conditions, correct inhaler technique is a key part of staying well. Critical errors in how inhalers are used are common and are linked to worse symptom control, more flare-ups, and higher healthcare use [3].

Current standard treatments and management options

- Asthma

- Daily controller medicines, most often inhaled corticosteroids (ICS) alone or combined with a long-acting bronchodilator such as formoterol (ICS–formoterol). Some people use one ICS–formoterol inhaler for both daily maintenance and as-needed relief (often called “SMART” or “MART”) [1].
- Reliever inhalers used as needed for symptoms, ideally ICS–formoterol; short-acting bronchodilators are alternatives where appropriate [1].
- Add-on options for more severe disease can include higher-dose ICS–LABA, long-acting muscarinic antagonists (LAMA), and biologic therapies for selected patients [1].
- Education, written action plans, and regular inhaler technique checks are recommended at every visit [1].

- COPD

- Bronchodilators (LABA, LAMA) as maintenance therapy; many patients benefit from dual LABA–LAMA. In those with frequent exacerbations and evidence of airway inflammation, triple therapy (ICS–LABA–LAMA) can be used [2].

- Pulmonary rehabilitation, smoking cessation, vaccinations, and management of comorbidities are core components of care. Some patients require oxygen therapy based on clinical need [2].
- Regular review of inhaler technique and adherence is advised at each encounter [2].

- Inhaler types and why technique matters

- Dry powder inhalers (DPI) deliver medicine when you breathe in quickly and forcefully. They rely on the user's inspiratory power. Some patients—such as older adults or people with more severe disease—may have trouble generating enough inspiratory flow for certain DPIs [3,4].
- Metered dose inhalers (MDI) deliver a spray that should be inhaled slowly and deeply, with good hand-breath coordination; spacers may help some users [1,2].
- Because DPIs and MDIs require different steps, education must be tailored to the specific device [1–3].

Why some patients remain untreated, ineligible, or insufficiently controlled

- Incorrect inhaler technique is widespread across asthma and COPD and is strongly associated with poor symptom control and more exacerbations [3].
- Some people cannot generate the inspiratory flow required for specific DPIs, leading to under-dosing despite regular use [4].
- Skills can fade over time without retraining; people may not have regular access to trained staff for hands-on coaching and feedback [1,2,5].
- Complexity of regimens, poor adherence, and comorbidities can further limit control even when appropriate medicines are prescribed [1,2].
- Not everyone is eligible for advanced therapies (for example, biologics in asthma) due to clinical criteria, access, or cost; for these patients, optimizing inhaler technique remains essential [1,2].

Why the investigational medical device may be relevant

- Many critical errors are related to steps users can learn and practice, such as inhaling slowly with an MDI or inhaling fast enough with a DPI [3,4]. However, most routine clinic visits provide limited time for repeated practice and objective feedback.
- The investigational inhalation app-module embedded in AsthmaTuner provides structured, at-home education and guided training. When used with a connected spirometer and an accessory called an Airflow Trainer, it can give objective information about inhalation, such as peak inspiratory flow (how fast you breathe in), time to reach that peak, and inspiration time. These measurements are not usually available during standard teaching but are important for matching a person's inhalation to their inhaler's needs, especially for DPIs [1,2,4,5].
- By making tailored training more accessible between clinic visits and by supplying immediate, objective feedback, the device aims to reduce inhaler errors and improve the chances of achieving and maintaining correct technique, which is a foundation of better asthma and COPD control [1–5].

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21.3 Why This Study Is Being Done

The medical problem and unmet need

Asthma and COPD are common long-term lung conditions managed largely with inhaled medicines. Correct inhaler technique is essential for these medicines to work as intended and is emphasized by international guidelines at every visit [1,2]. Yet, critical errors in how people use inhalers remain widespread and are linked to worse symptoms, more flare-ups, and higher healthcare use [3]. Dry powder inhalers (DPIs) are particularly sensitive to how strongly and quickly a person can breathe in; some users cannot generate enough inspiratory flow for certain DPIs, leading to under-dosing despite regular use [4]. Routine clinic visits often provide limited time for repeated practice and objective feedback, so skills may decay between visits [1,2,5]. There is a clear need for accessible, reliable training that helps people master and maintain correct technique at home.

How the device may help

The investigational inhalation app-module, embedded in the AsthmaTuner mobile application, is designed to provide step-by-step education and guided training tailored to DPI and/or MDI use. When paired with a connected spirometer and an accessory called an Airflow Trainer, the module can give objective feedback on inhalation performance (for example, peak inspiratory flow, time to peak, and inspiration time). These measurements are difficult to assess precisely during standard teaching but are directly relevant to matching a person's inhalation to their inhaler's needs—especially for DPIs that depend on sufficient inspiratory flow [1,2,4,5]. By delivering structured, at-home training with immediate, objective feedback, the device aims to reduce inhaler errors and increase the proportion of users who demonstrate correct technique.

What we still need to learn

Although education can improve inhaler technique, the real-world effectiveness of an app-based, at-home program with objective inspiratory feedback has not been confirmed in a rigorous Phase III trial against a well-standardized control [5]. Key uncertainties include:

- Whether adding the app-based module to standard education leads to a higher rate of correct technique at 6–12 weeks compared with standardized education alone.
- Which usability and feasibility factors (for example, engagement and completion of training sessions) are associated with better technique.
- How objective inspiratory performance relates to blinded technique success across different inhaler types (DPI, MDI, or both).
- The safety profile and any device deficiencies/malfunctions in routine home use.

A randomized, assessor-blinded, controlled Phase III study is the most reliable way to address these evidence gaps, minimize bias, and generate confirmatory data to support or refute the device's intended effect [6–8].

Balancing potential benefits and risks

Potential benefits include easier access to tailored inhalation training at home, objective performance feedback that is not typically available in standard teaching, and a higher chance of achieving correct technique—an essential foundation for better asthma/COPD control when combined with usual care [1–5]. Anticipated risks are low and may include brief discomforts during spirometry-like breathing efforts, device malfunctions/deficiencies, or data privacy concerns inherent to digital tools. The study includes safeguards consistent with good clinical practice and medical device regulations, such as validated systems, role-based access and encryption for data, systematic safety monitoring, and review by an independent Data and Safety Monitoring Board (DSMB) to help ensure that benefits continue to outweigh risks as the study progresses [6–9].

92. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2024 update. https://ginasthma.org
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100. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj

21.4 Why You Are Being Asked to Take Part

You are being asked to take part because you are 16 years or older, have a confirmed diagnosis of asthma and/or COPD, and use a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI) every day. People like you are the focus of this study because correct inhaler technique is essential for these conditions, and the study will compare two ways of learning and practicing that technique.

Typical features of people invited

- Age 16 years or older.
- A documented diagnosis of asthma and/or COPD.
- Daily use of a DPI, an MDI, or both.
- Able to manage your inhaler on your own and follow simple study instructions at home.
- Have a compatible Android or iPhone smartphone and can use an approved electronic ID service (for example, BankID) to activate the study app features.

Situations that may make participation unsafe or unsuitable

- Being younger than 16 years.
- Planning to stop using your DPI and/or MDI in the next 6–12 weeks.
- Not having a compatible smartphone or not being able to use an approved electronic identification service.
- Not being able to independently handle and inhale through a DPI or MDI.
- Health or practical issues that could make study tasks unsafe or unreliable (for example, a medical condition that limits safe performance of simple breathing assessments, a recent serious illness or hospitalization, inability to attend the follow-up visit, or other concerns judged by the study doctor).

How eligibility is confirmed

- The study team will carefully check all eligibility requirements with you before you are enrolled.
- This review may include technical checks (for example, smartphone compatibility and identity verification) and clinical review by the study doctor.
- When needed, eligibility may be reviewed by more than one type of specialist (multidisciplinary review). Certain information may also be reviewed centrally (for example, by a core team) or by a study committee to ensure the criteria are applied consistently across all sites.

21.5 What Will Happen If You Join This Study

Overview of your study path

If you join, your participation will last about 6–12 weeks. You will complete screening and baseline steps, be randomly assigned to a study group, receive education and (if assigned) app-based training, and return for one follow-up visit with a blinded assessment. Most activities occur at home, with one clinic or site visit at the end.

