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1 Title

Item	Details
Full title	Prospective longitudinal observational study of self-harm among high-risk hospitalized adolescents in Slovenia, with healthy controls: clinical, psychosocial, and genetic/epigenetic correlates and development/validation of the Adolescent Self-Harm Risk Scale (ASHRS)
Short title	Adolescent Self-Harm Risk Study (Slovenia)
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Sponsor	Slovenian Research Agency
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Country/region	Slovenia
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2 INTRODUCTION

2.1 Background and Rationale

Epidemiology and burden

Self-harm, including suicide attempts and non-suicidal self-injury (NSSI), is a leading cause of morbidity among adolescents and a major antecedent of suicide, which remains a top cause of death in young people worldwide [1,2]. Community-based meta-analyses estimate lifetime NSSI prevalence around 17–18% in adolescents, with higher rates in clinical and inpatient samples [2,3]. Self-harm frequently recurs: systematic reviews of hospital-presenting self-harm indicate repetition in a substantial minority within the first year, and repetition is a strong predictor of subsequent suicide [3,4]. The period immediately after psychiatric discharge carries an acutely elevated suicide rate compared with the general population, underscoring the importance of accurate assessment and intensive risk management during and following inpatient care [5].

Beyond mortality, adolescent self-harm is associated with functional impairment, academic difficulties, strained family and peer relationships, and high use of emergency, inpatient, and community mental health services [3]. Families experience significant psychological distress and caregiving burden, and educational and health systems face increased resource demands linked to crisis management and follow-up care [3]. Within the WHO European Region, suicide prevention remains a priority; however, country-level heterogeneity in rates, service organization, and cultural context supports the need for locally generated evidence to inform assessment and care pathways [6]. Slovenia's specialized child and adolescent psychiatric services provide a context in which systematic characterization of self-harm risk, incident events during hospitalization, and post-discharge trajectories can directly inform service design.

Determinants and functions of adolescent self-harm

Self-harm in adolescence is multiply determined. Robustly implicated correlates include depressive and anxiety symptoms, trauma exposure, emotion dysregulation, impulsivity, hopelessness, interpersonal stress, family conflict, and peer difficulties [3]. Functions of NSSI commonly include automatic negative reinforcement (downregulating aversive affect), self-punishment, and interpersonal communication or influence, with the balance of functions varying across individuals and time [7]. These functions align with biosocial models positing that heightened emotional reactivity, invalidating environments, and deficits in self-regulatory skills increase risk for self-injurious behavior as a maladaptive coping strategy [3,7]. Conversely, social support, adaptive coping, secure

attachment, and problem-solving skills are protective, highlighting potentially modifiable psychosocial targets to reduce risk [3].

Clinical course, short-term risk, and the inpatient window

Adolescents admitted with suicidal behavior or NSSI represent an especially high-risk subgroup. Short-term risk is dynamic and influenced by acute changes in mood, stressors, interpersonal events, and access to means. The weeks and months immediately post-discharge constitute a period of markedly elevated suicide risk across diagnoses and age groups, with the highest rates within the first 3 months [5]. Inpatient monitoring offers a unique opportunity to prospectively document self-harm and heteroaggressive incidents, observe proximal antecedents (e.g., affective surges, interpersonal conflicts), and evaluate the short-term predictive value of clinical and psychosocial indicators gathered at admission. Longitudinal follow-up into the community is essential to capture persistence, desistance, and recurrence patterns and to examine how baseline risk/protective factors and inpatient events relate to outcomes over 6 to 18 months.

Gaps in risk assessment and justification for a new adolescent-focused tool

Despite widespread use of risk scales in clinical practice, systematic evaluations show that commonly used tools have limited discrimination and calibration for predicting repeat self-harm or suicide, and guidelines caution against relying on risk scores alone to make management decisions [8–10]. Meta-analytic syntheses further indicate that the individual-level predictive power of traditional risk factors is modest, particularly for short-term outcomes, and that improvements are likely to come from integrating multi-domain data, repeated measures, and context-specific indicators [9]. Widely used instruments such as the Columbia Suicide Severity Rating Scale (C-SSRS) validly assess suicidal ideation and behavior but are not designed to quantify broader adolescent self-harm risk across suicidal and non-suicidal behaviors or to integrate psychosocial, interpersonal, and functional NSSI constructs into a parsimonious, rapid screening format [11]. Similarly, established NSSI assessments characterize topography and functions of self-injury but do not provide an empirically derived short- to medium-term risk index usable at the point of care in inpatient youth settings [7].

These gaps support the development and validation of a brief Adolescent Self-Harm Risk Scale (ASHRS) calibrated to short- and longer-term outcomes and optimized for inpatient admission and discharge workflows. Applying contemporary measurement standards, including clear construct definition, content validity, reliability, and predictive performance assessment in the intended population and setting, is essential to ensure clinical utility and minimize false reassurance or over-triage [12].

Rationale for a multimethod, longitudinal design with healthy controls

A prospective cohort design in a high-risk inpatient adolescent population enables: (a) systematic baseline characterization using validated measures of suicidality, NSSI features and functions, emotion regulation, personality and attachment, trauma symptoms, and social/family context; (b) real-time recording of self-harm and heteroaggression incidents during hospitalization; and (c) examination of outcomes at 6 and 18 months to evaluate persistence and change. Inclusion of a healthy adolescent comparison group provides age- and context-relevant reference distributions for psychosocial constructs, supports evaluation of discriminative features specific to high-risk youth, and helps distinguish trait from state influences. This multimethod approach aligns with evidence that multi-domain models outperform single-domain predictors and that repeated measurement improves estimation of dynamic risk [9].

Genetic and epigenetic context

Familial aggregation and twin studies indicate a heritable component to suicidal behavior and related phenotypes, with shared genetic liabilities overlapping with major depression and impulsive aggression [13]. Large genome-wide association studies have begun to identify polygenic contributions to suicide attempt risk, though effect sizes are small and require integration with clinical context [14]. Epigenetic mechanisms, including DNA methylation patterns linked to stress-response and neuroplasticity pathways, have been associated with suicidal behavior in preliminary studies,

suggesting environmentally modulated biological embedding of risk [13,15]. Incorporating genetic and epigenetic assays alongside rich psychosocial phenotyping may refine risk stratification and generate hypotheses about biopsychosocial pathways in adolescent self-harm, while acknowledging that biological markers alone are not currently sufficient for clinical prediction [9,13–15].

Relevance to the Slovenian inpatient setting and study objectives

Conducting this work at the Centre for Mental Health, University Psychiatric Clinic Ljubljana leverages a specialized inpatient environment where standardized assessment, close observation, and coordinated follow-up are feasible. The Slovenian context, including language-specific instrument versions and health-system pathways, necessitates local validation to ensure cultural and clinical fit and to support implementation in routine care. By quantifying the occurrence, frequency, characteristics, functions, and risk of self-harm among hospitalized adolescents, comparing them with healthy peers, and following outcomes over 18 months, the study directly addresses pressing clinical needs: improving identification of short- and longer-term risk, informing individualized safety planning at discharge, and guiding resource allocation for aftercare. The development and validation of the ASHRS are justified by the current limitations of risk scales, the dynamic nature of post-discharge risk, and the need for a brief, context-appropriate tool that integrates adolescent-specific self-harm constructs and can be embedded into Slovenian inpatient workflows [8–12]. These aims align with international guidance emphasizing comprehensive, person-centered assessment, avoidance of sole reliance on risk scores, and strengthening of evidence for decision-making in high-risk youth populations [8,10].

References

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Psychiatry. 2010;15(10):938–48.

2.2 Theoretical framework for behaviour

Overview and rationale

This study is grounded in a multilevel, ideation-to-action theoretical framework that integrates: (a) the Integrated Motivational–Volitional (IMV) model of suicidal behaviour to distinguish the emergence of suicidal ideation from the transition to self-harm and suicide attempts; (b) the Interpersonal Theory of Suicide (IPTS) to specify interpersonal mechanisms (perceived burdensomeness, thwarted belongingness) and acquired capability; and (c) contemporary models of nonsuicidal self-injury (NSSI) emphasizing affect-regulatory and interpersonal functions of self-injury within a biosocial context of emotion dysregulation and invalidation [16–20]. Adolescent-specific self-regulatory development is incorporated via the dual-systems model, which posits heightened socioemotional reactivity alongside still-maturing cognitive control, increasing susceptibility to acute precipitants and peer/contextual influences [21]. A stress–diathesis perspective links distal vulnerabilities (e.g., genetic/epigenetic liability, temperament, early adversity) with proximal stressors and state-dependent processes that shape short-term risk dynamics, consistent with ecological models that situate behaviour within family, peer, school, and inpatient milieus [22,23].

This integrated framework is appropriate for hospitalized adolescents at high risk because it: (1) captures the dynamic nature of proximal risk during inpatient care and post-discharge; (2) accommodates the co-occurrence and distinctions between suicidal and non-suicidal self-harm; and (3) aligns with multi-domain, longitudinal measurement to inform mechanism-focused risk stratification and the development/validation of a brief self-harm risk scale for adolescent inpatient workflows [16,18,24,25].

Key constructs and their operationalization

- Distal/background factors (pre-motivational): genetic and epigenetic liability; temperament/impulsivity; trauma exposure; attachment/relationship history; personality functioning. These shape sensitivity to stress and the likelihood that stressors will activate motivational processes leading to self-harm [16,20,22].
- Motivational phase (ideation formation): depressive affect, hopelessness, entrapment, self-criticism, perceived burdensomeness, and thwarted belongingness; emotion dysregulation as a cross-cutting amplifier; social support as a protective moderator [16,17,21,26,28].
- Volitional phase (enactment): acquired capability (pain tolerance, fear habituation), access to means, impulsivity, exposure to self-harm in peers/media, physiological arousal/agitation, and barriers/facilitators present in the setting (e.g., observation levels on the ward) [16,17,21,24].
- NSSI functions and processes: automatic negative reinforcement (downregulation of aversive affect), self-punishment, and interpersonal communication/influence functions that maintain behaviour through reinforcement learning; habituation processes that may generalize to suicidal capability [18,19].
- Developmental self-regulation: imbalance between socioemotional drive systems and still-maturing cognitive control in adolescence, which heightens reactivity to contextual cues (peers, interpersonal stress) and increases the salience of short-term relief functions of self-harm [21].
- Contextual ecology: micro- (family, peers, inpatient unit routines), meso- (school, community), and macro-level (cultural) influences that moderate exposure, modeling, support/invalidation, and access to means [23].

Construct-to-measure mapping in this study follows these domains: suicidal ideation/behaviour (C-SSRS) indexing motivational and volitional outcomes; NSSI frequency, topography, and functions (B-NSSI-AT, ISAS) indexing reinforcement mechanisms and acquired capability; emotion dysregulation and related personality/attachment/trauma measures indexing distal and motivational vulnerabilities; dynamic inpatient incident recording indexing volitional enactment and environmental moderators; and genetic/epigenetic assays indexing distal diathesis [16–19,22,24].

How the framework informs objectives, outcomes, and hypotheses

- Objectives: The IMV/IPTS components specify testable pathways from distal vulnerabilities and interpersonal cognitions to ideation and from volitional moderators to enactment, aligning with the primary objective to identify factors associated with occurrence and persistence of self-harm and to enhance short- and long-term risk identification [16,17].
- Outcomes: Primary behavioural outcomes separate ideation (motivational) from enactment (volitional), including inpatient incidents and post-discharge self-harm. NSSI functional indices serve as mechanistic outcomes mediating links between affective dysregulation and behaviour. Social support and belongingness indices are prespecified moderators [16–19,28].
- ASHRS development: Item generation prioritizes core motivational (e.g., entrapment/hopelessness, perceived burdensomeness/belongingness, self-critical cognitions) and volitional (e.g., capability, access, agitation, impulsivity, exposure/modeling) constructs, with protective buffers (support, coping efficacy) to reflect net risk. Predictive validation explicitly tests ideation-to-action transitions over short (inpatient/post-discharge) and medium (6–18 months) horizons [16,17,21,25].

Analytical implications

- Phase-specific modeling: Multivariable regression and survival models will be structured to first predict ideation severity (motivational phase) and then the transition from ideation to self-harm events (volitional phase), consistent with ideation-to-action theory [16,25].
- Mediation and moderation: Emotion dysregulation and interpersonal cognitions are posited mediators between distal factors (trauma, attachment) and outcomes; social support and environmental context (e.g., observation levels) are prespecified moderators of both phases [17,21,23,26,28].
- Functional mechanisms: NSSI function scales enter models as mediators of the relation between affective distress and NSSI frequency/severity and as contributors to acquired capability relevant for suicidal behaviour [18,19].
- Dynamic risk: Time-updated analyses will incorporate inpatient observations to model short-term fluctuations in proximal risk, reflecting evidence that suicidal states vary substantially over hours to days [24].
- Measurement model for ASHRS: Factor-analytic methods will test a priori motivational, volitional, and protective domains; item response theory will support calibration; and incremental validity will be evaluated over established measures (e.g., C-SSRS) for predicting near-term incidents [16,25].

Subgroup and contextual considerations

- Developmental stage: Younger adolescents may show stronger dual-systems imbalance, with greater influence of peer/contextual triggers and impulsivity in volitional transitions; older adolescents may show more stabilized patterns of capability and entrenched NSSI functions [21].
- Interpersonal context: Low belongingness/high burdensomeness combined with limited support is expected to elevate ideation and weaken naturalistic buffers against enactment; family cohesion and school connectedness are anticipated protective moderators [17,23,28].
- Clinical heterogeneity: Elevated emotion dysregulation and invalidating interpersonal environments (biosocial model) are hypothesized to characterize subgroups with recurrent NSSI and faster ideation-to-action transitions; trauma histories may potentiate both dysregulation and capability [19,20,22].
- Setting effects: Inpatient environmental controls (e.g., reduced access to means, observation) are treated as time-varying volitional moderators; ward-level factors may be explored as ecological covariates to explain between-unit variation in incidents [16,23,24].

Collectively, this theoretical integration supports a coherent chain from distal diathesis through

motivational states and volitional processes to behavioural outcomes, directly structuring construct selection, outcome definitions, analytic sequencing, and ASHRS content to enhance clinically actionable risk assessment in high-risk hospitalized adolescents and during early community re-entry [16–25,28].

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2.3 Evidence gaps and justification for the study

What is known

- Short-term risk following adolescent psychiatric admission and post-discharge is high, with the first weeks to months conferring markedly elevated risk of self-harm repetition and suicide compared with the general population, underscoring the need for intensive assessment during admission and early aftercare [31].
- Commonly used risk scales have limited ability to discriminate who will repeat self-harm or attempt suicide; guidelines advise against using risk scores in isolation to guide management and emphasize comprehensive, person-centered assessment [28,29].
- Decades of research indicate that traditional individual risk factors (e.g., depression, prior attempts) have modest predictive value at the individual level, particularly over short time horizons, and that improvement likely requires integrating multi-domain data and repeated measures of dynamic states [30,32].
- Widely used measures such as the Columbia Suicide Severity Rating Scale (C-SSRS) validly assess suicidal ideation and behavior but are not designed to provide a brief, integrative index of broader adolescent self-harm risk across suicidal and non-suicidal behaviors for point-of-care use in inpatient youth settings [33]. Instruments that assess nonsuicidal self-injury (e.g., ISAS) characterize functions and topography but do not yield empirically calibrated short- to medium-term risk estimates suitable for clinical triage [34].
- International and regional public health guidance highlights substantial heterogeneity across European countries in suicide and self-harm epidemiology and service organization, supporting a need for locally generated evidence to inform context-specific pathways of care [36].

- Genetic and epigenetic research suggests heritable and environmentally modulated biological contributions to suicidal behavior, but current effect sizes are small and insufficient for stand-alone clinical prediction; integration with clinical and psychosocial data is necessary [37–39].

Key limitations and gaps in the existing evidence

- Methodological limitations in prediction research:
  - Many studies rely on cross-sectional designs or single timepoint assessments, limiting insight into dynamic, short-term risk processes relevant to inpatient care and early post-discharge periods [30,32].
  - Prospective cohorts often have short follow-up, high attrition, or do not capture inpatient incidents, constraining understanding of proximal precipitants and transition from ideation to enactment [31,32].
  - Predictive models frequently omit multi-domain integration (clinical, psychosocial, contextual, and biological) and lack external validation, contributing to overfitting and limited transportability to real-world inpatient youth settings [28,30].

- Measurement constraints:
  - Existing instruments either focus narrowly on suicidal ideation/behavior (e.g., C-SSRS) or on NSSI functions (e.g., ISAS) without producing a concise, adolescent-specific risk index calibrated to near- and medium-term outcomes that can be embedded in admission/discharge workflows [33,34].
  - Few tools have been developed and validated in inpatient adolescent populations with head-to-head evaluation of predictive performance, calibration, and clinical utility; where tested, discrimination is modest and calibration frequently suboptimal [28,30].
  - Many measures lack formal cross-cultural adaptation and validation aligned with contemporary standards (e.g., COSMIN), limiting interpretability and implementation in non-Anglophone contexts [35].

- Population and context gaps:
  - Evidence from Central and Eastern Europe, and specifically from Slovenian adolescent inpatient services, is comparatively sparse despite documented regional heterogeneity, limiting applicability of findings derived primarily from Anglophone or mixed-age adult samples [36].
  - Under-representation of healthy, local comparison samples constrains interpretation of whether observed psychosocial profiles in high-risk youth reflect trait liabilities versus acute state effects.

- Inconsistencies and fragmentation:
  - Definitions and outcome ascertainment for self-harm vary across studies, with inconsistent capture of prevented events and inpatient incidents, impeding synthesis and precise estimation of short-term risk [28–30].
  - Biological studies in adolescents often lack concurrent, rich psychosocial phenotyping and prospective behavioral outcomes, reducing their translational value for risk stratification [37–39].

Why this study is needed

This protocol directly addresses the above evidence gaps in a high-risk adolescent inpatient population in Slovenia by:

- Implementing a prospective, multimethod design that:
  - Captures real-time inpatient self-harm and heteroaggressive incidents and follows participants at 6 and 18 months, improving characterization of short-term dynamics and medium-term trajectories central to clinical decision-making and aftercare planning [31,32].
  - Integrates multi-domain assessment (clinical, psychosocial, contextual, and genetic/epigenetic) to evaluate additive and interactive contributions to occurrence and persistence of self-harm, in line with evidence that single-domain models underperform [30,37–39].

- Developing and validating a brief Adolescent Self-Harm Risk Scale (ASHRS) tailored to inpatient admission and discharge workflows:
  - Item generation and validation focus on constructs linked to near-term transition from ideation to behavior, with prespecified evaluation of discrimination, calibration, and incremental utility over

established measures, responding to guideline warnings about sole reliance on generic risk scales [28–30,33–35].
- Slovenian-language implementation and local validation adhere to contemporary measurement standards to ensure cultural/clinical fit and facilitate uptake in routine care [35,36].

- Establishing a Slovenian cohort with a healthy, local comparison group:

- Provides reference distributions for psychosocial constructs and supports separation of trait versus state influences, addressing the lack of locally grounded, age-appropriate comparators in prior work.
- Generates context-specific evidence for service design within the Slovenian mental health system, where regional heterogeneity argues against simple transposition of findings from other settings [36].

- Enhancing outcome ascertainment:

- Harmonizes definitions across suicidal and non-suicidal self-harm, explicitly includes recorded and prevented inpatient events, and prespecifies outcomes across short- and medium-term horizons, reducing fragmentation seen in prior studies [28–30].

Link to primary objectives and outcomes

- By prospectively quantifying inpatient incidents and post-discharge self-harm while modeling multi-domain predictors, the study directly advances the primary objective to identify factors associated with the occurrence and persistence of self-harm in high-risk adolescents and to improve short- and long-term risk identification [30–32].
- By developing and validating the ASHRS against inpatient and follow-up outcomes, the study addresses the specific gap in brief, adolescent-focused, clinically usable tools and targets the key outcome domain of short- and medium-term self-harm risk, complementing but not replacing comprehensive clinical assessment as recommended by guidelines [28,29,33–35].
- By embedding genetic and epigenetic markers within a rich psychosocial framework, the study evaluates their incremental value without overstating standalone predictive utility, aligning with current evidence on the limited clinical prediction capacity of biological markers alone [37–39].

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2.4 Public and patient involvement

Approach and rationale

Public and patient involvement (PPI) has been integrated to enhance relevance, acceptability, and feasibility of study procedures and to strengthen content validity of the Adolescent Self-Harm Risk Scale (ASHRS). PPI activities are structured and reported in line with GRIPP2 guidance and the UK Standards for Public Involvement, with specific adaptations for adolescent participants in a psychiatric inpatient setting in Slovenia [1,2]. For ASHRS development, involvement of the target population is used to support content validity in accordance with COSMIN recommendations [3].

Involvement to date (design and materials)

- Early consultations: Three structured consultation sessions were held with adolescent service users (n=8; aged 14–18) previously hospitalized at UPKL, two parents/caregivers, and three school counsellors. Input prioritised the high-risk inpatient and early post-discharge window, emphasised inclusion of interpersonal belongingness/support and coping items, and recommended non-stigmatising, plain-language Slovene phrasing for sensitive questions.
- Participant burden and procedures: Adolescents advised on assessment length, preferred timing (daytime hours), breaks, and the option to skip items perceived as distressing, informing the final assessment schedule and safety procedures for inpatient and follow-up assessments.
- Consent/assent materials: Youth and caregiver feedback led to layered information sheets (short form with key points and a detailed appendix), clearer explanations of genetic/epigenetic sampling, and explicit statements that individual genetic results will not be returned (aggregate findings only).
- Safety messaging: Lived-experience contributors suggested adding brief debriefing scripts after sensitive questionnaires and clear signposting to ward clinicians and community supports, which were incorporated into the operating procedures.

Ongoing and planned involvement (conduct, analysis, dissemination)

- Youth Advisory Panel (YAP): A standing panel of 6–8 adolescents (including former inpatients and students from local schools) will meet quarterly to:

- Review participant-facing materials and follow-up contact strategies (e.g., preferred communication channels, reminder cadence).
- Advise on feasibility and acceptability of ward-based incident recording from a participant perspective.
- Contribute to item refinement and response options during ASHRS cognitive interviews and pilot testing.

- Caregiver and educator input: Periodic consultations with caregivers (biannual) and school counsellors (annual) will address follow-up feasibility, language appropriateness for school-based recruitment of healthy controls, and interpretation of school-context data.
- Analysis and interpretation: Near the time of interim analyses, the YAP and caregiver representatives will participate in facilitated interpretation sessions to contextualise quantitative and qualitative findings related to self-harm functions, social support, and short-term risk transitions, with attention to safeguarding.

- Dissemination: Co-produced plain-language Slovene summaries, infographics, and short presentations will be prepared with YAP input for:

- Participants and families (study updates, final results).
- UPKL clinical teams and regional child and adolescent mental health services.
- Schools involved in control recruitment.
- Youth organisations and policymakers. Youth advisors will be invited to co-present where appropriate and to be acknowledged or co-authored in outputs consistent with journal policies and individual preference.

ASHRS-specific involvement

- Content generation and refinement: Lived-experience adolescents will review candidate item pools for clarity, relevance, and burden, and suggest missing concepts (e.g., entrapment language, peer dynamics, online exposure).
- Cognitive interviewing: Iterative cognitive interviews (target n≈12–15 adolescents across inpatient and community contexts) will examine comprehension, recall period, and response processes, with modifications documented and adjudicated by the study team, consistent with COSMIN content validity methodology [3].
- Usability in workflows: Youth and ward staff will jointly assess ASHRS administration flow at admission/discharge to minimise duplication and distress and to ensure results are communicated appropriately as an adjunct—not a replacement—to comprehensive clinical assessment.

Training, support, and safeguarding for PPI contributors

- Preparation: YAP members will receive orientation covering study aims, roles, confidentiality, boundaries, and how their input will be used. A clinician will be present or on-call during sessions involving sensitive content.
- Distress protocols: Short well-being check-ins/outs will be standard; contributors can pause/withdraw without explanation. Immediate support and referral pathways are available if distress arises, reflecting best practice for involving young people with lived experience of self-harm [1,2].
- Data protection: PPI activities will avoid collection of personal health data; any incidental disclosures are handled under predefined clinical safeguarding procedures. No PPI contributor will access identifiable research data.

Recognition and practicalities

- Reimbursement: Youth and caregiver contributors will receive modest vouchers and travel reimbursement aligned with local institutional policy and international guidance on fair recognition of public involvement [2].
- Accessibility: Meetings will be scheduled at convenient times/locations (or online), with materials in Slovene and options for alternative formats.

Limitations of PPI

- While PPI has informed design, materials, and ASHRS content, adolescents did not co-design the genetic/epigenetic laboratory components; their role was limited to shaping consent language and preferences regarding return of results.
- Healthy control students were not directly involved in tool development but will be consulted on clarity and acceptability of school-based materials prior to wider rollout.

Reporting

PPI activities, membership, and impacts on study decisions (including ASHRS item revisions) will be documented and reported using the GRIPP2 short form in subsequent publications and the final study report [1].

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3 STUDY OBJECTIVES AND OUTCOMES

3.1 Primary objective(s)

Primary objective(s)

- To identify and quantify short- and medium-term self-harm risk among hospitalized adolescents by modeling the occurrence, timing, and recurrence of self-harm (suicidal behavior and nonsuicidal self-injury) from admission through 6- and 18-month follow-up, and to determine which clinical, demographic, psychosocial, and biological factors are independently associated with these outcomes.

- To develop and validate the Adolescent Self-Harm Risk Scale (ASHRS) for use at admission and discharge, evaluating its predictive performance for near-term (inpatient and early post-discharge) and medium-term self-harm, and its incremental utility over established measures of suicidality and self-harm.

The primary outcome domain is self-harm enactment, defined as any recorded or prevented self-harm incident during hospitalization and any self-harm event reported or clinically ascertained within 6 and 18 months post-discharge. This domain will be operationalized using time-to-first event (for short- and medium-term horizons) and event frequency within each interval, drawing on ward incident logs and standardized assessments (e.g., C-SSRS for suicidal behavior; B-NSSI-AT/ISAS for NSSI characteristics) to ensure harmonized ascertainment across suicidal and non-suicidal behaviors. Focusing on enactment directly captures the central behavioral phenomenon of interest—transition from ideation to self-injurious action—consistent with ideation-to-action models and the acute post-discharge risk window in adolescent inpatient populations [1,4].

This primary objective is fundamental to the study rationale because adolescents hospitalized for self-harm face markedly elevated short-term risk, yet existing risk scales have limited discrimination and should not be used in isolation to guide care [1–3]. By prospectively characterizing self-harm events and validating a brief, adolescent-focused risk scale against clinically salient near-term outcomes, the study addresses key evidence gaps in dynamic risk assessment and supports safer, context-appropriate decision-making in inpatient and early aftercare pathways [1–3,5].

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3.2 Secondary objective(s)

Overview

The secondary objectives extend the primary focus on self-harm enactment by characterizing multilevel determinants, mechanisms, and contextual moderators of self-harm risk in hospitalized adolescents, evaluating change-sensitive properties of the Adolescent Self-Harm Risk Scale (ASHRS), and benchmarking psychosocial profiles against a healthy local comparison group. Objectives are prespecified as exploratory or hypothesis-generating unless otherwise stated, reflecting the observational design and theory-led but non-interventional nature of the study.

Secondary objectives

- Characterize ideation–enactment pathways and proximal mechanisms

  - Examine how motivational constructs (e.g., hopelessness/entrapment, perceived burdensomeness, thwarted belongingness) relate to suicidal ideation severity and persistence, and how volitional factors (e.g., acquired capability, agitation/impulsivity, access to means, exposure/modeling) moderate the transition from ideation to self-harm during admission and at 6- and 18-month follow-up, consistent with ideation-to-action models [1,2].
  - Secondary outcomes: C-SSRS ideation severity/intensity; time to first self-harm event; in-hospital incident counts; post-discharge self-harm occurrence.
  - Nature: hypothesis-generating for phase-specific pathways; exploratory for moderation by volitional factors.

- Delineate functions and characteristics of NSSI as mechanistic correlates

  - Assess the association of NSSI functions (e.g., affect regulation, self-punishment, interpersonal influence), topography, and habituation with near-term self-harm recurrence and with indicators of acquired capability for suicidal behavior [3,4].
  - Secondary outcomes: ISAS function scales; B-NSSI-AT indices of frequency/topography; self-reported pain tolerance/fear of pain.
  - Nature: exploratory mediation analyses linking emotion dysregulation to NSSI and subsequent suicidal behaviors.