Screening and baseline

- Informed consent: The study team will explain the study and answer questions. You (and a parent/guardian if required by local law) will sign the consent form before any study-specific activities begin.
- Eligibility checks: We will confirm your age, asthma and/or COPD diagnosis, daily use of a dry powder inhaler (DPI) and/or a metered dose inhaler (MDI), ability to use an Android or iPhone smartphone, and access to an approved electronic personal identification service (for example, BankID). We will confirm that you are not planning to stop using your DPI and/or MDI during the next 6–12 weeks and that you can handle and inhale with your inhaler(s) independently.
- Baseline information: We will review your medical history and current inhalers, check your usual care plan, and record basic information (such as your contact details and preferred visit method for reminders or check-ins). There are no blood tests and no invasive procedures.
- If needed, a short, structured education session will be provided at baseline using standardized checklists that match your inhaler type(s). This is part of usual care and will be provided to participants in both groups.

Randomization and masking

- You will be randomly assigned (1:1) to one of two groups:

- Investigational group: Standard education plus app-based education and guided training using the AsthmaTuner inhalation app-module.
- Control group: Standard education using a checklist and non–app-based training.

- The person who evaluates your inhaler technique at the follow-up visit will not know which group you are in (assessor-blinded).

Study equipment and initial setup

- If you are assigned to the investigational group, you will download AsthmaTuner from the App Store or Google Play, verify your identity (for example, with BankID), and activate the inhalation app-module after enrollment.
- A compatible spirometer and the Airflow Trainer accessory will be shipped to your home or given to you at the clinic. The Airflow Trainer is made of the same type of plastic as the spirometer and does not contact your mouth or skin. The study team will guide you through pairing the spirometer with the app and checking that everything works.
- If you are in the control group, you will not activate the inhalation app-module and you will not need the app-connected spirometer/Airflow Trainer for training. You will receive structured, standardized education without the app.

What happens during the study period (6–12 weeks)

- Usual care: Continue using your prescribed inhalers and other treatments as directed by your regular healthcare providers.
- Investigational group:

- Use the inhalation app-module for step-by-step education and guided practice tailored to your inhaler type(s).
- Complete inhalation training sessions at home at times that suit you. The app may guide you to practice specific steps (for example, inhaling quickly and forcefully for a DPI or slowly and deeply for an MDI).
- When practicing with the spirometer and Airflow Trainer, the app can record objective inhalation performance (such as peak inspiratory flow, time to peak, and inspiration time) and provide feedback.

- You may receive reminders, tips, or short check-ins from the study team to support completion of training.

- Control group:

- Receive standardized education about inhaler technique without the app. You may receive printed or digital checklists and reminders from the study team.

- Technical support and safety:

- If any device or app issues occur, contact the study team. We will help you troubleshoot and, if needed, arrange replacement equipment.
- You should promptly report any health concerns or problems related to inhalation training or device use.

Follow-up visit at 6–12 weeks

At approximately 6–12 weeks after randomization, you will attend one follow-up visit:

- Blinded inhaler technique assessment: A trained evaluator who does not know your group assignment will assess your inhaler technique for each inhaler type you use (DPI, MDI, or both) using standardized criteria.
- Objective inhalation measurements: You will perform brief, spirometry-like inhalations with the spirometer and Airflow Trainer so the study can record objective inhalation performance. These efforts may cause brief shortness of breath or lightheadedness that usually passes quickly.
- Questionnaires and feedback: You will complete short questionnaires on usability and feasibility. You may be asked about your experience, any training barriers, and any device issues.
- Safety review: We will ask about any health changes, adverse events, or device problems since you joined the study.
- Equipment return: If study equipment was provided, instructions for returning it (by mail or at the site) will be given.

Discharge steps and instructions (if you visited the site before follow-up)

- After any in-person baseline/setup session, you can go home the same day. You will receive written instructions on how to:

- Use the app-module (investigational group only).
- Care for and store the spirometer and Airflow Trainer (investigational group only).
- Contact the study team for support or to report any problems.
- Prepare for the follow-up visit.

Unscheduled visits, early termination, or withdrawal

- Unscheduled contact or visit: If you experience health issues, have questions, or encounter equipment problems, contact the study team. We may handle the issue by phone or telehealth, or we may ask you to come to the clinic if an in-person evaluation is needed.
- Early termination visit: If you stop the study early, we may invite you to an early termination visit to complete key safety questions, collect information on your inhaler technique, and arrange equipment return. This is optional.
- Withdrawal: You can withdraw from the study at any time without penalty. If you withdraw, we will provide instructions for returning study equipment (if applicable). We may ask to collect final information, but this is your choice.

Which activities can be in-person or remote

- In-person:

- Eligibility confirmation (may also be remote if permitted by local regulations).
- Any hands-on setup or troubleshooting that cannot be completed remotely.
- The final blinded inhaler technique assessment and objective inhalation measurements are typically performed in person.

- Remote:

- Study reminders, education support, and troubleshooting when feasible.
- App-based training sessions (investigational group) are designed for completion at home.

- Safety check-ins may be conducted by phone or telehealth when appropriate.

After your participation ends

- You will return any study-provided equipment if requested.
- You will continue your usual medical care with your regular providers.
- A lay summary of the study results will be made available when the study is completed.

21.6 The Study Device

What the device is

- The study device is the inhalation app-module embedded in the AsthmaTuner mobile application (version later than 5.4.13.5), developed and manufactured by MediTuner AB (SRN: SE-MF-000028534).
- It is a software-as-a-medical-device (SaMD) used on a participant's own smartphone (iOS or Android). The module supports inhalation training for people who use dry powder inhalers (DPIs) and/or metered dose inhalers (MDIs) for asthma and/or COPD [1,2,4].
- When training with objective feedback is required, the app pairs with a compatible handheld spirometer and an accessory called an Airflow Trainer. Breathing is performed through the spirometer's mouthpiece; the Airflow Trainer component does not contact the mouth or skin during use. These accessories are supplied to participants in the investigational group by shipment to the home or at a clinic visit [3].

What the device is intended to do in this study

- Provide structured education about correct DPI and/or MDI technique.
- Guide at-home inhalation practice sessions tailored to the participant's inhaler type(s).
- When paired with the spirometer and Airflow Trainer, display objective inhalation metrics such as peak inspiratory flow, time to peak, and inspiration time to help align technique with inhaler requirements [3].

How the device is delivered and used (high level)

- Participants in the investigational group download AsthmaTuner from the app store and activate the inhalation app-module for study use. Identity verification via an approved electronic personal identification service (for example, BankID) may be required to enable the module.
- The study team provides or ships a compatible spirometer and the Airflow Trainer accessory, and assists with initial pairing to the app.
- Participants complete brief, app-guided education and practice sessions at home. No changes are made to prescribed inhaled medications; the module focuses on how to use the inhaler(s) correctly.
- Participants in the control group receive standardized education without activating the inhalation app-module and without app-connected training accessories.

Key features important for participants

- Tailored training for DPI and/or MDI use, reflecting that these inhalers require different techniques.
- Objective feedback on inhalation performance (if using the spirometer and Airflow Trainer), displayed in the app to support learning and retention of correct technique [3].
- Use on the participant's own smartphone; the inhalation app-module is enabled only for study participants. The spirometer and Airflow Trainer are provided for the study period and must be returned if requested.

Investigational use statement

- The inhalation app-module is being used under clinical investigation and/or in a protocol-defined manner to evaluate its effectiveness, usability, feasibility, and safety in improving inhaler technique compared with standardized education alone. Use, data collection, monitoring, and reporting follow good clinical practice and applicable medical device regulations for investigational devices [1,2].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
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21.7 Randomization, Study Groups, and Blinding

How you are assigned to a study group

- This study uses randomization. After you join, a computer assigns you by chance to one of two groups in a 1:1 ratio. This means you have a 50% chance of being placed in either group.
- To keep the groups balanced, randomization is stratified by the type of inhaler you use: dry powder inhaler (DPI), metered dose inhaler (MDI), or both. This helps ensure that each group has a similar mix of inhaler types.
- This assignment is part of research and may be different from how care is chosen in routine practice.

What the study groups are

- Investigational group: You receive standard education plus app-based education and guided training using the AsthmaTuner inhalation app-module, with a connected spirometer and Airflow Trainer for at-home practice.
- Control group: You receive standardized education about inhaler technique using checklists and non–app-based training.
- Your usual prescribed medications do not change in either group.

Who knows your assignment (blinding/masking)

- You and your care team will know which group you are in because the investigational group uses the app, spirometer, and Airflow Trainer.
- The person who evaluates your inhaler technique at the follow-up visit will not know which group you are in (assessor-blinded). This helps make the comparison fair.
- Certain study committees or monitors may review group-level data to ensure safety and data quality. They are not involved in your clinical care or the blinded technique assessment.

If the blind needs to be broken

- Because only the outcome assessor is blinded, emergency “unblinding” is usually not needed. If a safety issue arises that requires sharing your group assignment, the study doctor may disclose it to appropriate medical staff. If the assessor’s blinding is accidentally broken, the study will, when feasible, arrange for a different blinded assessor to complete your technique evaluation.

21.8 Risks and Possible Discomforts

Overview of foreseeable risks

This study involves app-based education and guided inhalation training, plus brief spirometry-like breathing efforts using a handheld spirometer with an Airflow Trainer accessory. There are no needles, surgery, anesthesia, imaging, or radiation. Most risks are mild and short-lived. Rarely, breathing maneuvers can provoke symptoms in people with underlying heart or lung conditions. Potential device and software issues (for example, malfunction or inaccurate feedback) and data privacy risks are also possible and will be monitored and managed per good clinical practice and medical device regulations [1–3].

Breathing and procedure-related risks

- Temporary symptoms during or after spirometry-like efforts: cough, throat irritation, chest tightness, shortness of breath, lightheadedness, dizziness, headache, or fatigue. These typically resolve within minutes with rest [4].
- Bronchospasm or asthma/COPD flare: rare, but forceful inhalation or repeated efforts could trigger wheeze or increased symptoms. A rescue inhaler should be available per your usual care plan [4].
- Fainting (syncope) or near-fainting: very uncommon; risk is higher if standing. Training should be performed seated, with rest between efforts [4].
- Chest pain, arrhythmia, hemoptysis, or pneumothorax: very rare events reported with spirometry in susceptible individuals (for example, certain cardiac conditions, recent surgery, or severe underlying lung disease). The study excludes people for whom breathing maneuvers are not safe, and staff will stop any procedure if concerning symptoms occur [4].
- Musculoskeletal strain: brief discomfort of the chest wall, abdomen, or throat may occur with forceful breathing [4].

Planned mitigations

- Perform practice maneuvers while seated, with rests between efforts, and stop immediately if you feel unwell.
- Use a reliever inhaler according to your usual plan if symptoms occur, and contact the study team.
- Initial screening excludes participants for whom such maneuvers are unsafe; in-clinic activities are supervised by trained personnel using standardized procedures [1,4].
- Any concerning symptoms prompt clinical assessment and, if needed, referral for medical care. Serious events are reported and followed until resolved or stabilized per ISO 14155 and MDR requirements [1–3].

Device and software-related risks

- Device malfunction, deficiency, or complaint: the spirometer, Airflow Trainer, or app could fail, disconnect, freeze, give delayed or incorrect feedback, or record incomplete data. This could lead to frustration, extra time and effort, or suboptimal training guidance. Report all issues promptly; the team will troubleshoot, replace equipment if needed, and document device deficiencies per protocol [1–3].
- Inaccurate performance feedback: incorrect inspiratory flow or timing values could lead to practicing an unsuitable technique. Blinded, standardized assessments at follow-up help detect and correct discrepancies; users are instructed not to change prescribed medications based on app feedback [1,2,4].
- Cybersecurity and data privacy: while safeguards such as role-based access and encryption are used, unauthorized access or data loss is a residual risk with digital tools. Any suspected breach will be investigated and managed per regulatory and institutional requirements [1–3,5].
- Materials/contact risks: breathing is performed through the spirometer mouthpiece. The Airflow Trainer does not contact the mouth or skin. Single-participant use and cleaning per instructions reduce cross-contamination risk. Replace mouthpieces that are damaged or visibly soiled [4].

- Power/compatibility issues: low battery, incompatible smartphone settings, or operating system updates may interrupt training until resolved. Technical support is available.

Planned mitigations

- Defined processes for device deficiency, malfunction, complaint handling, and recall (tracking, quarantine, replacement, root-cause analysis, and reporting of any unanticipated serious device effects) [1–3].
- User training, quick-start guides, and remote/phone support.
- Secure data handling aligned with good clinical practice and applicable device regulations [1–3,5].
- No medication changes are made by the app; participants continue usual care directed by their clinicians.

Organ system–specific considerations

- Respiratory: transient cough, wheeze, chest tightness, or breathlessness; rare severe bronchospasm. Stop training and use your reliever as directed; seek urgent care for severe or persistent symptoms [4].
- Cardiovascular: rare provocation of chest pain, palpitations, or arrhythmias during forceful breathing in susceptible individuals. Stop immediately if these occur and seek care [4].
- Neurologic: brief dizziness, lightheadedness, or fainting. Perform maneuvers seated and pause between efforts [4].
- Ear, nose, and throat: sore throat or hoarseness after repeated efforts; usually mild and temporary [4].
- Musculoskeletal: transient strain of chest or abdominal muscles with forceful efforts [4].
- Infection control: low risk when using personal mouthpieces and following cleaning instructions; do not share equipment [4].

Serious risks that may require urgent care or reporting

- Severe or rapidly worsening shortness of breath or wheeze not relieved by usual reliever therapy.
- Fainting with injury, chest pain suggestive of a heart problem, coughing blood, or sudden severe chest pain/shortness of breath (possible pneumothorax).
- Any event leading to hospitalization, significant disability, or other medically significant outcomes.

Such events are classified and reported as serious adverse events (SAEs) and, if device-related and unanticipated, as unanticipated adverse device effects (UADEs) per ISO 14155 and EU MDR. They will be promptly evaluated, medically managed, and followed to resolution or stabilization, with independent oversight by the Data and Safety Monitoring Board (DSMB) as applicable [1–3].

Rare, unexpected, or unanticipated device-related problems

- Previously unrecognized software behavior, cybersecurity vulnerabilities, or hardware faults could emerge in real-world use. Any such issues will be documented, investigated, corrected, and reported in accordance with good clinical practice and medical device regulations, including field safety corrective actions or recalls if warranted [1–3,5,6].

What you can do to reduce risks

- Perform training only when you feel well; skip a session if you have a respiratory infection or an exacerbation.
- Sit upright, follow the app’s pacing, rest between efforts, and stop immediately if you feel unwell.
- Keep your rescue inhaler available and follow your usual action plan.
- Do not share your mouthpiece; clean the spirometer as instructed; store equipment dry and protected.
- Keep your smartphone and spirometer updated and charged; contact the study team for any technical or health concerns.

- Report all adverse events and device issues promptly; this enables timely support, mitigation, and required safety reporting [1–3].

References

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6. US Food and Drug Administration. Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees

21.9 Possible Benefits

Participation in this study may or may not provide direct benefit to you. Any potential benefits cannot be guaranteed.

- Potential improvements the device might provide: By delivering structured education and guided at-home practice tailored to your inhaler type(s), the investigational app-module may help you perform all the critical steps correctly and achieve inhalation patterns that are better matched to your device (for example, a fast, forceful breath for DPIs or a slow, deep breath with coordinated actuation for MDIs). Better inhaler technique can lead to more consistent medication delivery to the lungs, which may be associated with improved day-to-day symptom control, fewer errors, and better disease control for some people with asthma and/or COPD [7–10]. The app-enabled objective feedback on inhalation performance (for example, flow and timing) is intended to support technique learning and retention; however, clinical benefits such as symptom relief or fewer exacerbations are not assured and may vary by individual [7–9].

- Timeframe for assessing benefits: The study is designed to evaluate whether app-based education and training improves the rate of successful inhaler technique at the 6–12 week follow-up visit compared with standardized education alone. Any changes in symptoms or quality of life, if they occur, would likely be observed over a similar timeframe and will be explored as protocol-defined outcomes, but are not guaranteed.

- Individual variability: Some participants may notice improved confidence with inhaler use or fewer technique errors, while others may not experience any noticeable change. Your usual prescribed treatments will not change because of study participation, and you should not expect the device to replace your regular medical care.

- Value for future patients and device evaluation: Even if you do not personally experience benefit, information from this study may help improve how inhaler education is delivered in the future, inform clinicians about effective ways to support correct inhaler use in asthma and COPD, and contribute evidence for the future evaluation of the app-module [7–9].