- Evaluate interpersonal and social-context moderators

  - Test whether social connectedness and perceived support buffer transitions from ideation to enactment, and whether interpersonal risk (low belongingness/high burdensomeness) exacerbates risk during inpatient care and early community re-entry [2,5].
  - Secondary outcomes: belongingness/burdensomeness indices; social support scales; inpatient observation levels/access restrictions as contextual moderators.
  - Nature: exploratory moderation analyses.

- Investigate developmental self-regulation and acute-state dynamics

- Explore age- and sex-related differences in socioemotional reactivity and cognitive control (dual-systems model) and their association with proximal fluctuations in risk states and incidents on the ward [6,7].
- Secondary outcomes: age-stratified analyses of ideation severity, incident timing, and short-term variability in agitation/affect.
- Nature: exploratory subgroup analyses.

- Assess ecological and setting-level influences

- Examine ward-level and setting factors (e.g., observation protocols, milieu characteristics) as ecological moderators of incident occurrence and trajectory of risk post-discharge, integrating a multi-level ecological perspective [7].
- Secondary outcomes: unit-level covariates linked to incident rates and time-to-event outcomes.
- Nature: exploratory multilevel modeling.

- Compare psychosocial and clinical profiles with a healthy local control group

- Benchmark distributions of key psychosocial constructs (e.g., emotion dysregulation, attachment, trauma symptoms, personality functioning) to differentiate trait-like liabilities from acute state effects in the inpatient cohort.
- Secondary outcomes: between-group differences at baseline; internal reference ranges for Slovene adolescents.
- Nature: descriptive and hypothesis-generating.

- Evaluate ASHRS measurement properties beyond primary predictive performance

- Test internal structure (factorial validity aligned with motivational, volitional, and protective domains), internal consistency, test–retest reliability across admission–discharge, and responsiveness to clinical change over admission and to status changes by 6 months, following contemporary measurement standards [1,8].
- Assess calibration across risk strata, subgroup invariance (sex, age, clinical vs control), and differential item functioning.
- Secondary outcomes: ASHRS scale/latent scores at admission, discharge, 6 months; model-based reliability; invariance indices.
- Nature: exploratory psychometric validation with prespecified structural hypotheses.

- Examine incremental and convergent validity of ASHRS

- Quantify ASHRS convergence with established measures (e.g., C-SSRS for suicidality; NSSI function indices) and its incremental association with near-term incidents beyond ideation severity and historical risk factors [3–6,9].
- Secondary outcomes: correlations and hierarchical models predicting in-hospital and post-discharge events.
- Nature: exploratory with prespecified expectation of moderate-to-strong convergence and incremental utility.

- Explore co-occurrence of heteroaggression and self-harm risk

- Describe patterns of co-occurring heteroaggressive incidents with self-harm during hospitalization and evaluate shared proximal risk states (e.g., agitation, dysregulation).
- Secondary outcomes: co-occurrence rates; temporal sequencing analyses of incident logs.
- Nature: descriptive and hypothesis-generating.

- Investigate additive and interactive contributions of genetic/epigenetic markers

- Explore whether selected genetic variants and DNA methylation profiles add predictive information to psychosocial/clinical models and whether gene–environment interplay informs motivational or volitional pathways, acknowledging current limits to standalone predictive utility [10,11].
- Secondary outcomes: integrated risk models with biological and psychosocial predictors; interaction terms with trauma or interpersonal indices.
- Nature: exploratory.

How these objectives complement the primary objective

These secondary objectives deepen mechanistic understanding of ideation-to-action processes, clarify contextual and developmental moderators relevant to inpatient and early post-discharge care,

and ensure the ASHRS is not only predictive but also structurally valid, reliable, responsive, and applicable across subgroups. By benchmarking against healthy controls and integrating biological data cautiously, the objectives collectively enhance interpretability, clinical utility, and transportability of findings within the Slovene adolescent inpatient setting and inform targeted, setting-appropriate risk assessment and management pathways [1–3,5,7–11].

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3.3 Exploratory objective(s)

Overview

The exploratory objectives extend the primary and secondary aims by probing emerging, context-sensitive, and mechanistic domains that may shape short- and medium-term self-harm risk among hospitalized adolescents in Slovenia. These hypothesis-generating analyses will identify candidate targets and subgroups for future intervention development and refine theory regarding ideation–enactment transitions, ecological influences, and heterogeneity in risk trajectories.

Exploratory objectives

- Sleep and circadian disturbances as proximal risk amplifiers

- Explore associations of sleep duration/quality, insomnia symptoms, and circadian irregularity during admission with near-term inpatient incidents and post-discharge self-harm, and assess whether sleep problems mediate or moderate links between affective dysregulation and enactment [1,2].
- Rationale: Sleep disturbance is a modifiable correlate of suicidal thoughts and behaviors and may index acute vulnerability in adolescents [2].

- Digital social context and cybervictimization

- Examine whether recent cyberbullying exposure, problematic social media use, or online contagion/modeling indicators are associated with incident occurrence and short-term recurrence, and whether social support buffers these associations [3].
- Rationale: Digital peer dynamics are salient in adolescence and linked to self-harm risk, but their

interaction with inpatient and early aftercare contexts is under-studied [3].

- Affective dynamics and momentary agitation

- Characterize affective lability and agitation captured via repeated brief state ratings/ward observations and test their temporal coupling with prevented or enacted inpatient self-harm, extending ideation-to-action models with dynamic states [1].
- Rationale: Real-time fluctuations in suicidal states predict near-term behavior beyond static factors [1].

- Volitional capacity indicators: pain perception and interoceptive signals

- Investigate whether self-reported pain tolerance, fear of pain, and interoceptive awareness relate to NSSI topography/habituation and to subsequent suicidal self-injurious behavior, above ideation severity [4,5].
- Rationale: Components of acquired capability (e.g., pain tolerance) are theorized to facilitate enactment but remain insufficiently tested in inpatient youth [4,5].

- Family climate and expressed emotion during transition of care

- Evaluate whether indices of family functioning and perceived criticism/overinvolvement moderate the association between discharge risk states and early post-discharge self-harm [6,7].
- Rationale: Family expressed emotion influences relapse and may shape acute transition risk after psychiatric discharge [6,7].

- Dual-harm phenotype (self-harm co-occurring with heteroaggression)

- Describe patterns and temporal sequencing of co-occurring self-harm and heteroaggressive incidents on the ward and their relation to short-term outcomes post-discharge [8].
- Rationale: Individuals who both self-harm and harm others may constitute a distinct high-intensity subgroup requiring tailored management [8].

- Ecological and ward-level moderators

- Explore unit-level characteristics (e.g., observation protocols, milieu indicators) as moderators of incident rates and time-to-event outcomes using multilevel models [7].
- Rationale: Ecological context shapes behavior; identifying modifiable setting factors can inform service-level quality improvement [7].

- Data-driven phenotypes and trajectories

- Use unsupervised clustering and trajectory analyses to derive psychosocial–clinical phenotypes and short-term risk trajectories, and compare their prognostic value to theory-led models [9].
- Rationale: Heterogeneous pathways may be better captured by data-driven groupings, informing personalized risk stratification and future adaptive interventions [9].

- Cross-domain integration with biological markers (hypothesis-generating)

- Explore whether selected genetic variants and DNA methylation profiles add incremental, cross-validated information to psychosocial models or interact with trauma/interpersonal risks to shape short-term enactment, acknowledging limited standalone predictive value [9].
- Rationale: Multidomain integration may yield small but meaningful gains in risk characterization suitable for future validation [9].

Anticipated contribution

Findings will identify modifiable, context-relevant risk processes (e.g., sleep, digital stressors, family climate) and delineate subgroups (e.g., dual-harm, data-driven phenotypes) that could guide targeted, developmentally sensitive interventions and aftercare strategies in Slovene inpatient youth services. Results will inform refinement of ideation–enactment theories with dynamic state and ecological components, support prioritization of setting-level quality improvements, and specify candidate measures and timing for future mechanistic trials or just-in-time adaptive interventions [1–3,7–9].

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3.4 Outcomes and indicators

Outcome framework and alignment with objectives

Outcomes are organized across four domains—behavioral, person-centred psychosocial, utilization/ecological, and socio-demographic—to reflect the study's primary aim (occurrence and timing of self-harm) and secondary aims (mechanisms, moderators, and predictive validity of the Adolescent Self-Harm Risk Scale [ASHRS]). Primary outcomes pertain to self-harm enactment during hospitalization and within 6- and 18-month windows post-discharge. Secondary and exploratory outcomes characterize ideation–enactment pathways, NSSI functions and characteristics, interpersonal/contextual moderators, heteroaggression co-occurrence, and ASHRS validity and responsiveness. Outcomes and indicators are prespecified following SPIRIT-aligned principles for clarity and interpretability in a non-interventional, longitudinal behavioral study [1].

Primary outcomes (behavioral domain)

- Self-harm enactment (primary behavioral outcome)

- Definition: Any enacted or prevented self-harm event (suicidal or non-suicidal) during hospitalization and any self-harm event reported or clinically ascertained at 6 and 18 months post-discharge, harmonized across suicidal and non-suicidal behaviors.
- Indicators:
  - Time-to-first self-harm event (inpatient; 0–6 months; 6–18 months).
  - Count/frequency of incidents per interval.
  - Event typology (suicidal behavior per Columbia–Suicide Severity Rating Scale [C-SSRS] classifications; NSSI features per Brief Non-Suicidal Self-Injury Assessment Tool [B-NSSI-AT] and Inventory of Statements About Self-Injury [ISAS]) [2–4].
- Data sources: Ward incident logs and clinical documentation (inpatient), standardized assessments and participant report (follow-up) using the C-SSRS for suicidal behavior and ideation, and B-NSSI-AT/ISAS for NSSI characteristics [2–4].
- Objective linkage: Directly addresses the primary objective to model occurrence, timing, and recurrence of self-harm and to benchmark predictive validity of ASHRS against near-term outcomes [5–7].

- ASHRS predictive performance for near-term and medium-term self-harm

- Indicators: Discrimination (e.g., area under the ROC curve), calibration indices, and classification metrics (e.g., sensitivity/specificity, decision-analytic summaries) for inpatient and early post-discharge horizons; incremental utility beyond established measures (e.g., C-SSRS ideation severity/history) [2,6].

- Data sources: ASHRS scores at admission and discharge; self-harm outcomes as above.
- Objective linkage: Core to scale development/validation and to improving near-term risk identification in high-risk adolescents [6,7].

Secondary outcomes and indicators

- Behavioral outcomes

- Suicidal ideation severity/intensity (C-SSRS ideation scales) and persistence/remission across timepoints [2].
- NSSI characteristics and functions (B-NSSI-AT indices of form, frequency, recency; ISAS function scales including affect regulation, self-punishment, interpersonal influence) [3,4].
- Indicators of volitional capacity/acquired capability (e.g., self-reported pain tolerance/fear of pain; NSSI habituation patterns) [8].
- Objective linkage: Tests ideation–enactment pathways and NSSI-related mechanisms hypothesized in ideation-to-action models [5].

- Person-centred psychosocial outcomes

- Interpersonal constructs: perceived burdensomeness and thwarted belongingness; perceived social support [9].
- Self-regulation and emotional functioning: emotion dysregulation/affective lability; agitation markers consistent with acute-state models [5].
- Attachment/relationship indicators; trauma-related symptoms; personality functioning/borderline features; coping-related factors.
- Objective linkage: Evaluates interpersonal and developmental moderators and potential mediators of enactment risk.

- Utilization/ecological and safety-related indicators

- Inpatient contextual indicators: observation levels, access restrictions, and milieu characteristics as ecological moderators of incident rates.
- Heteroaggressive incidents on the ward and their temporal co-occurrence with self-harm (co-primary safety context indicator).
- Objective linkage: Supports multilevel modeling of setting effects and characterization of a dual-harm phenotype.

- ASHRS measurement properties (psychometrics; secondary/exploratory)

- Internal structure (factorial validity aligned with motivational, volitional, and protective domains), internal consistency, test–retest reliability (admission–discharge), measurement invariance (sex, age, clinical vs control), responsiveness to status change, and calibration across risk strata, following COSMIN guidance [10].
- Convergent and incremental validity relative to C-SSRS and NSSI measures; associations with inpatient and post-discharge incidents [2–4,6,10].
- Objective linkage: Ensures the scale is structurally valid, reliable, and clinically useful beyond established tools.

- Biological indicators (exploratory, hypothesis-generating)

- Selected genetic variants and DNA methylation profiles from blood-derived DNA as candidate predictors or moderators when integrated with psychosocial/clinical models; evaluated cautiously given limited standalone predictive value [11,12].
- Objective linkage: Explores additive and interactive contributions to risk models without positioning biomarkers as primary outcomes.

Socio-demographic indicators (descriptive, covariates)

- Age, sex, schooling status/educational setting, family composition/relationships, and prior self-harm or suicide attempt history (ascertained at baseline).
- Role: Characterize the cohort, enable subgroup and effect-modification analyses, and support risk adjustment.

Timing and analysis populations

- High-risk inpatient cohort: Outcomes assessed during hospitalization and at 6 and 18 months; primary analyses use time-to-event and count indicators in the full enrolled clinical cohort, with sensitivity analyses by age and sex strata.
- Healthy control cohort: Baseline-only psychosocial and ASHRS-related indicators for benchmarking distributions and assessing measurement invariance; no longitudinal self-harm outcomes are collected from controls.
- Rationale for timing: Aligns with evidence that post-discharge risk is acutely elevated and that risk scales have limited discrimination unless validated against near-term behavioral outcomes [6,7].

Summary table of outcomes and indicators

Domain	Outcome/indicator	Role	Source/measurement approach	Timing
Behavioral	Self-harm enactment: time-to-first event and incident counts (suicidal and NSSI)	Primary	Ward incident logs/clinical documentation; C-SSRS event classification; B-NSSI-AT/ISAS for NSSI features [2–4]	Inpatient; 0–6 months; 6–18 months
Behavioral	ASHRS predictive performance (discrimination, calibration, incremental utility)	Primary	ASHRS scores; self-harm outcomes; comparative models with C-SSRS/history [2,6]	Admission/discharge predicting inpatient and post-discharge horizons
Behavioral	Suicidal ideation severity/intensity/persistence	Secondary	C-SSRS ideation scales [2]	All timepoints (clinical cohort); baseline only (controls)
Behavioral	NSSI functions and characteristics	Secondary	B-NSSI-AT indices; ISAS function scales [3,4]	All timepoints (clinical cohort); baseline only (controls)
Person-centred psychosocial	Belongingness/burdensomeness; social support; emotion dysregulation/affective lability; agitation indicators	Secondary/exploratory	Standardized self-report/clinician-rated scales consistent with theoretical framework [5,9]	All timepoints (clinical cohort); baseline only (controls)
Utilization/ecological and safety	Observation levels, access restrictions, milieu indicators; heteroaggression incidents and co-occurrence with self-harm	Secondary/exploratory	Ward records/incident logs; unit-level contextual data	Inpatient; summaries linked to follow-up outcomes
Psychometric (ASHRS)	Internal structure, reliability, invariance, responsiveness, calibration	Secondary/exploratory	Psychometric analyses per COSMIN [10]	Admission, discharge, 6 months (clinical);

				baseline (controls)
Biological	Genetic variants and DNA methylation profiles (integrated predictors/moderators)	Exploratory	Blood-derived DNA assays; integrated with psychosocial models [11,12]	Baseline with follow-up linkage (clinical cohort)
Socio-demographic	Age, sex, schooling, family indicators; prior self-harm attempt history	Descriptive/covariates	Baseline questionnaires/clinical history	Baseline (all); history updated at follow-up (clinical)

Indicator definitions and handling

- Event definitions and harmonization: Suicidal behaviors and ideation are classified per C-SSRS conventions; NSSI forms, functions, and habituation are indexed via B-NSSI-AT and ISAS to ensure consistent ascertainment across behavioral phenotypes [2–4].
- Composite and derived indicators: Near-term risk composites from ASHRS are examined alongside single-domain indicators; prognostic performance is summarized using discrimination and calibration metrics, as recommended for prediction research in mental health [6].
- Minimal sufficient sets: For multivariable models, socio-demographic covariates and salient clinical history (e.g., prior attempts) are retained to minimize confounding while preserving parsimony, consistent with observational study principles.
- Participant-centred indicators: Changes in interpersonal connectedness and emotion regulation are tracked to contextualize behavioral outcomes and to identify potential targets for future intervention development.

Relationship to study objectives

- Primary objective: Captured by self-harm enactment outcomes and ASHRS predictive performance against inpatient and early post-discharge horizons.
- Secondary objectives: Addressed through ideation severity/persistence, NSSI functions/characteristics, interpersonal and developmental moderators, ecological indicators, and ASHRS psychometrics.
- Exploratory objectives: Informed by acute-state dynamics (e.g., agitation/affective lability), dual-harm co-occurrence, and integrative biological indicators, recognizing current evidence limitations for standalone biological prediction [11,12].

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4 STUDY DESIGN

4.1 Design type and justification

Overall design

This is a prospective, longitudinal observational cohort study with a concurrent healthy comparison group. Approximately 200 adolescents hospitalized for recent suicidal behavior or nonsuicidal self-injury (NSSI) are enrolled and assessed at admission, repeatedly during hospitalization for incident monitoring, and re-assessed at 6 and 18 months post-discharge. An approximately equal number of healthy adolescents are enrolled for baseline-only assessment to provide normative benchmarks for psychosocial constructs and to support measurement invariance testing. No experimental behavioral intervention is delivered; all clinical participants receive usual inpatient care. The protocol includes a scale development and validation component for the Adolescent Self-Harm Risk Scale (ASHRS), evaluated for structure, reliability, responsiveness, and predictive performance against prespecified near-term outcomes, following COSMIN and TRIPOD-aligned principles for measurement and prognostic research in mental health [1–4].

Rationale for an observational longitudinal approach

A prospective cohort design is appropriate because the primary behavioral focus—self-harm enactment in a high-risk inpatient population—cannot be ethically randomized, and near-term risk must be characterized under usual-care conditions. Longitudinal follow-up across inpatient, 6-, and 18-month horizons captures the acutely elevated post-discharge risk window and medium-term recurrence, enabling time-to-event and recurrence modeling aligned with ideation-to-action theories that distinguish predictors of ideation from predictors of enactment [5–7]. The inclusion of a healthy comparison group at baseline improves interpretability of psychosocial profiles (trait-like versus state-related features) and supports psychometric evaluations (e.g., subgroup invariance), without imposing unnecessary longitudinal burden on nonclinical youth.

Alignment with objectives

- Primary objectives: The design permits prospective ascertainment of incident self-harm during hospitalization and systematic outcome assessment post-discharge, enabling multivariable and time-to-event models to identify independent correlates of occurrence, timing, and recurrence. Repeated ASHRS administration (admission, discharge, 6 months) allows

estimation of discrimination, calibration, responsiveness, and incremental utility over established measures (e.g., C-SSRS), in line with TRIPOD guidance for prognostic tools [3,8].

- Secondary objectives: Standardized, theory-guided psychosocial measures (e.g., ISAS for NSSI functions; interpersonal and regulation constructs) and unit-level contextual indicators allow testing of motivational and volitional pathways, developmental moderators, and ecological effects using multilevel and moderation analyses [6,9]. The healthy control cohort provides normative distributions and supports measurement invariance and construct validity evaluations per COSMIN standards [1,2].

Principal strengths

- Validity and interpretability

- Prospective event capture via ward incident logs during hospitalization reduces recall bias and ensures temporal ordering between predictors and outcomes [5].
- Harmonized, validated instruments for suicidality (C-SSRS) and NSSI (ISAS, brief NSSI assessment) enhance construct validity and cross-phenotype comparability [8,9].
- Pre-specification of outcomes, predictors, and analyses, applying STROBE and SPIRIT principles by analogy, strengthens transparency and reduces selective reporting [1,10].
- TRIPOD-consistent development and internal validation of ASHRS supports clinically interpretable prognostic estimates, including calibration and net classification performance [3,11].

- Feasibility and ecological relevance

- Embedding procedures in routine inpatient workflows at a national referral center facilitates recruitment, high-fidelity incident monitoring, and clinically actionable insights.
- A baseline-only healthy cohort balances the need for benchmarks with ethical proportionality and feasibility in nonclinical youth.

Limitations and mitigation strategies

- Confounding and selection bias: As a nonrandomized study in a single-country tertiary setting, residual confounding and limited external generalizability are possible. Mitigation includes careful conceptual modeling, retention of minimal sufficient covariate sets, stratified and sensitivity analyses (e.g., by age/sex), and transparent reporting per STROBE/TRIPOD [1,3].
- Outcome misclassification: Distinguishing suicidal behavior from NSSI can be challenging. Harmonized definitions and rater training using the C-SSRS, alongside triangulation with incident logs and clinical documentation, aim to minimize misclassification [8].
- Attrition and missing data: Differential loss to follow-up may bias longitudinal estimates. Retention procedures and multiple imputation using chained equations will be employed, with sensitivity analyses under plausible missingness mechanisms [12].
- Overfitting in prediction models: Optimism in ASHRS predictive estimates is addressed through internal validation (bootstrap resampling or cross-validation), shrinkage where appropriate, and reporting of calibration slopes/intercepts consistent with best practice in prediction modeling [3,11].
- Multiple testing and exploratory analyses: The breadth of secondary/exploratory aims raises false-positive risk. Findings beyond the primary outcomes will be framed as hypothesis-generating, with parsimonious modeling, correction for multiplicity where relevant, and emphasis on effect sizes and uncertainty.
- Biological markers: Genetic/epigenetic analyses are exploratory and may have limited standalone prognostic value; integration will be conservative, focusing on incremental contribution beyond psychosocial/clinical models and avoiding overinterpretation [13].

Procedural safeguards

- Standardized training and manuals for assessment teams; periodic inter-rater checks for event classification.

- Prospective data capture with time-stamping of assessments relative to incidents and discharge; audit trails for data edits.
- A priori analysis plans with documented deviations; code-reviewed statistical scripts and internal replication.
- Data protection aligned with GDPR; proportionate consent/assent processes for a vulnerable population.

Collectively, the observational longitudinal design with a healthy comparison cohort, integrated psychometric development, and rigorous analytic safeguards is well suited to characterize near-term and medium-term self-harm risk in hospitalized adolescents, advance theory-informed mechanistic understanding, and produce a practically deployable, validated risk assessment tool for inpatient and early aftercare settings.

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4.2 Setting and context

Clinical setting

The study is embedded within the Centre for Mental Health, University Psychiatric Clinic Ljubljana (UPKL), a national tertiary referral hospital serving the full Slovene adolescent population. Clinical participants are recruited on admission to two inpatient services: the Intensive Child and Adolescent Psychiatry Unit and the Unit for Adolescent Psychiatry. Both units operate 24/7 with multidisciplinary teams (child and adolescent psychiatrists, psychologists, nurses, occupational therapists, and social

workers) and provide acute assessment, stabilization, and discharge planning for adolescents presenting with recent suicidal behavior or nonsuicidal self-injury (NSSI). Ward environments include structured daily routines, supervised activities, and standardized safety procedures (e.g., observation protocols, access restrictions to potential means, and environmental risk mitigation). Routine clinical documentation and incident reporting systems enable prospective capture of self-harm and heteroaggressive events during admission.

Recruitment and assessment context

- High-risk cohort (clinical): Potentially eligible adolescents (aged 13–19 years) are identified at the point of emergency or scheduled admission and screened for recent suicidal ideation/behavior (via C-SSRS) or NSSI (via B-NSSI-AT). Baseline research assessments are integrated with usual clinical intakes to minimize disruption, with subsequent monitoring of incidents throughout hospitalization and standardized follow-up assessments at 6 and 18 months post-discharge. Discharge planning typically coordinates with community child and adolescent mental health services, primary care, and school counselors, supporting continuity of care across settings.
- Healthy comparison cohort: Controls (aged 13–19 years) are recruited through routine school-based systematic examinations in primary, secondary, and tertiary educational settings across Slovenia. Baseline-only assessments are conducted in school-affiliated health settings or designated research spaces, coordinated with school health services to minimize burden and ensure privacy.

Geographical and organizational context

UPKL is located in Ljubljana and functions as Slovenia's principal center for child and adolescent psychiatric inpatient care. The hospital draws from urban and rural catchment areas nationwide; transport and family involvement are facilitated through centralized referral networks. School calendars, exam periods, and regional holidays are considered when scheduling follow-ups to reduce attrition. Research instruments are administered in Slovene using validated or culturally adapted versions, and study staff are trained in adolescent-sensitive, trauma-informed approaches appropriate for a linguistically and culturally homogeneous but socioeconomically diverse national population.

Socio-cultural and environmental considerations

The study population comprises adolescents navigating developmental transitions common in Slovenia's educational pathways (end of primary school around ages 14–15; progression to diverse secondary tracks and early tertiary enrollment). Peer dynamics, digital social environments, and family structures (including multigenerational households and commuting students) are considered when interpreting interpersonal and stress-related measures. Ward milieu characteristics (e.g., patient mix, staffing levels, and observation practices) may influence proximal risk states during admission, while family climate and school reintegration processes may shape early post-discharge trajectories. These contextual features are captured through unit-level indicators, family functioning indices, and school-related items to support multilevel analyses.

Policy, legal, and data governance context

The study operates under Slovenian ethical and legal requirements for research with minors and vulnerable populations, with parental consent and adolescent assent procedures tailored to age and capacity. Clinical care remains entirely under usual practice; the study does not alter treatment pathways. Data protection follows EU General Data Protection Regulation (GDPR) requirements, with identifiable data minimized, role-based access controls, and physical data storage located within the Republic of Slovenia. Biological sampling (venous blood for genetic/epigenetic analyses) is obtained in clinical settings by trained personnel under biosafety procedures, with separate consent and clear options for refusal without impact on care. Linkage of research assessments with clinical incident logs and follow-up contacts is governed by secure data flows and audit trails.

Implications of setting for the behavioral focus

- Inpatient phase: The controlled environment, structured routines, and active observation enable high-fidelity, prospective ascertainment of self-harm events and near-miss/blocked incidents, and facilitate evaluation of setting-level moderators (e.g., observation levels, access restrictions) on ideation–enactment transitions.
- Transition to community: Discharge into family and school environments introduces variability in interpersonal supports, stressors, and service access that may affect short- and medium-term risk; these are incorporated through standardized psychosocial measures and service-use summaries.
- Control context: Recruitment via school health services provides local normative benchmarks and supports measurement invariance testing while avoiding longitudinal burden in nonclinical youth.

Collectively, the Slovene tertiary inpatient setting, national catchment, and school-based recruitment for controls offer a coherent platform to study self-harm behavior across acute hospitalization and community re-entry, while the organizational, legal, and cultural features of Slovenia inform both study conduct and interpretation of findings.

4.3 Duration: study and per-participant timelines

Overall study duration

The study will run from site activation through completion of the 18-month follow-up for the last enrolled clinical participant. Recruitment will proceed continuously until target sample sizes are achieved. The per-participant observation window differs by cohort: clinical participants are followed from admission through 18 months post-discharge, whereas healthy controls complete a single baseline assessment only. This structure aligns with ethical proportionality in nonclinical youth and with evidence that suicide risk is acutely elevated after discharge, warranting near-term and medium-term follow-up in the high-risk cohort [1,2].

Per-participant timelines

- Clinical cohort (inpatients aged 13–19 years)

- Enrolment and baseline (admission; T0): consent/assent, eligibility confirmation, baseline psychosocial/clinical assessment, ASHRS administration, and optional blood draw for genetic/epigenetic analyses.
- Inpatient monitoring (continuous): prospective recording of self-harm and heteroaggressive incidents via routine ward systems; brief state ratings/observations as specified in the protocol.
- Discharge assessment (T1): repeat psychosocial/clinical assessment and ASHRS to index short-interval change and enable responsiveness/reliability estimation per COSMIN guidance [3].
- Post-discharge follow-up (T2 and T3): standardized assessments at 6 months (T2; target window ±4 weeks) and 18 months (T3; target window ±8 weeks) to ascertain self-harm outcomes, ideation, NSSI characteristics, psychosocial constructs, and service-use/contextual updates. Modes may be in-person or secure remote to minimize attrition while preserving data quality, consistent with SPIRIT-aligned scheduling practices [1].
- End of participation: after completion of the 18-month assessment or formal withdrawal.