References

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21.10 Alternatives to Taking Part

Alternatives to Taking Part

You have options other than joining this study. These include continuing with usual care and education provided by your regular healthcare team or choosing not to add any new training tool at this time. Examples of alternatives are:

- Continue usual care with your clinician, including review and reinforcement of inhaler technique using standard checklists and demonstrations during routine visits or telehealth appointments [11–13].
- Receive inhaler technique education from trained staff such as nurses, pharmacists, or respiratory therapists; this may include teach-back, demonstration with placebo devices, and scheduled refreshers [11–13].
- Use a spacer/valved holding chamber with a metered dose inhaler (MDI), if appropriate, to help coordination and reduce local side effects; receive device-specific coaching based on your current inhaler(s) [11].
- Discuss with your clinician whether changing inhaler device type, dose, or regimen is appropriate for you; optimize pharmacologic therapy following current asthma or COPD guidelines [11,12].
- Follow a written self-management/action plan for asthma and/or COPD, including instructions for daily management and what to do if symptoms worsen; consider home peak flow monitoring if recommended for your situation [11].
- For COPD, consider referral to pulmonary rehabilitation and exercise programs; for asthma or COPD, address smoking cessation, trigger avoidance, and vaccinations (for example, influenza, pneumococcal) as recommended in guidelines [11,12].
- Use printed or digital educational materials from your clinic or professional societies about correct inhaler technique and disease self-management, outside of this research study [11–13].
- Choose not to receive any new intervention or extra education beyond your current routine care at this time, if that is consistent with how you and your clinician usually manage your condition [11,12].

Deciding not to join, or choosing to leave the study later, will not affect your access to usual medical care, your legal rights, or your relationship with your current or future healthcare providers. This is required by international good clinical practice standards and medical device research guidance [14,15].

If you would like help comparing these alternatives, please tell us. The study team can explain the potential advantages and disadvantages of each option for your situation and encourage you to discuss them with your regular healthcare provider [11,14,15].

101. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2024 report. https://ginasthma.org/gina-reports/
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21.11 Confidentiality and Use of Your Data

What information we collect about you

- Contact details and demographics (for example, name, date of birth, sex, contact information) collected for screening, consent, scheduling, and safety follow-up [1–4].
- Medical information relevant to the study: diagnosis (asthma and/or COPD), inhaler type(s) and use, medical history and concomitant medications, prior exacerbations, and clinician assessments [1–3].
- Study visit data: eligibility checks, randomization assignment, checklists of inhaler technique steps, results of in-clinic assessments, and adverse event/device issue reports [1–3].
- App/device data in the investigational group: timestamps of training sessions, inhalation performance metrics (for example, peak inspiratory flow, time to peak, inspiration time) from the spirometer when paired, app interaction logs needed for quality and safety monitoring, and device deficiency/complaint information [1–3,5].
- Questionnaires or usability/feasibility feedback you provide (if used at your site).
- Images, audio, or video only if specifically described in your site's consent materials; if collected, these are coded and may be reviewed centrally by qualified assessors for quality control and outcome assessment [1,2].
- Follow-up information: attendance, retention, reasons for withdrawal, and contact attempts needed for safety and outcome ascertainment [1–3].

How your data are identified, coded, stored, and transferred

- A unique study code will be assigned to you. This code, not your name, is used in the electronic case report form (eCRF), core laboratory or central reviewer systems (if used), analysis files, and reports. Your direct identifiers are kept separately and securely at the site's file location and are not shared with the sponsor except where required for safety, monitoring, auditing, or legal reasons [1–3].
- Electronic data systems used in the study apply role-based access controls, audit trails, and technical safeguards. Data are encrypted in transit and at rest where supported by the platform, and transfers use secure, industry-standard protocols [1–3,6,7].
- The AsthmaTuner inhalation app-module and connected spirometer transmit training metrics and logs to secure servers designated for the study. Identity verification through an approved electronic personal identification service (for example, BankID) may be used to activate the study module; this verification is separate from study data used for analysis [1–3,5].
- Paper records, if any, are stored in locked areas with controlled access at the study site. Electronic records are protected by passwords and institutional security controls in accordance with good clinical practice and applicable privacy laws [1–4,6].

Who may access or use your information and why

Access is limited to authorized personnel who need the information to conduct, oversee, or ensure the quality and safety of the study:

- Your site's research team and healthcare providers for your care and study conduct [1–3].
- The study sponsor and its designated contract research organizations (CROs) for data management, monitoring, safety oversight, and analysis [1–3].
- Independent monitors, auditors, and inspectors from regulatory authorities to verify that the study is conducted and recorded properly [1–3].

- Institutional Review Board/Independent Ethics Committee (IRB/IEC) members for ethics oversight [1–3].
- Core laboratories, central reviewers, adjudication committees, and statistical centers involved in blinded assessment or analysis, if used; they receive coded data only [1–3].
- The Data and Safety Monitoring Board (DSMB), if convened, for independent safety and data quality oversight [1–3].

All such parties are bound by confidentiality obligations and applicable laws/regulations.

Where your data may be processed

- Your coded data may be transferred to and processed in your country and, if necessary, in other countries where the sponsor or service providers operate. When data are transferred across borders, appropriate legal safeguards are applied, such as standard contractual clauses or other recognized transfer mechanisms, to protect your privacy rights [2–4].

How long we keep your records

- Study records will be retained for at least the minimum period required by applicable laws and regulations and the clinical investigation agreement. For non-implantable medical devices in the EU, essential documents are typically kept for a minimum of 10 years after the end of the clinical investigation or market placement, whichever is longer; some countries or institutions may require longer retention [1–3]. If your site's local requirement differs, that local retention period will apply.

Publications, trial registries, and public results

- You will not be identified by name or any direct identifier in any report, scientific publication, public results summary, or data presentation. Results may be posted in public trial registries or scientific venues in coded, aggregated form [1–4].

Data sharing for future research

- Coded study data may be shared with qualified researchers, regulators, or health authorities to support regulatory submissions, safety evaluations, methodology validation, or secondary analyses consistent with the consent you provide and with applicable laws. Any such sharing will exclude your direct identifiers and will occur under agreements that protect confidentiality and limit use to approved purposes [1–4].

Your privacy rights

- Depending on local laws, you may have rights to access, correct, or restrict certain uses of your personal data. Because research data must be reliable and verifiable, deletion of data already collected may not be possible where continued retention is required by law or to protect scientific integrity and safety reporting. You can withdraw your permission for future data collection at any time without penalty; this will not affect your regular medical care. To exercise your rights, contact your study doctor or the data protection contact listed in your site's consent materials [1–4].

Protections against cybersecurity and misuse

- The sponsor and its vendors maintain information security programs designed to protect confidentiality, integrity, and availability of study data, including governance, risk assessment, access controls, encryption, secure software practices, monitoring, and incident response. Any suspected data breach will be investigated and, if required, reported to authorities and affected participants in line with applicable regulations [1–4,6,7].

If you choose not to share certain data

- If you decline optional data uses described by your site (for example, optional re-contact for future studies), those choices will be honored. Core data needed for safety, regulatory

obligations, and primary study analyses are required for participation in this investigation [1–3].

Questions

- If you have questions about privacy or confidentiality, please contact your study team. You may also contact your IRB/IEC or, where applicable, your local data protection authority for independent advice [1–4].

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21.12 Use of Specimens, Images, and Optional Substudies

What may be collected beyond routine assessments

- No blood, urine, saliva, tissue, or genetic samples will be collected in this study.
- Core study data include:

- In-clinic inhaler-technique checklists and assessor ratings.
- App and device training data in the investigational group, such as timestamps of training sessions and breathing performance metrics from the paired spirometer (for example, peak inspiratory flow, time to peak flow, inspiration time) and limited app interaction logs needed for quality and safety monitoring.
- User feedback from brief usability/feasibility questionnaires, if used at your site.

- Images, audio, or video:

- Some sites may invite you to allow brief photos or videos of your inhaler use for training quality control and blinded outcome review. These recordings will focus on your hands, inhaler, and breathing actions whenever possible. Your face will not be recorded unless needed to evaluate technique. If your face appears, it will be treated as identifiable information and protected accordingly.

- Device files and technical logs:

- If a device issue occurs, technical logs, error reports, and de-identified performance files may be collected to investigate the problem, improve safety, and fulfill regulatory reporting requirements.