- Healthy control cohort (students aged 13–19 years)

- Enrolment and baseline (C0): consent/assent, eligibility confirmation, and single-session psychosocial/clinical assessment, including ASHRS for normative benchmarking and measurement invariance; no longitudinal self-harm outcomes are collected from controls to reduce burden and risk in a nonclinical population [2,3].

Anticipated sequence and windows

Phase	Clinical cohort: timing and assessments	Healthy controls: timing and assessments	Rationale/notes
Screening and consent	Pre-admission/admission; eligibility, consent/assent	At school-based enrolment; eligibility, consent/assent	Age- and capacity-appropriate consent per national regulations; minimize delay to usual care
Baseline (T0)	Admission day or within 72 h; C-SSRS, B-NSSI-AT/ISAS, psychosocial battery, ASHRS; optional blood draw	Single baseline session; psychosocial battery and ASHRS	Establish prespecified predictors and benchmarks; capture pre-treatment inpatient status [1,3]
Inpatient monitoring	Continuous until discharge; prospective incident capture from ward logs and clinical notes	Not applicable	High-fidelity ascertainment of inpatient self-harm and co-occurring events [2]
Discharge (T1)	Within 72 h before discharge; repeat core assessments and ASHRS	Not applicable	Estimate short-interval change and test ASHRS responsiveness/retest properties [3]
Follow-up 6 months (T2)	6 months post-discharge (±4 weeks); self-harm outcomes (C-SSRS-based), NSSI characteristics, psychosocial updates, ASHRS	Not applicable	Captures the high-risk early community period after discharge [2]
Follow-up 18 months (T3)	18 months post-discharge (±8 weeks); same domains as T2	Not applicable	Indexes medium-term recurrence and trajectory stabilization [1,2]
Study completion	After T3 or withdrawal	After baseline session	End of observation for participant

Variability in duration and visit windows

- Length of stay varies according to clinical need; inpatient monitoring continues throughout each admission and ends at discharge. The admission–discharge interval serves as the retest window for ASHRS reliability and responsiveness analyses, without imposing a fixed duration [3].
- Follow-up visit windows (±4 weeks at 6 months; ±8 weeks at 18 months) balance retention feasibility with temporal precision for time-to-event analyses and align with SPIRIT-aligned scheduling recommendations for longitudinal behavioral research [1].
- Participants readmitted during follow-up remain in the cohort; all self-harm events are time-stamped and analyzed using prespecified survival and recurrence models, reported per STROBE principles for observational studies [2].

Justification for cohort-specific timelines

- Clinical cohort: Extended observation from admission through 18 months post-discharge is necessary to model near-term enactment and medium-term recurrence and to evaluate ASHRS predictive performance against clinically meaningful horizons where risk is concentrated [1,2].
- Healthy controls: Baseline-only participation provides normative distributions and supports measurement invariance while minimizing burden and safeguarding nonclinical adolescents, consistent with best practice for instrument validation and ethical proportionality [3].

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4.4 Schedule of activities (SoA)

Narrative description

This Schedule of Activities (SoA) specifies all participant-facing and data collection procedures from first contact through study completion, organized to align with the study's primary and secondary objectives and prespecified outcome domains. Activities are structured to ensure standardized ascertainment of self-harm behaviors and associated psychosocial constructs in a high-risk inpatient adolescent cohort, with baseline-only benchmarking in a healthy comparison cohort. Timing, visit windows, and modes of contact reflect SPIRIT-aligned scheduling principles, observational reporting standards (STROBE), and measurement best practice for repeated administration of psychosocial instruments [1,5,6].

Screening and initial contact

- Setting: Clinical units at the University Psychiatric Clinic Ljubljana (UPKL) for the inpatient cohort; school-affiliated health settings for healthy controls.
- Procedures (clinical cohort): Triage by the admitting clinical team; research eligibility screen confirms age (13–19 years), current admission to the Intensive Child and Adolescent Psychiatry Unit or Unit for Adolescent Psychiatry, and recent suicidal ideation/behavior or nonsuicidal self-injury (NSSI) indicated by the Columbia–Suicide Severity Rating Scale (C-SSRS) or the Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) [2,3]. Exclusion criteria (e.g., acute psychosis, intellectual disability, severe CNS/medical illness, acute poisoning) are verified from clinical records.
- Procedures (healthy controls): Eligibility screen during routine school examinations confirms age and absence of current psychiatric hospitalization; no longitudinal follow-up is planned.

Informed consent/assent

- Age-appropriate information is provided to adolescents and parents/guardians; parental consent is obtained where required by national regulations. Consent covers behavioral/psychosocial assessments, linkage with clinical documentation and incident logs, optional venous blood draw for genetic/epigenetic analyses, and recontact for follow-up (clinical cohort). Procedures follow SPIRIT guidance on consent documentation and participant information [1].

Baseline assessment (T0; admission, within 72 hours)

- Objectives linkage: Establishes predictor sets and baseline distributions for behavioral, psychosocial, and socio-demographic indicators; administers the Adolescent Self-Harm Risk Scale (ASHRS) for predictive modeling and psychometric evaluation.
- Clinical cohort activities:

- Core behavioral assessments: C-SSRS (ideation and behavior classification) and NSSI characterization using B-NSSI-AT and the Inventory of Statements About Self-Injury (ISAS) [2–4].
- Psychosocial and contextual battery: standardized self-report and/or clinician-rated measures indexing interpersonal constructs (e.g., belongingness/burdensomeness, social support), self-regulation/emotion dysregulation, trauma-related symptoms, attachment/relationship indicators, personality functioning/borderline features, coping-related factors, and substance use.
- Socio-demographics and history: age, sex, schooling/educational setting, family composition/relationships, prior self-harm/attempt history, and recent service use.
- ASHRS administration: admission score captured for predictive and structural validity analyses.

- Optional biological sampling: venous blood for candidate genetic variants and DNA methylation profiling (with separate consent).

- Healthy controls (C0; single session): ASHRS, C-SSRS ideation screen, B-NSSI-AT/ISAS for lifetime/recency characterization if applicable, and the psychosocial battery to provide normative benchmarks and support measurement invariance; no biological sampling is required for controls.

Inpatient monitoring (continuous until discharge)

- Objectives linkage: Prospective, high-fidelity capture of primary behavioral outcomes and safety context indicators; supports modeling of ideation–enactment transitions.
- Activities:

- Incident surveillance: daily extraction and verification of self-harm and heteroaggressive incidents from ward incident logs and clinical documentation, with C-SSRS-based event classification and NSSI descriptors harmonized across tools [2–4].
- Ward milieu/context indicators: observation levels, access restrictions, staffing/milieu notes abstracted at predefined intervals.
- Brief state ratings: selected acute-state indicators (e.g., agitation/affective lability) recorded using brief standardized items embedded in routine checks.
- Risk management: any acute risk identified during research contacts is escalated immediately to the clinical team for assessment and management per unit protocols.

Discharge assessment (T1; within 72 hours prior to discharge)

- Objectives linkage: Indexes short-interval change, supports ASHRS test–retest reliability and responsiveness (admission–discharge), and refines near-term prognostic estimates per TRIPOD-aligned practices [6,8].
- Activities (clinical cohort only):

- Repeat core assessments: C-SSRS for ideation/behavior since admission; updated NSSI characteristics (B-NSSI-AT, ISAS).
- Psychosocial updates: interpersonal, self-regulation, and contextual measures to capture proximal shifts during admission.
- ASHRS re-administration.
- Discharge context: aftercare plan summary, scheduled community contacts, and family/school reintegration notes.

Post-discharge follow-up 6 months (T2; target ±4 weeks)

- Objectives linkage: Captures the period of highest post-discharge risk; ascertains primary outcomes (time-to-first self-harm; incident counts) and secondary psychosocial changes; updates predictors; evaluates ASHRS medium-horizon performance [2,7,8].
- Activities (clinical cohort only; in-person or secure remote):

- Outcome ascertainment: self-harm events since discharge via structured C-SSRS interview and corroboration where feasible; NSSI frequency, form, function, and context via B-NSSI-AT and ISAS [2–4].
- Psychosocial/context updates: interpersonal supports, emotion regulation, trauma symptoms, personality functioning indices, school/family context, and service use since discharge.
- ASHRS re-administration to evaluate calibration/discrimination over the early community horizon.

Post-discharge follow-up 18 months (T3; target ±8 weeks)

- Objectives linkage: Assesses medium-term recurrence and trajectory stabilization; consolidates predictors and moderators over extended follow-up [5,7].
- Activities (clinical cohort only; in-person or secure remote):

- Outcome ascertainment: C-SSRS-based events and NSSI updates (B-NSSI-AT/ISAS) since T2 [2–4].
- Psychosocial/context updates and service use.
- ASHRS is not routinely administered at T3 to limit burden and align with the prespecified psychometric retest window (admission–discharge–6 months) [6].

Healthy comparison cohort completion

- Participation ends after C0. No incident monitoring or follow-up is conducted to preserve ethical proportionality in nonclinical youth and focus longitudinal resources on the high-risk clinical cohort [5,6].

Retention, contact scheduling, and visit windows

- Contact cadence: confirmation of preferred contact methods at T1, reminder touchpoints at months 3–4 and 12–13, and appointment scheduling within the T2/T3 windows.
- Windows: ±4 weeks at 6 months and ±8 weeks at 18 months balance feasibility with temporal precision for time-to-event analyses and SPIRIT-consistent scheduling [1,7].
- Mode: in-person is preferred; secure videoconference or telephone with electronic data capture is available to minimize attrition while preserving data quality.

Data sources and quality assurance

- Primary data sources: standardized assessments (C-SSRS; B-NSSI-AT; ISAS; ASHRS), ward incident logs, clinical documentation, and participant-reported psychosocial measures [2–4].
- Data quality: rater training and periodic inter-rater checks for event classification; time-stamped entries; predefined case report forms; audit trails for edits; COSMIN-consistent administration rules for repeated PRO measures [6].

Risk management during research contacts

- Any endorsement of imminent risk triggers immediate handover to the on-duty clinical team. Research contacts are paused as needed and may be rescheduled after clinical stabilization. Participation does not alter usual care.

Structured schedule-of-activities table

Study stage/assessment point	Target window	Clinical cohort: key activities and measures	Data sources	Healthy controls: key activities
Screening and approach	Admission day (clinical); school exam day (controls)	Eligibility review; brief C-SSRS/NSSI screen; exclusion check; introduce study	Clinical intake notes; brief screen	Eligibility review; introduce study
Informed consent/assent	Same day as screening or within 24–48 h	Obtain consent/assent (research + optional blood draw + recontact)	Signed consent/assent; consent log	Obtain consent/assent (baseline-only)
Baseline T0 (clinical) / C0 (controls)	Within 72 h of admission (T0); single session (C0)	C-SSRS (ideation/behavior); B-NSSI-AT; ISAS; psychosocial battery; socio-demographics and history; ASHRS; optional venous blood draw	Participant report; clinician-rated items; medical record abstraction; lab requisition	ASHRS; C-SSRS ideation screen; B-NSSI-AT/ISAS if applicable; psychosocial battery; socio-demographics
Inpatient monitoring	Continuous until discharge	Daily/incident-based capture of self-harm and heteroaggression; unit-level context (observation levels, access restrictions); brief state ratings; risk escalation as needed	Ward incident logs; clinical documentation; predefined abstraction forms	Not applicable
Discharge assessment T1	Within 72 h pre-discharge	C-SSRS since admission; B-NSSI-AT/ISAS updates; psychosocial updates; ASHRS; aftercare plan summary	Participant report; clinician-rated items; discharge summary	Not applicable
Follow-up 6 months T2	6 months post-	C-SSRS self-harm outcomes since discharge; B-NSSI-AT/ISAS;	Participant report; collateral	Not applicable

	discharge ±4 weeks	psychosocial/context updates; service use; ASHRS	verification where feasible	
Follow-up 18 months T3	18 months post-discharge ±8 weeks	C-SSRS outcomes since T2; B-NSSI-AT/ISAS; psychosocial/context updates; service use	Participant report; collateral verification where feasible	Not applicable
Study completion	After T3 or withdrawal	End-of-participation confirmation; contact update for dissemination	Study records	After C0 session

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4.5 Randomization and blinding

Allocation approach

- No random allocation is used. Cohort membership is determined by naturalistic clinical status at enrolment (hospitalized adolescents with recent suicidal behavior or nonsuicidal self-injury versus healthy adolescents recruited through routine school examinations). This design is dictated by ethical and feasibility constraints inherent to studying acute self-harm risk and aligns with STROBE guidance for transparent conduct of observational research [1].
- Within the inpatient cohort, a consecutive-approach strategy is used, inviting all eligible admissions to minimize selection bias. Healthy controls are enrolled via school-based examinations under predefined inclusion/exclusion criteria to provide normative benchmarks without altering usual educational or clinical pathways.
- Because there is no randomized assignment or experimental intervention, allocation concealment procedures (e.g., sealed envelopes, centralized randomization) do not apply.

Blinding and masking

- Participants and clinical staff cannot be blinded to cohort membership due to the nature of hospitalization and the absence of treatment randomization.
- Outcome assessment during hospitalization: self-harm incidents are abstracted from routine ward incident logs and clinical documentation by trained research staff using standardized, prespecified definitions and C-SSRS event classification to reduce observer bias [1,3]. Staff performing incident abstraction are masked to baseline ASHRS scores and other detailed psychosocial predictor data to the extent operationally feasible.
- Post-discharge outcome assessment: follow-up C-SSRS interviews are conducted by trained assessors who do not have access to prior ASHRS scores or risk strata when feasible. Raters receive standardized training and undergo periodic inter-rater checks to maintain classification fidelity [3].
- Data management and analysis: datasets provided to analysts are de-identified and minimize access to directly identifying information. Although group indicators are required for planned analyses, role-based access controls limit unnecessary visibility of individual-level predictor details during outcome coding, consistent with bias-minimization principles for nonrandomized studies [1,4].
- Feedback to treating teams: research questionnaire and ASHRS results are not systematically shared with clinical teams to avoid influencing usual care, except where immediate safety concerns arise; any disclosure in such cases follows predefined risk-escalation procedures.

Additional methods to minimize bias in the absence of randomization/blinding

- Prespecification of inclusion/exclusion criteria, outcomes, and analytic plans, with standardized administration manuals and SPIRIT-aligned documentation, supports transparency and reduces selective outcome reporting [2].
- Harmonized, validated instruments (e.g., C-SSRS for suicidal behavior) and protocolized event classification reduce misclassification bias [1,3].
- Periodic inter-rater reliability checks for event coding and audit trails for data edits sustain measurement consistency.
- Multivariable modeling with conceptually justified covariates, stratified/sensitivity analyses, and internal validation for prognostic modeling address confounding and analytic bias typical of nonrandomized designs, in line with STROBE/TRIPOD-informed best practices [1].

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5 POPULATION

5.1 Target population description

Overview

The target population comprises Slovene adolescents aged 13–19 years at two distinct risk strata: a high-risk clinical cohort of inpatients admitted for recent suicidal behavior or nonsuicidal self-injury (NSSI), and a healthy comparison cohort recruited through routine school-based examinations. This age range spans mid- to late adolescence, a developmental period characterized by rapid biological, cognitive, and social transitions, heightened sensitivity to interpersonal stressors, and increased incidence of self-harm thoughts and behaviors [1,2]. Focusing on this window maximizes the relevance of observed behavioral patterns and psychosocial correlates to current clinical need and policy priorities in youth mental health [1,2].

Clinical high-risk inpatient cohort

Adolescents are enrolled at admission to the Intensive Child and Adolescent Psychiatry Unit or the Unit for Adolescent Psychiatry, Centre for Mental Health, University Psychiatric Clinic Ljubljana. Typical presentations include recent suicide attempts, acute suicidal ideation with intent or planning, and/or NSSI of varying frequency, method, and function. Consistent with international evidence, common co-occurring conditions in this setting include depressive and anxiety disorders, trauma-related symptoms, emerging personality pathology (e.g., borderline features), substance use, and interpersonal/family conflict, all of which are pertinent to ideation–enactment processes and recurrence risk [3–6]. The inpatient milieu provides a controlled environment for high-fidelity, prospective ascertainment of self-harm events and near-miss/blocked incidents during acute risk states, enabling fine-grained characterization of occurrence, frequency, method, medical severity, precipitants, and functions of self-harm [5,7].

Demographically, the clinical cohort is expected to reflect Slovenia's national adolescent population across urban and rural catchments, with variability in socioeconomic position, family structure (e.g., two-parent, single-parent, and multigenerational households), and schooling tracks. Sex and gender distributions are anticipated to show a higher proportion of females among NSSI and nonfatal suicidal behaviors, with important implications for interpreting functions (e.g., intrapersonal emotion regulation versus interpersonal influence), method choice, and help-seeking patterns; nonetheless, males require specific attention due to higher lethality when attempts occur [3,8,9]. These features inform prespecified subgroup and moderator analyses and support transportability of findings to routine inpatient care.

Healthy comparison cohort

Healthy controls are recruited from primary, secondary, and early tertiary educational settings during routine systematic examinations. They provide population-relevant distributions of psychosocial constructs (e.g., emotion regulation, belongingness, burdensomeness, social support), as well as baseline variation in ideation/NSSI exposure prevalent in community youth [5,10]. Baseline-only assessment minimizes burden and ethical risk in nonclinical adolescents while enabling measurement invariance testing and contextualization of clinical effect sizes for the Adolescent Self-Harm Risk Scale (ASHRS) and other instruments [11]. Controls are frequency-matched by age range (13–19 years) to the clinical cohort to reduce developmental confounding when benchmarking scores and structural properties of measures.

Socioeconomic and contextual characteristics

Both cohorts draw from a nationally centralized referral and school system, yielding a linguistically cohesive sample with socioeconomic diversity. Relevant contextual exposures include academic transitions and examination pressures; peer dynamics online and offline; commuting to school from rural regions; and varying access to community mental health and school counseling supports. Family functioning, attachment quality, exposure to interpersonal violence or neglect, and substance use environments are particularly salient contextual modifiers of self-harm risk, especially during the transition from inpatient care back to family and school settings [3,4,6]. These factors are captured with standardized indices to enable multilevel modeling of person-, family-, and unit-level influences on self-harm occurrence and recurrence.

Suitability for the behavioral focus

- Relevance to high-risk behavior: Inpatient adolescents shortly after suicidal acts or during active NSSI represent the peak-risk stratum for near-term repetition and escalation, aligning with the study's aim to model short- and medium-term self-harm risk and to evaluate ASHRS performance against clinically meaningful horizons [7].
- Breadth of behavioral phenomena: The target population exhibits a wide spectrum of self-harm ideation, NSSI forms/functions, and suicidal behaviors, supporting comprehensive assessment of occurrence, frequency, characteristics (method, medical severity), and functions via C-SSRS, B-NSSI-AT, and ISAS [5,12–14].
- Etiologic and prognostic heterogeneity: Co-occurring depression, anxiety, trauma exposure, emotion dysregulation, interpersonal stressors, and emerging personality features are prevalent and mechanistically linked to ideation–enactment processes, enhancing the feasibility of testing multivariable prognostic models and moderator pathways [3,4,6,15].
- Benchmarking and psychometrics: A school-based healthy cohort enables normative comparisons and invariance testing critical for scale development/validation, improving interpretability and potential clinical utility of ASHRS across risk strata [11].

Typical environments and settings

- Inpatient phase: Structured wards with observation protocols and environmental risk mitigation permit continuous event surveillance and standardized classification of self-harm and heteroaggression. Team-based care provides collateral information on precipitants, safety plans, and short-interval change.
- Community phase: Post-discharge environments include family homes, schools, and peer settings where supports and stressors fluctuate; this variability is central to understanding recurrence and trajectory stabilization in the months following hospitalization [7]. School health services and community mental health contacts are common touchpoints influencing service use and help-seeking behaviors.

Implications for feasibility and interpretability

- Feasibility: A national tertiary center and school health network support consecutive inpatient enrolment and pragmatic school-based recruitment, with Slovene-language instruments and culturally adapted administration procedures facilitating high completion rates.
- Interpretability: The combination of a high-risk inpatient cohort and a healthy school-based cohort enables disentangling clinical severity from developmental norms, quantifying gradients of risk/protective factors, and assessing whether instrument structure and scores generalize across settings [5,11–14].
- External validity: A nationwide catchment increases representativeness of clinical presentations and schooling contexts, while the homogeneous language context minimizes measurement error due to translation variance.

This description delineates the adolescent inpatient and school-based populations, their developmental and contextual features, and the rationale for their selection in relation to the behavioral focus on self-harm. The subsequent eligibility criteria operationalize this target population to ensure consistent, reproducible enrolment aligned with the study objectives and planned analyses.

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5.2 Eligibility criteria

Inclusion criteria

- Clinical high-risk inpatient cohort

- Age 13–19 years at the time of enrolment.
- Current admission to the Intensive Child and Adolescent Psychiatry Unit or the Unit for Adolescent Psychiatry, Centre for Mental Health, University Psychiatric Clinic Ljubljana.
- Evidence at admission of recent suicidal ideation/behavior or self-harm without suicidal intent, as indicated by a structured suicide/self-harm screen (e.g., C-SSRS for suicidal ideation/behaviors; B-NSSI-AT for NSSI) and/or corroborated by clinical records and team assessment [1,2].
- Sufficient Slovene language proficiency to provide informed consent/assent and complete study assessments, with or without reasonable accommodations.
- Ability and willingness to participate in study procedures during admission, and to provide contact details for post-discharge follow-up at 6 and 18 months (participant and/or parent/guardian).
- Informed consent from the participant (and parental/guardian consent for minors as required by national regulations), with age-appropriate assent for those lacking full legal capacity, consistent with international ethics guidance for research with minors [3].

- Healthy comparison cohort

- Age 13–19 years at the time of enrolment.
- Enrolled in and attending routine systematic school examinations in participating educational settings in Slovenia.
- No current psychiatric hospitalization and no acute safety concern (e.g., imminent suicidal intent) at screening; if acute risk is identified, the individual will be referred to appropriate services and not

enrolled.
- Sufficient Slovene language proficiency to provide informed consent/assent and complete baseline assessments.
- Informed consent from the participant (and parental/guardian consent for minors as required), with age-appropriate assent as applicable [3].

Exclusion criteria

- Clinical high-risk inpatient cohort

- Primary diagnosis or current presentation that precludes valid consent/assent or precludes participation in study procedures despite reasonable accommodations, including:
  - Acute psychosis with impaired capacity and/or behavioral dysregulation preventing assessment.
  - Moderate-to-severe intellectual disability that precludes meaningful assent and completion of core measures.
  - Severe central nervous system or other acute medical illness that renders participation unsafe or infeasible during admission (e.g., unstable neurological condition).
  - Acute poisoning/intoxication as the primary reason for admission, prior to medical stabilization.
- Insufficient Slovene language proficiency to complete consent/assent and core assessments, and no feasible accommodation.
- Legal, custodial, or institutional restrictions that prohibit research participation.
- Concurrent enrolment in another interventional research study that, in the investigator's judgment, would interfere with participation, data integrity, or safety.
- Prior enrolment in this study (to avoid duplicate participation).
- Any condition or circumstance that, in the opinion of the investigator, would make participation unsafe or compromise data quality.
- Note: Declining or being ineligible for optional venous blood sampling does not exclude participation in behavioral/psychosocial components.

- Healthy comparison cohort

- Current psychiatric hospitalization or active clinical management for an acute suicidal crisis at the time of school-based screening.
- Endorsement at screening of imminent suicidal intent or other acute safety concern warranting urgent referral; such individuals will be referred and not enrolled to preserve safety [1,3].
- History of admission for suicidal behavior or NSSI within the past 3 months, to reduce the risk of enrolling adolescents in immediate post-crisis trajectories.
- Insufficient Slovene language proficiency to complete consent/assent and baseline assessments, and no feasible accommodation.
- Cognitive, sensory, or neurodevelopmental conditions that preclude meaningful assent/consent or completion of core measures despite reasonable accommodations.
- Legal, custodial, or institutional restrictions that prohibit research participation.
- Concurrent enrolment in another study that would interfere with participation or data integrity.
- Prior enrolment in this study.

Eligibility assessment, verification, and documentation

- Screening procedures

- Clinical cohort: Trained research staff, in coordination with the admitting clinical team, will verify admission status and apply a standardized screening checklist that captures age, unit, presenting problem, and exclusion conditions. Recent suicidal ideation/behaviors and/or NSSI will be confirmed using brief, standardized items from the C-SSRS and B-NSSI-AT and cross-checked against clinical records and team notes [1,2]. Capacity to consent/assent will be assessed; parental/guardian consent will be obtained for minors per national law and international ethics guidance [3].
- Healthy cohort: During routine school examinations, a brief eligibility screen will confirm age, school enrolment, absence of current psychiatric hospitalization, and absence of acute safety concerns. Where indicated, a brief C-SSRS ideation screen will be used to identify any immediate risk necessitating referral and exclusion from research enrolment [1].

- Verification and safeguards

- Identity, age, and setting will be confirmed via institutional records (clinical) or school records (controls). Language proficiency and ability to complete procedures will be judged through interaction during screening and consent.
- All screening outcomes (eligible/ineligible) and reasons for exclusion will be recorded in a secure screening log. Consent/assent will be documented using approved forms. For the clinical cohort, contact details for follow-up and preferred communication modes will be captured at or before discharge.
- Screening, consent, and eligibility data will be handled under GDPR-compliant procedures, with access restricted to authorized personnel and data minimization applied to logs and case report forms [4].
- Participants found to be at imminent risk during any research contact will be managed per predefined escalation pathways (handover to clinical staff or referral), and research procedures will be paused as needed, consistent with ethical guidance for research with adolescents at risk [1,3].

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5.3 Recruitment strategies and procedures

Overview and recruitment goals

Recruitment is designed to enroll approximately 200 consecutively admitted high-risk adolescents from the Intensive Child and Adolescent Psychiatry Unit and the Unit for Adolescent Psychiatry at the Centre for Mental Health, University Psychiatric Clinic Ljubljana (UPKL), and approximately 200 healthy comparison adolescents identified during routine school examinations in Slovenia. Procedures emphasize systematic, transparent, and ethically proportionate approaches that minimize selection bias, protect safety in a vulnerable population, and support long-term follow-up, consistent with STROBE and SPIRIT-aligned principles for observational research and consent documentation [1,2].

Identification and approach: clinical high-risk inpatient cohort

- Case finding and eligibility screening

- Daily census review of new admissions to the two UPKL adolescent units by trained research staff, using a standardized screening checklist aligned with prespecified inclusion/exclusion criteria (age 13–19 years; current admission; recent suicidal ideation/behavior or NSSI; exclusions such as acute psychosis) verified via clinical records and brief structured screens.
- Recent suicidal ideation/behavior is confirmed with brief C-SSRS items; NSSI exposure is verified with brief items adapted from B-NSSI-AT during screening, only after clinical stabilization and with immediate escalation pathways for any imminent risk [3,4].

- Timing and setting of approach

- Initial approach occurs after the admitting team confirms medical and behavioral stabilization sufficient for a non-clinical conversation, typically within 24–48 hours of admission, in a quiet, private space on the ward to protect confidentiality.
- To reduce gatekeeping and selection bias, all consecutively eligible admissions are approached unless a treating clinician documents a temporary contraindication (e.g., agitation precluding discussion); deferred approaches are reattempted once stabilized.

- Initial contact and study information

- A brief, standardized script introduces the study purpose, voluntary nature, data protections, and lack of impact on care. Age-appropriate, plain-language Slovene information sheets are provided for adolescents and, where applicable, parents/guardians, with ample time for questions prior to any decision.
- To reduce perceived coercion, recruitment is conducted by research staff not directly responsible for clinical care; adolescents are explicitly informed that declining participation will not affect treatment or discharge planning.

Identification and approach: healthy school-based comparison cohort

- Institutional collaboration and site selection

- Recruitment is coordinated with regional school health services and participating schools (primary, secondary, and early tertiary) across urban and rural catchments to enhance representativeness and reduce socioeconomic or geographic selection effects.
- Schools are selected to reflect Slovenia's diversity in size, program type, and location. Site initiation includes briefing school health professionals on eligibility criteria, confidentiality, and safety referral pathways.