Mandatory versus optional elements

- Required for participation in the main study:

- In-clinic inhaler-technique assessments and checklists.
- App and spirometer training data in the investigational group (these are necessary to deliver the

training and evaluate the study's primary outcome).
- Safety and device performance information (for example, adverse events and device issues).
    - Optional (you may decline and still take part in the main study):
- Photos or videos of your inhaler use for quality control or blinded assessment.
- Storage and use of your coded data for future research beyond this study's aims.
- Re-contact for clarification, additional questionnaires, or future studies.

How samples, images, and additional data are labeled and protected

- Labeling and coding:

- All materials collected for the study (including any images or device files) are labeled with your study code. Your name or direct identifiers are not placed on research files used for analysis. The key that links your identity to your code is kept securely at the site with restricted access.

- Transfer and storage:

- Electronic data (including any optional photos/videos and device performance files) are transferred and stored using secure systems with access controls, audit trails, and encryption where supported. Data may be hosted on secure servers designated for this study and processed by authorized vendors under confidentiality agreements.
- If identity verification via an approved electronic personal identification service (for example, BankID) is used to activate the app module, this verification step is kept separate from the coded research data used for analysis.

- Access and review:

- Only authorized personnel who need the information to conduct or oversee the study may access your coded materials, including the study team, sponsor or its delegates (such as contract research organizations), independent monitors/auditors, regulators, and the ethics committee, as permitted by law and ethics approval. Any central reviewers or adjudicators, if used, will receive coded materials only and will be blinded to your study group.

- Retention:

- Records will be kept for at least the minimum period required by applicable laws and regulations for medical device clinical investigations. Some sites or countries may require longer retention.

Use, analysis, and publication

- Photos, videos, and device files (including breathing performance metrics) collected for this research will be used only for the purposes described in this consent and the protocol, such as quality control, training evaluation, blinded assessment, safety monitoring, and regulatory reporting.
- Your identity will not be disclosed in study reports, presentations, or publications. Any materials used for teaching or public communication would require separate permission if there is any chance of identifying you.

Future research use and separate consent

- You may be asked to allow the study team and sponsor to store your coded data (including device performance files and any optional images/videos) for future research related to inhaler technique, respiratory care, digital health, or device safety/quality improvement.
- Future research use is optional. If you agree, your coded materials may be shared with qualified researchers under agreements that protect confidentiality and limit use to approved purposes. No genetic testing will be done.
- You may decline future use now or withdraw your permission later. If you withdraw, materials already used or shared cannot be retrieved, but no new future research use will be made.

Your choices and how to change them

- You can say no to any optional elements (for example, photos/videos, future research storage/use, or re-contact) and still participate in the main study without penalty.
- If you later change your mind about an optional element, contact the study team. They will document your new preference and confirm what can be stopped or deleted going forward, consistent with legal, regulatory, and data integrity requirements.

Questions

- If you have questions about any collection or use of images, device files, or other optional data, please ask the study team. They will explain what is required for the main study and what is optional at your site.

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. European Parliament and Council. Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj
5. International Medical Device Regulators Forum (IMDRF). Software as a Medical Device (SaMD): Key Definitions. IMDRF/SaMD WG/N10FINAL:2013. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf
6. International Organization for Standardization/International Electrotechnical Commission. ISO/IEC 27001:2022 Information security, cybersecurity and privacy protection—Information security management systems—Requirements. Geneva: ISO/IEC; 2022. https://www.iso.org/standard/82875.html

21.13 Device Deficiency, Malfunction, Complaint, or Recall

If there is a problem with the study device

- What these terms mean in plain language:

- Device deficiency: something about the app, spirometer, Airflow Trainer, or instructions that is not working quite right or is missing, even if it has not caused harm. Examples include error messages, connection failures, wrong or delayed feedback, damaged parts, or confusing instructions [1,2].
- Malfunction: the device does not do what it is supposed to do, such as freezing, not recording breaths, or showing clearly incorrect values [1,2].
- Complaint: any concern you report about the device or its use (performance, reliability, labeling, packaging, or instructions), whether it happens at home or in the clinic [1–3].
- Recall or field safety action: a safety-driven correction or removal of the app or hardware from use (for example, a software update, replacement, or asking you to stop using some part) to reduce a risk [2,4,5].

What you should do

- If you think the device is not working as expected, stop the training session, sit and rest, and follow your usual care plan if you feel unwell.
- Contact the study team using the numbers provided to you. If you have urgent medical symptoms (for example, severe shortness of breath, chest pain, fainting), seek emergency care first and then inform the study team [1–3].
- Do not try to repair the device yourself. Keep any parts and packaging until the study team advises you.

What the study team will do

- Ask you what happened, review screenshots/photos if available, and guide you through simple checks (for example, battery charge, Bluetooth pairing, app version, cleaning and fit of parts).
- If needed, arrange to examine, replace, or remove the device or any part of it at no cost to you. You may be asked to return the device so it can be safely quarantined and investigated.
- If the device cannot be used safely or reliably, you may continue in the study with standard education only. Your usual medical care will not be affected [1–3].
- Document the issue as a device complaint/deficiency, collect technical logs, and perform a root-cause investigation. If the problem meets reporting rules, the sponsor will notify the ethics committee and regulatory authorities as required [1,2,4,5].

Safety checks and follow-up that may occur

- A clinician may review your symptoms and vital signs, check your inhaler technique in the clinic, and repeat assessments at a later date if needed.
- The team may update or reinstall the app, switch you to a different study unit, or replace accessories (for example, mouthpieces) if they are damaged.
- If a device-related problem caused or might have caused harm, the event will be followed until it has resolved or is stable. Serious or unexpected device-related problems are treated as reportable safety events and handled under Good Clinical Practice [1–3].

How you will be informed about new risk information

- If the sponsor or study team learns new information about device risks, limitations, or required precautions that might affect your willingness to continue, we will contact you promptly. This may include:

- Explaining the new information in clear terms and answering your questions.
- Providing updated instructions, software updates, or replacement parts.
- Asking you to sign an updated consent form if important changes affect your participation or choices [1–3].

Reporting to oversight bodies

- Serious, unexpected, or important device-related issues (including unanticipated problems that could have led to harm) may be reported to the sponsor, the Institutional Review Board/Independent Ethics Committee, and national authorities, as required by law and Good Clinical Practice. Your identity will be protected in these reports to the extent allowed by law [1–5].

Costs to you

- There is no cost to you for evaluation, replacement, or return shipping of study devices when issues arise due to device problems.

How to get help

- If you notice a problem, or if you have questions about the device or its use, please contact your study doctor or the study team using the contact details provided to you. For urgent medical issues, call emergency services first.

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
3. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
4. US Food and Drug Administration. Medical Device Recalls (Recalls, Corrections and Removals) under 21 CFR Part 806. Guidance and resources. 2020. https://www.fda.gov/medical-devices/postmarket-requirements-devices/medical-device-recalls
5. International Medical Device Regulators Forum (IMDRF). Software as a Medical Device (SaMD): Key Definitions. IMDRF/SaMD WG/N10FINAL:2013. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf

21.14 Costs and Compensation

What costs the study pays for

- Study devices and software: The investigational inhalation training app-module within AsthmaTuner, the study-provided spirometer and Airflow Trainer, related accessories, software activation, updates, technical support, and any device evaluation, replacement, or return shipping needed for study purposes will be provided at no cost to you.
- Study-specific procedures: Screening and baseline assessments done only for the research, randomization, in-clinic inhaler technique assessments using standardized checklists, app/spirometer pairing and training (for those assigned to the investigational group), study safety checks related to device use, and protocol-scheduled follow-up visits occurring within the 6–12-week study period will be paid for by the study.
- Study questionnaires and optional substudy procedures that are part of this research (if used at your site) will be provided at no cost to you.
- If there is a confirmed device deficiency or malfunction, investigation activities required by the protocol (including evaluation, quarantine, replacement, and safety follow-up) will be covered by the study.

What costs may be billed to you or your insurer

- Usual medical care unrelated to the research: Your routine care for asthma and/or COPD (including clinic visits not required solely by the study, diagnostic tests ordered by your clinician as part of usual care, and any treatment changes) may be billed to you or your insurer according to normal practice.
- Usual medications: Your regular prescription or over-the-counter medications (including inhalers) are part of your standard care and are not paid for by the study.
- Non-study health needs: Any medical visits, procedures, hospitalizations, or emergency care that are not part of the protocol-required research procedures may be billed to you or your insurer according to local policy.
- Country/site-specific details: [Site to insert country-specific billing practices, whether national health insurance covers routine care during research participation, and contact information for the site’s billing office.]