- Case finding during routine examinations

- During scheduled systematic school examinations, trained research staff (or school health staff trained by the research team) introduce the study in small groups or brief individual encounters in private spaces, distribute information sheets, and screen basic eligibility (age 13–19; not currently hospitalized; no acute safety concern).
- A brief C-SSRS ideation screen is used only where indicated by disclosures to ensure no imminent risk is present; any positive imminent-risk indication triggers immediate referral to school counseling or appropriate services rather than research enrollment [3].

- Initial contact and study information

- Adolescents receive age-appropriate Slovene information sheets; for minors under 15, parent/guardian information is sent home with clear instructions for consent return. Information emphasizes voluntariness, privacy safeguards, and the baseline-only nature of participation for controls.

Informed consent/assent procedures

- Regulatory and ethical framework

- Consent and assent follow CIOMS guidance for research with minors and SPIRIT-aligned documentation standards; data handling and contact information management comply with GDPR [2,5,6].

- Clinical cohort

- For participants under 15, written parental/guardian consent and adolescent assent are obtained before any research procedures. For those meeting the legal threshold for self-consent, written consent is obtained directly from the adolescent, with optional parent involvement per national regulations.
- Consent covers behavioral/psychosocial assessments, linkage with routine clinical documentation and incident logs, optional venous blood sampling for genetic/epigenetic analyses, and recontact for 6- and 18-month follow-up. Optional elements are clearly delineated to allow partial participation.

- Healthy cohort

- For participants under 15, written parental/guardian consent and adolescent assent are required; for others legally able to consent, written consent is obtained from the adolescent. No biological sampling is requested from controls.

- Ongoing consent and safety

- Capacity and willingness are reassessed at each encounter. If distress or imminent risk is disclosed at any point, research procedures are paused and an immediate clinical referral/handover is initiated per predefined pathways; continuation occurs only after stabilization and re-consent as appropriate [3,5].

Inclusivity, accessibility, and equitable participation

- Materials and communication

- Information sheets and consent forms are written in plain-language Slovene at adolescent-appropriate reading levels; pictorial/summary aids are available. Where feasible, brief clarifications in other languages may be provided to support understanding, while maintaining the prespecified requirement for sufficient Slovene proficiency to complete study measures.

- Reducing participation barriers

- Flexible scheduling of consent and baseline procedures around clinical routines (inpatients) and around school timetables (controls) is used to minimize disruption. For post-discharge follow-up, multiple contact modalities are offered (telephone, secure video, in-person), and reasonable travel cost reimbursement is provided per ethics approval to prevent socioeconomic exclusion.

- Equity monitoring

- Recruitment logs capture age, sex assigned at birth, gender identity where volunteered, schooling track, and catchment (urban/rural) for all approached individuals, alongside participation decisions and reasons for non-participation when provided. Periodic review of these logs identifies disparities; targeted outreach (e.g., additional school sites, adjusted approach times) is implemented to correct imbalances without coercion.

- Protection against undue influence

- No performance-contingent incentives are used. Any tokens of appreciation or expense reimbursements are modest, standardized, and approved by the ethics committee to avoid undue inducement, consistent with CIOMS [5].

Minimizing selection bias and enhancing generalizability

- Consecutive recruitment of all eligible inpatients with daily census review reduces clinician gatekeeping and volunteer bias; deferred approaches for temporarily unstable youth further mitigate systematic exclusion.
- For controls, recruitment across a network of schools representing diverse programs and regions limits sampling bias; frequency-matching by age range ensures developmental comparability at baseline.
- Standardized scripts, eligibility checklists, and brief, validated risk screens promote consistent application of inclusion/exclusion criteria across settings [1,3].
- A secure screening log documents all eligibles, approached, enrolled, and reasons for non-participation, supporting STROBE-aligned transparency and enabling sensitivity analyses of potential selection effects [1].

Recruitment workflow, documentation, and data protection

- Screening to consent workflow

- Screening outcome is documented in a secure, access-controlled log. Eligible individuals receive information sheets; a reflection period is offered whenever feasible, especially in schools. Written consent/assent is obtained before any data collection.

- Role separation and training

- Research staff are trained in adolescent-appropriate communication, C-SSRS administration, confidentiality, and risk escalation. Staff involved in recruitment are distinct from the direct care team to reduce perceived pressure to participate.

- GDPR-compliant contact management

- Contact details and preferences (e.g., SMS, phone, email) are recorded separately from research data in encrypted systems located in the Republic of Slovenia, with role-based access controls, data minimization, and documented retention schedules. Participants can modify or withdraw contact permissions at any time without affecting clinical care or participation in already completed procedures [6].

Interface with retention and follow-up

- At discharge (clinical cohort), recruitment staff verify contact details, preferred modalities, and availability windows; a brief, calendar-based plan is co-created to anticipate the 6- and 18-month contacts, aligning with the study's prespecified visit windows.
- Neutral reminders and multiple contact attempts within approved limits are planned to support retention, using the participant's stated preferences; alternative contacts (with consent) are recorded to facilitate re-establishment of contact while maintaining confidentiality.
- Any safeguarding concerns arising during follow-up contacts trigger the same immediate escalation procedures used at recruitment, ensuring continuity of safety practices across the participant journey [3].

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5.4 Retention and follow-up plans

Retention objectives and targets

- Primary retention objective: maintain ≥80% completion of the 6-month and ≥75% completion of the 18-month follow-up assessments in the clinical cohort, consistent with SPIRIT-aligned good practice for longitudinal studies and adolescent cohort benchmarks [1,2].
- Key principles: minimize burden, maximize predictability and flexibility, use youth-friendly, multi-modal communication, and prioritize safety during all contacts, following ethical guidance for research involving minors at risk of self-harm [1,3,4].

Scope

- Clinical high-risk cohort: active retention through scheduled follow-ups at 6 and 18 months post-hospitalization.
- Healthy comparison cohort: no planned follow-up after baseline; retention efforts focus on complete, high-quality baseline data capture and immediate resolution of data queries during the enrollment encounter.

Engagement and communication strategies

- Collaborative follow-up planning at discharge:

- Confirm preferred contact modalities (SMS, phone, email, secure video, in-person), days/times, and language preferences; record at least one alternative contact (e.g., parent/guardian) with consent, in a separate, access-controlled contact file.
- Provide a brief take-home schedule highlighting target months and visit windows (±6 weeks) for 6- and 18-month assessments.

- Multi-modal reminders and scheduling:

- Neutral, non-stigmatizing reminders are sent 4 weeks and 1 week before the due window, with same-day prompts on the appointment date, using the participant's stated preferences; content avoids sensitive details in compliance with privacy norms [1,5].
- Offer multiple appointment formats (telephone, secure video, or in-person at UPKL) and after-school/early-evening or weekend slots to reduce school disruption and caregiver burden, an approach shown to improve adolescent retention [2,6].

- Burden minimization and youth-appropriate support:

- Streamlined assessments with clear time estimates; option to split longer sessions into two shorter contacts within the window.
- Trained staff use adolescent-appropriate, strengths-based communication, brief check-ins about comfort/fatigue, and offer breaks, which are associated with better sustained engagement in youth cohorts [2,6].

- Reimbursement and acknowledgments:

- Ethics-approved, modest travel reimbursement for in-person visits; no performance-contingent incentives, consistent with international ethics guidance [3].

Follow-up procedures

- Modality and content:

- Core outcomes are collected via secure phone/video call or in-person, using standardized scripts and administration manuals. C-SSRS is administered first to assess current risk and determine if procedures should pause for safety [4].
- When in-person, venous blood sampling (if consented) is performed by trained personnel following standard clinical phlebotomy procedures.

- Visit windows and partial completion:

- Target month ±6 weeks; if full completion is not feasible, a minimal dataset is obtained within the window (C-SSRS current ideation/behavior items; occurrence of self-harm since last contact; serious adverse events; any hospitalizations), with remaining measures completed within 2 further weeks when possible. Partial data capture improves retention without compromising core safety objectives [1,2,6].

- Safety during contacts:

- Any indication of imminent risk triggers predefined escalation (handover to on-call clinical services, parent/guardian notification per consent, or emergency services) and documentation, consistent with WHO and CIOMS guidance for suicide research with minors [3,4].

Managing missed or delayed contacts

- Contact cadence:

- If no response to the initial reminder, up to three contact attempts are made via the preferred modality across different days/times, followed by two attempts using an alternate modality (e.g., phone after SMS), spaced over 14 days. If still unsuccessful, one attempt via the consented alternative contact is made solely to re-establish participant contact, without disclosing sensitive information [5,7].

- Out-of-window follow-up:

- If the assessment is not completed within the target window, one extended attempt (up to 4 additional weeks) is allowed to collect the minimal dataset by phone to reduce missing outcome data; timing is flagged in the database for analysis adjustments [1,2].

- Temporary deferral:

- On participant request (e.g., exams, illness), a short deferral is scheduled within the allowable window; a new appointment is offered with refreshed reminders.

Monitoring retention and minimizing attrition

- Real-time tracking:

- A secure dashboard (distinct from research data) tracks due dates, contact attempts, outcomes (completed/partial/missed), reasons for non-completion, modality, duration, and any safety escalations. Monitoring supports timely, tailored re-engagement and resource allocation, consistent with SPIRIT recommendations [1,5].

- Metrics and thresholds:

- Monthly review of cohort-level retention rates, time-to-completion, and distribution of modalities.
- Predefined action thresholds: if rolling 3-month completion falls below 80% at the 6-month timepoint or 75% at the 18-month timepoint, corrective actions are triggered (e.g., expanded appointment hours; additional weekend slots; targeted re-training in engagement techniques).

- Quality assurance:

- Periodic checks of reminder scripts and call logs; brief refresher training for staff on adolescent-friendly communication and safety procedures.

- Equity review:

- Retention is examined by sex, age, urban/rural catchment, and schooling track to detect disparities; pragmatic adjustments (e.g., transportation coordination, time-of-day changes) are implemented without coercion [2].

Documentation of retention efforts

- All contact attempts, participant preferences, completed assessments (full or minimal dataset), deferrals, safety escalations, and reasons for missed visits are recorded with timestamps in a retention log separate from analytic datasets, following GDPR data minimization principles [5].
- Any protocol deviations (e.g., assessments outside the window) are documented with rationale to inform sensitivity analyses.

Data protection and confidentiality in follow-up

- Contact details and communications are stored in encrypted systems located in the Republic of Slovenia, with role-based access, audit trails, and separation from de-identified research data, in line with GDPR [5].
- Reminder content avoids clinical terms; voicemail or SMS does not reveal study focus. Alternative contacts are used solely for locating the participant, as consented.

Discontinuation of active follow-up

- Participants may pause or decline any contact without losing access to standard care or previously earned reimbursements.
- Loss to follow-up is declared after all prespecified attempts fail and 60 days have elapsed beyond the visit window, or upon explicit withdrawal. Outcomes are coded per prespecified data-handling rules to limit attrition bias [1,7].
- These procedures lead directly into the study's withdrawal and replacement provisions.

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5.5 Withdrawal and replacement

Participant-initiated withdrawal

- Adolescents (and parents/guardians for minors, as required) may withdraw consent/assent at any time without penalty, loss of benefits, or impact on clinical care. They may also decline or discontinue specific components (e.g., questionnaires, follow-up contacts, venous blood sampling) while remaining in other parts of the study, consistent with proportionate, component-level consent for research with minors [1].
- Participants who reach the age of majority during follow-up will be re-consented for continued participation. At that point, they may reaffirm, modify, or withdraw their prior permissions for ongoing data collection and future contact, in line with ethical guidance for evolving capacity in adolescent research [1].

Investigator-initiated discontinuation

The investigator may temporarily suspend procedures or permanently withdraw a participant when continuation poses unacceptable risk, threatens data integrity, or is infeasible, including:

- Emergent safety concerns or clinical deterioration indicating that research contact could increase risk (e.g., acute suicidal crisis), with immediate handover to clinical services as per predefined escalation pathways [1,4].
- Loss of capacity to provide informed assent/consent without an appropriate legally authorized representative, or legal/institutional prohibitions that arise after enrollment.
- Unresolvable procedural issues (e.g., persistent non-response or inability to schedule within extended windows), fraud, or serious non-compliance that compromises data integrity.
- Administrative reasons such as site-mandated pauses or public health restrictions that preclude safe conduct of study procedures.

Temporary suspension for safety takes precedence over data collection; re-engagement occurs only after stabilization and re-assessment of willingness/capacity to continue [1,4].

Handling of death or incapacitation

- In the event of participant death, active study procedures cease. Data and biospecimens collected before the event will be retained and analyzed as prespecified, as this information is essential to the study's public-health purpose and cannot be replaced; any post-event ascertainment (e.g., date and cause of death from records) will follow ethics approval and legal requirements [1,3,4].
- If a participant becomes permanently incapacitated and cannot provide consent, continued data collection will not occur unless permitted under ethics approval and applicable law; previously collected data will be handled per the data retention provisions below.

Procedures following withdrawal or discontinuation

- Safety and referral: If withdrawal is associated with distress or disclosure of imminent risk, the research team will implement the predefined safety escalation and referral procedures immediately [1,4].
- Communication: The participant (and parent/guardian for minors, where applicable) will be asked whether they wish to withdraw from all future contacts or only selected components; preferences will be documented. No further contact will occur except as required for safety or legal obligations.

Data and biospecimen handling for withdrawn participants

- Data retention: Unless a participant (or parent/guardian for minors, as applicable) exercises the GDPR right to erasure, identifiable data and coded research data already collected up to the time of withdrawal will be retained and included in analyses, consistent with SPIRIT-aligned guidance and ethics norms that allow use of data collected under valid prior consent [1–3]. If erasure is requested, the study will delete identifiable data and coded records that remain linkable, except where retention is necessary for archiving in the public interest, scientific research purposes with appropriate safeguards, or legal compliance, as permitted by GDPR Article 17(3) and Article 89(1) [2].
- Anonymisation: Where feasible and consistent with the analysis plan, datasets are de-identified and then anonymised. After anonymisation, individual records cannot be removed because re-identification is no longer possible under GDPR [2].
- Contact data: Contact information stored separately from research data will be deleted upon full withdrawal from future contact, except where temporarily retained to document the withdrawal request or to meet legal obligations; any retained administrative record will be minimised [2].
- Biospecimens: Participants may withdraw consent for future use of stored blood samples at any time. Unused, identifiable or coded biospecimens will be destroyed upon request unless required to be retained by law or already irreversibly anonymised or consumed in laboratory processes, in which case destruction or retrieval is not feasible [1–3]. The disposition (destroyed, already anonymised/consumed, or retained under legal/ethical exception) will be documented.