If you have questions about which items are paid by the study versus billed to you or your insurer, please ask the study team before you agree to take part. Explaining anticipated costs and responsibilities is required by international good clinical practice standards for medical device research [1–4].

Reimbursement and compensation

- Reimbursement for expenses: You may be reimbursed for reasonable, documented out-of-pocket expenses related to protocol-required visits (for example, local travel, parking, public transportation).

- Amounts and process: [Site to insert specific reimbursement amounts per visit, caps per participant, acceptable receipts, and payment method/timing].

- Compensation for time: [Select one and delete the other at your site]

- Option A (no time compensation): You will not receive payment for your time or lost wages. This helps avoid any sense of pressure to join the study and follows ethics guidance to prevent undue influence [1–3].

- Option B (time compensation): You may receive modest compensation for your time spent on required study visits. This is not a benefit for health improvement but a token for your time and inconvenience. Amounts and schedule: [Site to insert per-visit/time compensation, payment schedule, and any tax reporting requirements].

- No bonuses for completion: You will not be penalized for leaving the study early, and there are no completion bonuses that could pressure you to stay against your wishes [1–3].
- Taxes and reporting: [Site to insert any country-specific tax thresholds, forms, or reporting requirements that may apply to reimbursements or compensation.]

If you are injured as a result of the study

- Medical care for study-related injury: If you are injured or made ill as a direct result of the study device, device procedures, or protocol-required activities, you will receive necessary medical evaluation and treatment. Please contact the study doctor promptly so we can arrange appropriate care and assess whether the injury is related to the study.
- Who pays for treatment of study-related injury: [Select the statement that applies at your site and delete the others]

- Option A (sponsor pays): The sponsor or its insurer will pay for the reasonable costs of necessary medical treatment for injuries determined by the study doctor to be related to the study device or protocol-required procedures, in accordance with local laws and the clinical investigation agreement. This does not include payment for other expenses such as lost wages, pain and suffering, or non-medical damages.

- Option B (no automatic payment; billed to insurer first): The costs of necessary medical treatment for a study-related injury will be billed to you or your insurer in the usual way. If your insurer denies payment, you may request that the sponsor consider covering reasonable, necessary treatment costs, as described in the clinical investigation agreement and local laws.

- Option C (national no-fault insurance or mandatory subject insurance): Compensation and coverage for study-related injuries will be provided under [insert name of national no-fault subject injury scheme or mandatory clinical investigation insurance], in line with applicable laws. The study team will help you submit a claim.

- What is not covered: Except where required by law, payment is not routinely offered for other costs such as lost income, childcare, travel beyond standard reimbursement, or compensation for non-economic damages.
- How to report and seek help: If you believe you have a study-related injury, contact your study doctor or the study team immediately using the numbers provided to you. In an emergency, seek urgent medical care first, then notify the study team as soon as possible. Information about study-related injuries and compensation must be explained in the consent process under applicable regulations and standards [1–4].

Additional information and contacts

- Insurance/indemnity details: [Site to insert the name of the insurer, policy number, coverage period, scope of coverage, limitations, and contact information for claims related to study-related injury, if applicable under local law].
- Billing questions: [Site to insert contact information for the site billing office or research finance contact].
- Sponsor contact for injury claims: [Site to insert sponsor contact information for study-related injury inquiries].
- Your rights: Taking part in this study does not limit your legal rights. Any compensation or coverage for injury will be provided as required by local laws and the clinical investigation

agreement. Ethics and regulatory standards require that consent forms describe costs, available compensation, and contacts for questions or emergencies [1–4].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. US Food and Drug Administration. 21 CFR 50.25: Elements of informed consent. Revised 2018. https://www.ecfr.gov/current/title-21/part-50/section-50.25

21.15 What Happens If You Are Injured or Have a Problem Related to the Study Device

If you have symptoms, feel unwell, or have concerns

- For urgent or severe symptoms (for example, trouble breathing, chest pain, fainting, severe dizziness), call emergency services or go to the nearest emergency department first. After you are safe, contact the study team to let us know what happened [1–3].
- For non-urgent symptoms or device concerns, contact your study doctor or the study team as soon as possible using the phone numbers and email provided to you. If you call outside business hours, use the after-hours number on your study contact card. If you cannot reach the study team and you are worried about your health, seek medical care and inform the provider that you are in a clinical study of a medical device [1–3].

How problems and adverse events are checked and treated

- A clinician will review your symptoms, examine you if needed, and may ask you to come to the clinic or a nearby facility. Tests or assessments may be ordered if they will help guide safe care (for example, vital signs, breathing checks, or other evaluations) [1–3].
- Your event will be documented, including what happened, when it started, how serious it is, and whether it might be related to the study device, procedures, or your usual condition. You will be followed until the issue resolves or is stable, and you will be told about any recommended treatments or changes to your study participation [1–3].
- You will receive necessary medical care. If the study team believes the event may be related to the study device or required procedures, this will be assessed and managed according to the protocol and clinical judgment. Your usual medical care will continue regardless of study participation [1–3].

If there is an unanticipated adverse device effect or a device malfunction

- Stop using the study device if you think it is not working correctly or is causing a problem. Do not try to fix it yourself. If it is safe to do so, keep the device and any accessories for evaluation, and contact the study team for instructions [1–3].
- The study team may ask you to pause or permanently stop using the device while they evaluate the issue. They may provide updated instructions, a software update, a replacement device, or switch you to standard education only, depending on what is safest for you [1–3].
- If the event is an unanticipated adverse device effect (a harmful or life-threatening effect not previously identified in nature, severity, or incidence), or a device deficiency that could have

led to a serious incident, the sponsor and study doctor must promptly investigate and, when required, report it to the ethics committee and regulatory authorities. Your identity will be protected to the extent allowed by law [1–6].

Medical care and who pays

- Necessary medical evaluation and treatment will be arranged or coordinated by your study doctor for any health problem during the study, whether or not it is related to the device.
- If you are injured or become ill as a direct result of the study device or protocol-required procedures, you will receive necessary medical care. How costs are handled is described in the Costs and Compensation section of this consent. Site-specific insurance or sponsor coverage may apply, or usual billing to you or your insurer may occur first, depending on local laws and the clinical investigation agreement [1–4].
- There is no cost to you for study device evaluation, investigation, or replacement when the issue is related to a device deficiency or malfunction required to be assessed by the study [1–3].

Safety oversight and required reporting

- Serious or unexpected problems related to the study or device may be shared with oversight bodies, including the Institutional Review Board/Independent Ethics Committee, regulators, study monitors/auditors, and the Data and Safety Monitoring Board (if convened). These reviews help protect participant safety and data quality [1–3,5,6].
- The sponsor and investigators are required to follow applicable timelines and procedures for reporting serious adverse events, unanticipated adverse device effects, and important device deficiencies, and to implement any needed risk controls (for example, software updates, labeling changes, or stopping device use) [1–3,5,6].

Changes to your participation if new safety information emerges

- If we learn new information that might affect your safety or your willingness to continue (for example, new or increased risks, new precautions, or required changes to device use), we will contact you promptly. This may include:

- Explaining the new information and answering your questions.
- Providing updated instructions, added monitoring, or replacement of device components/software.
- Asking you to review and sign an updated consent form if the changes are important.
- Pausing or ending your device use, or discussing withdrawal from the study if that is the safest choice for you [1–3].

How to reach us

- You will receive a study contact card with phone numbers and email for business hours and after-hours help. Keep this card with you.
- If you change your phone number, email, or address, please tell the study team so we can reach you quickly if safety information becomes available [1–3].

If you seek care outside the study

- Tell the healthcare provider that you are participating in a clinical investigation of a medical device for inhalation training. Share the study team's contact information so your provider can coordinate care if needed.
- Ask the provider to send a note about your visit to your study doctor, so we can update your study records and complete any required safety reporting [1–3].

Your rights

- Reporting a problem, stopping device use, or withdrawing from the study will not affect your access to usual medical care or your legal rights. Required safety reporting will protect your privacy as permitted by law [1–4].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. US Food and Drug Administration. 21 CFR 50.25: Elements of informed consent. Revised 2018. https://www.ecfr.gov/current/title-21/part-50/section-50.25
5. US Food and Drug Administration. 21 CFR 812: Investigational Device Exemptions (including definitions at 812.3 and reporting at 812.150). Revised 2022. https://www.ecfr.gov/current/title-21/part-812
6. European Commission. MDCG 2020-10/1: Safety reporting in clinical investigations of medical devices under the MDR. 2020. https://health.ec.europa.eu/system/files/2021-10/md_mdcg_2020-10-1_en_0.pdf

21.16 Voluntary Participation and Your Right to Withdraw

Your choice to take part

- Taking part in this study is completely your choice. You can decide not to join, or to join and then change your mind later, without giving a reason [1–4].
- Your current and future medical care will not be affected if you choose not to participate or if you withdraw after joining [1–4].

If you decide to stop participating

- You may stop participating at any time. Tell the study team so they can explain how to return study devices (if any) and discuss next steps for your safety [1–3].
- We may ask you to complete a brief final safety visit or phone check and to allow continued safety follow-up for a short period, so your study doctor can make sure you are well and document any device-related issues [1–3].
- Data already collected up to the time you withdraw will still be kept and used to the extent allowed by law and ethics approvals, to protect the integrity of the study and to meet safety and regulatory obligations. New data will not be collected after withdrawal unless needed for safety or required by law [1–4].

Optional elements and changing your choices

- You can say yes or no to optional parts (for example, photos/videos of inhaler use, storage/use of your coded data for future research, or re-contact) and still be in the main study.

- You may withdraw your permission for one or more optional elements later without leaving the main study. Materials already analyzed or shared cannot usually be retrieved, but no new optional use will occur after you change your preference [1–4].

Situations when the study team may stop your participation

For your safety, to protect study quality, or if the study must change, the investigator or sponsor may pause or stop your participation without your consent if, for example:

- Continuing could put you at risk (for example, a device-related safety concern, a serious adverse event, or a health change that makes participation unsafe) [1–3,5].
- You can no longer follow key study requirements needed for safety, device accountability, or valid results (for example, loss of required smartphone access or identity verification for app activation) [1–3].
- The device is recalled, the protocol changes, or the study is modified or stopped early by the sponsor, ethics committee, regulators, or the Data and Safety Monitoring Board (DSMB) [1–3,5].

If this happens, the team will explain why and discuss safe transition back to your usual care.

What happens to your usual care

- Whether you take part, choose not to, or withdraw, you will continue to receive your usual medical care for asthma and/or COPD from your healthcare providers. You and your clinician can make any treatment decisions you need at any time [1–4].

How to withdraw

- Contact the study team using the details on your contact card. You can also tell your regular clinician, who can inform the study team on your behalf.
- Please return any study devices as instructed. The team will confirm whether a brief final safety check is recommended and document your preferences about optional elements going forward [1–3].

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. US Food and Drug Administration. 21 CFR 50.25: Elements of informed consent. Revised 2018. https://www.ecfr.gov/current/title-21/part-50/section-50.25
5. US Food and Drug Administration. 21 CFR 812: Investigational Device Exemptions (including definitions at 812.3 and reporting at 812.150). Revised 2022. https://www.ecfr.gov/current/title-21/part-812

21.17 Study Results, Data Sharing, and Participant Communication

How overall study results will be shared

- This study will be publicly registered on a recognized clinical trial registry before participants are enrolled, such as ClinicalTrials.gov and/or another World Health Organization–recognized platform. Where required in the European Union, information about the clinical investigation and a lay (plain-language) summary of results may also be posted to the European database for medical devices. You may ask the study team for the registry name and registration number once available [1–5].

- After the study ends and results are analyzed, the sponsor and investigators plan to share overall results in public trial registries, scientific journals, conference presentations, and regulatory reports. Your identity will not be revealed in any public sharing of results; information will be combined across many participants and presented without names or direct identifiers [1–5].

Information you may receive about the study

- You may receive a plain-language (lay) summary of the overall study results when available and after the main analysis is complete. The summary will explain what was studied, the main findings, and any important safety information, in non-technical language. How and when you will receive this summary (for example, secure email or postal mail) will be confirmed by your study site. If new safety information emerges that could affect your willingness to continue, you will be informed as soon as possible during the study [1,3].
- If you would like a copy of any journal articles that report the main results of this study after they are published, please ask the study team.

What individual information may be shared with you

- The study team may share information from your own study visits that is important for your care (for example, safety findings or issues related to device use) as described in the protocol and required by local laws. Otherwise, you will not routinely receive your individual, raw device files or detailed research analyses. Any personal medical information shared with you will follow Good Clinical Practice and local requirements [1–4].

What data may be shared with other researchers

- To support scientific transparency, the sponsor may share de-identified (coded) study data with qualified researchers after the main results are published or posted. Shared materials may include:

- A limited set of de-identified individual participant data (for example, age group, diagnosis category, baseline and follow-up inhaler-technique checklist results, and device performance metrics such as peak inspiratory flow and inspiration timing), study group assignment, and dates in relative or generalized form.
- Supporting documents such as the final protocol, the statistical analysis plan, the analytic code, and the clinical study report, with confidential or proprietary information removed [1–4,6,7].

- Conditions for access:

- Researchers must submit a proposal describing the purpose, analysis plan, and data protection measures. Access will be granted only for uses consistent with the original consent and applicable laws.
- Data will be shared through a secure system under a data-use agreement that prohibits attempts to identify participants, restricts data linkage with other sources unless approved, and requires data destruction or return after the project ends.
- Direct identifiers (for example, name, full date of birth, address, contact details, national ID, BankID or other e-ID information) will not be shared. Images or videos will not be shared unless you provided separate permission and local ethics approval covers that use [3,4,6,7].

Privacy protections in public sharing and data sharing

- All public reporting of study results will use aggregated data without names or contact details. Any shared research dataset will be de-identified (coded) and handled under Good Clinical Practice, data-minimization, and security principles, with technical and organizational

safeguards to reduce the risk of re-identification. Despite safeguards, there is a small residual risk that someone could try to link de-identified data to a person; strict agreements and oversight are used to reduce this risk [1–4,6,7].

Your choices

- You do not have to agree to optional future research use or broader data sharing beyond this study's main goals. If you do agree and later change your mind, tell the study team. Materials already analyzed or shared cannot usually be retrieved, but no new sharing for optional purposes will occur after you withdraw permission, consistent with laws and study integrity requirements [1–4].

Where you can find the results

- When available, the study registration record will be updated with summary results and links to key publications. You may also request the registry identifier and copies of public summaries from your study team [2,5–7].

Questions

- If you have questions about how results will be shared or how your data may be used, please contact the study team. They can explain what information you may receive and the safeguards in place to protect your privacy.

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. European Parliament and Council. Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR). 2016. https://eur-lex.europa.eu/eli/reg/2016/679/oj
5. World Health Organization. International Clinical Trials Registry Platform (ICTRP): WHO policy on clinical trials registration and disclosure of results. 2017. https://www.who.int/clinical-trials-registry-platform
6. US Department of Health and Human Services. Clinical Trials Registration and Results Information Submission (42 CFR Part 11) Final Rule. 2016. https://www.ecfr.gov/current/title-42/part-11
7. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. N Engl J Med. 2017;376(23):2277–9. doi:10.1056/NEJMe1705439

21.18 Who to Contact With Questions or in an Emergency

How to reach us for questions or help

- Study doctor/Principal Investigator: [Name, degrees], [Department], [Institution]; Phone (business hours): [XXX-XXX-XXXX]; Email: [address]; Address: [clinic address].

- Study coordinator/Research nurse: [Name], Phone (business hours): [XXX-XXX-XXXX]; Secure Email: [address].
- 24-hour urgent line (on-call study clinician): [XXX-XXX-XXXX]. If you have severe or worsening breathing problems, chest pain, fainting, or other emergency symptoms, call local emergency services first. After you are safe, contact the study team.

You will receive a wallet-sized contact card with these numbers. Please keep it with you and update us if your phone number or address changes.

For non-urgent questions about the study or device

- Contact the study coordinator or your study doctor during business hours for questions about appointments, device setup or troubleshooting, study procedures, side effects that are not urgent, reimbursements, or changes to your medications or health.

For medical concerns outside business hours

- Call the 24-hour urgent line for health concerns that cannot wait until the next business day, including problems you think may be related to the study device or procedures. If you cannot reach the study team and are worried about your health, seek medical care and inform the provider that you are in a clinical study of a medical device.

In an emergency

- Call local emergency services or go to the nearest emergency department immediately. After you are safe, contact the study doctor or the 24-hour urgent line to report what happened. This approach is consistent with Good Clinical Practice and participant safety guidance [1–3].

Questions about your rights, complaints, or concerns

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC): For questions about your rights as a research participant, concerns about the study, or to make a confidential complaint, contact: [IRB/IEC name]; Phone: [XXX-XXX-XXXX]; Email: [address]; Address: [address]. You may contact the IRB/IEC instead of, or in addition to, contacting the study team. Consent forms must provide this contact under applicable regulations [1–4].

Coordinating center and sponsor contacts

- Coordinating center: [Coordinating Center Name]; General study operations and scheduling support. Phone: [XXX-XXX-XXXX]; Email: [address].
- Sponsor: MediTuner AB (Manufacturer of the investigational app-module; SRN SE-MF-000028534). For questions about sponsorship, device complaints, or data protection not resolved by your site, contact: [Sponsor contact name/office]; Phone: [XXX-XXX-XXXX]; Email: [address]; Address: [address]. Sponsor contact details are provided to support required device complaint handling and subject communications per Good Clinical Practice and applicable device regulations [1–3].

If you cannot reach us

- If you do not receive a call back within a reasonable time for a non-urgent question, try the alternative contacts listed above. For urgent medical issues, use the 24-hour urgent line or seek immediate care. Required contact information and clear instructions are part of informed consent to help you obtain timely assistance [1–4].

What to have available when you call

- Your full name and date of birth.
- The name of this study and your study ID (if known).
- Brief description of your question or symptoms, when they started, and any device messages or error codes.
- Current medications and allergies.
- Your location and a call-back number.

References

1. International Organization for Standardization. ISO 14155:2020 Clinical investigation of medical devices for human subjects—Good clinical practice. Geneva: ISO; 2020. https://www.iso.org/standard/71690.html
2. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
3. European Parliament and Council. Regulation (EU) 2017/745 on medical devices (MDR). 2017. https://eur-lex.europa.eu/eli/reg/2017/745/oj
4. US Food and Drug Administration. 21 CFR 50.25: Elements of informed consent. Revised 2018. https://www.ecfr.gov/current/title-21/part-50/section-50.25

21.19 Consent Statement and Signature Page

Consent statement

By signing below, you confirm that:

- You have read this information (or it was read to you), had the chance to ask questions, and received clear answers.
- You understand the purpose of the study, what your participation involves, the potential risks and benefits, and available alternatives.
- Your participation is voluntary. You may refuse to join or may withdraw at any time without penalty or loss of benefits to which you are otherwise entitled.
- You will receive a copy of the signed and dated consent form (paper or electronic).
- You meet the eligibility requirements to the best of your knowledge and have told the study team about any conditions that might affect your participation.

Authorization to collect, use, and share your information

By signing below, you authorize the study doctors, staff, sponsor (MediTuner AB), their authorized representatives, study monitors/auditors, the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and health authorities to collect, use, and share your study data and health information as described in this consent for the purposes of conducting, monitoring, analyzing, and reporting this study, complying with legal and regulatory requirements, ensuring device complaint handling and safety reporting, and for scientific and quality assurance purposes consistent with the consent you provide.

- What will be collected: contact details; demographics; relevant medical history and medications; device-use data; questionnaire answers; clinic assessments; and safety information.
- How long: your information will be kept as required by law and research standards. If you withdraw, no new data will be collected except as needed for safety or required by law; already collected data will be kept and used as described.
- Your choices: you may withdraw this authorization at any time by contacting the study doctor. If you do, no new data will be collected after the date of withdrawal except as needed for safety or required by law. Data already collected may still be used to protect study integrity and meet legal obligations.
- Privacy safeguards: your information will be protected using security controls, with access limited to authorized persons. When results are shared publicly, they will not identify you.

[Site to insert country/region-specific privacy statement (for example, GDPR/HIPAA language), data controller/contact, lawful basis, retention period, and rights of data subjects.]

Version control and consent format

- Protocol title: [Auto-filled]
- Protocol ID/number: [Auto-filled]
- Consent form version and date: [Site to insert]
- Language: [Site to insert]
- Site name and number: [Site to insert]
- Participant initialed each page: [Yes/No]

Consent format used:

- In-person paper consent: [Yes/No]
- Electronic consent (e-consent) with BankID or similar secure e-ID: [Yes/No]. By signing electronically, you agree that your electronic signature has the same legal effect as a handwritten signature.
- Telephone/video consent with impartial witness (if applicable): [Yes/No]. If used, a copy of the consent will be provided to you as soon as possible.

Optional permissions

Your choices below are optional. You can say yes or no to any item and still take part in the main study. You can change your choices later by telling the study team. Materials already analyzed or shared cannot usually be retrieved, but no new use will occur after you change your choice.

1) Optional training images or short videos of inhaler use (for technique coaching, quality review, and training of study staff; not for public use)

- I agree to allow recording and use as described: [Yes] [No]

Initials: _____ Date: ____/____/_____

2) Future research use of my de-identified (coded) study data related to breathing technique and device performance, for research consistent with this consent and approvals

- I agree: [Yes] [No]

Initials: _____ Date: ____/____/_____

3) Sharing of my de-identified (coded) data with qualified researchers under a data-use agreement after the main results are published

- I agree: [Yes] [No]

Initials: _____ Date: ____/____/_____

4) Re-contact for future studies on inhaler technique or respiratory health

- I agree to be contacted: [Yes] [No]

Preferred contact method: [Phone/Email/Postal]

Initials: _____ Date: ____/____/_____

5) Optional substudy at this site (if offered): [Substudy title]

- I agree to participate in the optional substudy: [Yes] [No]

Initials: _____ Date: ____/____/_____

[If any optional specimen collection is planned at your site:] 6) Optional storage of leftover specimens for future research under coded conditions

- I agree: [Yes] [No]

Initials: _____ Date: ____/____/_____

Signatures

Participant

- I confirm that I have read this information (or it was read to me), my questions were answered, and I freely agree to take part in this study.

Name of participant (print): _____
Signature of participant: _____ Date (YYYY-MM-DD): ____/____/_____ Time (HH:MM): _____

Date of birth (YYYY-MM-DD): ____/____/_____

For participants aged 16–17 years: [Site to confirm local law]

- Minor participant assent (if required)

Name (print): _____
Signature: _____ Date: ____/____/_____
Time: _____

- Parent/guardian permission (if required)

Name of parent/guardian (print): _____
Relationship: _____
Signature: _____ Date: ____/____/_____
Time: _____

Legally Authorized Representative (LAR) [Complete only if participant cannot consent under local law]
Name of LAR (print): _____
Relationship/authority: _____
Signature of LAR: _____ Date: ____/____/_____ Time: _____

Person obtaining consent

- I have explained the study, answered questions, and believe that the participant (or LAR) understands what participation involves and is giving informed consent freely.

Name (print): _____
Role: _____
Signature: _____ Date: ____/____/_____
Time: _____

Witness (if required by local regulations or for telephone/video or non-written consent)

- I attest that the information in this consent was accurately explained in language understandable to the participant (or LAR), that consent was given freely, and that a signed copy will be provided.

Name (print): _____
Signature: _____ Date: ____/____/_____
Time: _____
Reason witness required: [Non-written consent/Low literacy/Local requirement/Other: _____]

Interpreter (if used)

- I certify that I accurately interpreted the consent discussion between the study team and the participant (or LAR).

Name (print): _____ Language: _____
Signature: _____ Date: ____/____/_____
Time: _____

Electronic consent attestation (if applicable)
- Method of e-signature (for example, BankID): _____
- Authentication ID/reference: _____
- Date/time stamp (system-generated): ____/____/_____ _____:____
- Signed copy delivery method: [Secure email/Portal/Postal]

Confirmation of copies provided

- Participant/LAR received a complete copy of the signed and dated consent form: [Yes/No]
- Participant/LAR received a copy of any optional permissions they selected: [Yes/No]
- Participant/LAR received a study contact card: [Yes/No]

For site use only

- Screening/enrollment ID: _____
- Randomization (if assigned at consent): [Not applicable/Assigned later]
- IRB/IEC approval date for this consent version: ____/____/_____
- Local requirements satisfied (check all that apply):

- Identity verified using BankID or similar e-ID [Yes/No/Not applicable]
- All pages initialed by participant/LAR [Yes/No/Not applicable]
- Required witness present [Yes/No/Not applicable]
- Interpreter used [Yes/No]
- Copies provided to participant/LAR [Yes/No]