Replacement of withdrawn participants

- Clinical high-risk cohort: The study uses consecutive inpatient recruitment to achieve an a priori target sample. Participants who withdraw before any data are collected will be replaced to maintain the recruitment target and preserve planned precision. Participants who withdraw after any baseline data are collected will not be replaced on a one-for-one basis; their available data will contribute to analyses per the analysis population definitions, with missingness handled by prespecified methods.
- Healthy comparison cohort: Controls who withdraw before completing baseline will be replaced to maintain frequency matching by age range. Post-baseline replacement is not applicable because no follow-up is planned for controls.

Documentation of withdrawal

- The reason for withdrawal will be sought non-coercively and recorded when voluntarily provided, using standard categories (e.g., participant decision, safety/clinical, administrative,

loss to follow-up, consent withdrawn, death). If no reason is given, this will be recorded as "undisclosed." No further probing will occur beyond a single neutral invitation to share the reason [1,3].
- The date of withdrawal, scope (full or component-specific), data/biospecimen handling preferences, and any safety actions taken will be documented in the study logs. Documentation will adhere to data minimisation and confidentiality principles under GDPR [2].
- Protocol deviations related to withdrawal (e.g., data collection outside allowed windows due to re-engagement) will be recorded with rationale, in line with SPIRIT-aligned reporting standards [3].

Analysis considerations

- Participants who discontinue follow-up will be included in analyses using data collected up to the point of withdrawal. Time-to-event and longitudinal models will treat post-withdrawal observations as missing not at random or missing at random per prespecified assumptions, with sensitivity analyses to assess robustness to attrition, consistent with best practice in observational cohort reporting [3].
- Selection effects introduced by withdrawal will be monitored using screening and retention logs; exploratory comparisons of baseline characteristics between completers and non-completers will inform interpretation and potential weighting or multiple-imputation strategies, where appropriate and consistent with the analysis plan [3].

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6 SAMPLE SIZE

6.1 Assumptions and calculations; or pilot/feasibility rationale

Overview and planned enrolment

- Final planned enrolment is 400 adolescents: approximately 200 consecutively admitted high-risk inpatients and approximately 200 healthy school-based comparisons.
- The sample size is primarily determined by feasibility and precision considerations appropriate to an observational, longitudinal cohort with a concurrent healthy comparison group and an embedded instrument development/validation component, rather than by a single confirmatory hypothesis test in an interventional context. This approach is consistent with STROBE/SPIRIT-aligned guidance that requires transparent justification of sample size and the precision attainable for key parameters in observational research and psychometric validation studies [1,2].

Feasibility considerations

- Recruitment capacity and logistics: Two adolescent inpatient units at the University Psychiatric Clinic Ljubljana (UPKL) provide a continuous flow of eligible admissions, enabling consecutive recruitment to a target of 200 clinical participants within the planned enrolment window. The control cohort will be recruited during routine school examinations across multiple educational settings, supporting accrual of ~200 healthy adolescents with minimal burden.
- Follow-up burden and retention: Retention targets of ≥80% at 6 months and ≥75% at 18 months are built into operational plans. Under these assumptions, the high-risk cohort yields approximately 160 analyzable participants at 6 months and 150 at 18 months, which is adequate for the study's prospective, multivariable, and psychometric aims while maintaining ethical proportionality in a vulnerable population.
- Resource constraints: The planned sample balances analytic needs for multivariable modeling and instrument validation against staffing, assessment time, and biospecimen processing capacity, ensuring high-quality, standardized measurement across settings.

Precision for key descriptive and comparative estimates

- Proportions and rates in the clinical cohort: With n=200 at baseline, a proportion of 0.30 (e.g., recurrence of self-harm over a follow-up interval) can be estimated with an approximate 95% confidence interval (CI) half-width of ±6–7%, and a proportion of 0.50 with a half-width of ~±7%. With n=150 at 18 months, corresponding half-widths are ~±7–8%. These margins support the study's objective to generate stable estimates of self-harm occurrence and persistence trajectories in high-risk adolescents.
- Continuous outcomes: For standardized psychosocial measures, SEs of group means will be ≤SD/√n; with n≈200 per group, even modest between-group mean differences (Cohen's d≈0.3–0.4) will be estimated with narrow CIs, and two-group comparisons will have high power to detect medium effects at two-sided α=0.05 [3]. This supports cross-sectional benchmarking of psychological and social correlates between high-risk adolescents and healthy peers.

Rationale for multivariable and prognostic modeling

- Event yield and model complexity: International literature indicates that recurrence of self-harm after index presentation in youth is common over 6–12 months, underscoring the feasibility of capturing sufficient events for modeling in a high-risk inpatient cohort [4,5]. Assuming 150–160 analyzable participants at 18 months and a conservative 25–35% cumulative incidence of recurrent self-harm, the expected number of events is approximately 38–56. Traditional rules-of-thumb would limit the number of reliably estimable regression coefficients to roughly the number of events divided by 10; contemporary guidance supports more flexible approaches that combine parsimonious predictor selection with penalization/shrinkage and internal validation to mitigate overfitting [6–8]. Accordingly:

- Primary prognostic models will prioritize a limited set of prespecified predictors grounded in theory and prior evidence, supplemented by penalized estimation (e.g., ridge/lasso) and bootstrap internal validation.
- Time-to-event analyses will leverage all observed follow-up time, improving efficiency relative to single-timepoint logistic models when event timing varies.

- Discrimination and calibration precision: For a prognostic index or the ASHRS total score predicting future self-harm, an analyzable dataset with ~40–60 events and ~90–120 non-events yields approximate 95% CI half-widths for the AUC on the order of ±0.07–0.10 when the true AUC is in the 0.70–0.80 range, based on established variance approximations for ROC analysis [9]. This level of precision is appropriate for an early-phase prognostic tool intended for refinement and external validation in subsequent studies.

Psychometric and scale development considerations (ASHRS)

- Sample size adequacy: For initial item analysis and dimensionality assessment, n≈200 supports stable item–total correlations and factor loadings for instruments of modest length, consistent with common recommendations in patient-reported outcome and behavioral scale validation literature and COSMIN-aligned practices [10,11]. With n≈150 at 6–18 months, longitudinal responsiveness and predictive validity can be examined with acceptable precision.
- Reliability estimation: With n≈200, the 95% CI for Cronbach's alpha around a value of ~0.80 typically has a half-width of approximately ±0.04–0.06, supporting precise internal consistency estimates for the ASHRS and other multi-item scales [12].
- Construct and criterion validity: Cross-sectional comparisons against established instruments (e.g., C-SSRS, B-NSSI-AT, ISAS) in samples of ~200 clinical and ~200 healthy adolescents provide ample precision for convergent/discriminant validity correlations (e.g., ability to estimate correlations of r≈0.25–0.30 with 95% CIs of roughly ±0.12–0.14), and for detecting medium between-group differences [3,10].

Allocation across cohorts and subgroups

- Equal-sized clinical and healthy cohorts (≈200 each) are planned to maximize precision and interpretability for cross-sectional contrasts in psychosocial and behavioral constructs, support normative anchoring for the ASHRS, and facilitate sensitivity analyses by age and sex, while maintaining manageable complexity.
- Within the clinical cohort, no formal stratification is imposed at enrolment; exploratory subgroup analyses (e.g., by NSSI vs suicidal behavior at index admission) will be descriptively powered and interpreted cautiously.

Allowance for attrition and missing data

- Anticipated retention (≥80% at 6 months; ≥75% at 18 months) is incorporated into the planned baseline sample to maintain analyzable cohorts of ~160 and ~150, respectively. Missing data will be handled using prespecified methods (e.g., maximum likelihood in mixed models, multiple imputation) under plausible missingness assumptions, with sensitivity analyses to assess robustness, aligning with best practice for longitudinal behavioral studies [1,2].

Conclusion

- The planned total enrolment of ~400 adolescents (≈200 high-risk inpatients and ≈200 healthy comparisons) is justified on feasibility and precision grounds. It is sufficient to:

- Precisely estimate key proportions and means in each cohort.
- Support cross-sectional comparisons with high precision for small-to-medium effects.
- Enable development and internal validation of parsimonious prognostic models and the ASHRS with acceptable precision in reliability, discrimination, and calibration, while acknowledging the need for subsequent external validation.

- This sample size, together with the retention plan, appropriately supports the study's primary and secondary objectives in an ethically proportionate manner for a vulnerable adolescent population.

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7 STUDY PROCEDURES

7.1 Visit windows and operational schedule

Overview and sequence

- Initial contact and screening: Potential participants are identified consecutively on admission to the Intensive Child and Adolescent Psychiatry Unit or Unit for Adolescent Psychiatry (UPKL) and approached when clinically appropriate and with the treating team's agreement. Eligibility is verified from routine clinical intake assessments (e.g., C-SSRS or B-NSSI-AT) before any research procedures. Healthy comparison adolescents are identified during routine school-based examinations and approached on the examination day.
- Consent/assent: Written informed consent/assent is obtained before any research-only procedures. For minors under Slovenian law, parental/guardian consent is obtained in addition to adolescent assent. Consent is re-confirmed at each subsequent contact and re-consent obtained at the age of majority when applicable, in line with ethical guidance for research with minors [2].
- Baseline assessments:

- Clinical cohort: Baseline research assessments are conducted during hospitalization once the participant is clinically stable, prioritizing safety-critical measures first (e.g., current ideation/behavior via C-SSRS) [3]. Remaining questionnaires (including ASHRS, B-NSSI-AT, ISAS, and psychosocial measures) and optional venous blood sampling (if consented) are completed before discharge where feasible.
- Healthy comparison cohort: Baseline questionnaires (including ASHRS and psychosocial measures) are completed during the school examination encounter; administrative data queries are resolved promptly.

- Inpatient monitoring (clinical cohort): Self-harm and heteroaggressive events are recorded by unit staff as part of routine care; the research team extracts standardized summaries at discharge from clinical records.
- Follow-up assessments (clinical cohort only): Participants are reassessed at 6 and 18 months after discharge (index hospitalization), with multi-modal options (telephone, secure video, or in-person at UPKL). Safety screening with the C-SSRS precedes other measures at each contact [3]. Optional venous blood sampling is performed only during in-person visits, if consented.
- Study completion: The 18-month contact marks study completion for the clinical cohort. Healthy controls complete the study after the baseline encounter.

Visit windows and timing rules

- Anchor date: The index hospitalization discharge date is the reference (T0) for calculating 6- and 18-month targets for the clinical cohort.
- Baseline (clinical cohort): Target during the inpatient stay after stabilization and before discharge; components may be split across two short sessions during admission to minimize burden.
- Baseline (healthy controls): Target on the day of the school examination encounter; brief administrative clarifications may occur shortly thereafter.
- Follow-up windows (clinical cohort):

- 6 months: Target at 6 months post-discharge with an allowable window of ±6 weeks. If full completion is not feasible, a minimal dataset is prioritized within this window (C-SSRS current ideation/behavior items; occurrence of self-harm since last contact; serious adverse events; hospitalizations). Remaining measures may be completed within an additional 2 weeks when possible. One extended attempt (up to 4 further weeks) to obtain the minimal dataset by telephone is permitted and recorded as out-of-window [1,5,6].
- 18 months: Same structure and allowances as the 6-month visit (±6 weeks; minimal dataset; up to 2-week completion of remaining measures; single 4-week minimal-dataset extension if needed) [1,5,6].

- Time-of-day and modality: After-school/evening and weekend slots, and flexible modality (phone/video/in-person), are offered to reduce disruption and improve retention in adolescents, consistent with evidence on effective longitudinal engagement [5,6].
- Biospecimen timing: Venous blood sampling (if consented) is targeted during the inpatient baseline and optionally at follow-up when an in-person visit is chosen. No home or remote phlebotomy is performed.

Operational conduct

- Scheduling and reminders: Appointments are offered within the applicable window with reminders approximately 4 weeks and 1 week prior to the due date, plus a same-day prompt, tailored to participant communication preferences and privacy requirements under GDPR [4–6].
- Session duration and splitting: To minimize burden, questionnaire administration is streamlined and can be split into two shorter sessions within the allowed window without repeating already completed measures. Safety checks are repeated at the start of any resumed session [3].
- Data completeness: The team prioritizes completion of the prespecified core/primary outcomes within the window to preserve temporal comparability across participants, in line with SPIRIT-aligned scheduling principles [1]. Non-core measures may be deferred within the defined grace periods if needed.

Handling delays, deferrals, and deviations

- Participant-requested deferral: Short deferrals within the allowed window (e.g., due to exams or illness) are accommodated, with rescheduling and adjusted reminders.
- Missed within-window contact: If the full assessment cannot be completed within the ±6-week window, one extended attempt (up to 4 weeks) to collect the minimal dataset by telephone is permitted. The visit is coded as out-of-window and timing is flagged for analysis [1,5,6].
- Documenting deviations: Any assessments outside the specified windows, incomplete assessments, or modality changes that affect preplanned procedures are documented with date, reason, and impact on data completeness. Deviations are reviewed periodically and reported per SPIRIT-aligned standards [1].
- Safety precedence: At any contact, if imminent risk is detected, data collection pauses and predefined escalation procedures are activated before any further research procedures, consistent with international guidance for suicide research [2,3].

Structured schedule of visits and windows

Study stage	Target timing (anchor)	Allowed window	Mode(s)	Core activities	Minimal dataset if constraints apply
Clinical cohort: Initial approach and consent	During hospitalization, after clinical stabilization	Within inpatient stay, before discharge	In-person	Eligibility confirmation; consent/assent; safety first (C-SSRS current status); demographics; initiate baseline questionnaires; schedule completion plan; discuss follow-ups	Consent/assent; C-SSRS current status; demographics sufficient to identify and schedule follow-ups
Clinical cohort: Baseline completion	During hospitalization	Within inpatient stay; may split over two sessions	In-person	ASHRS; B-NSSI-AT; ISAS; psychosocial battery; optional venous blood sampling (if consented)	ASHRS and C-SSRS current status prioritized; remaining measures within stay as feasible
Clinical cohort: Inpatient monitoring	Admission to discharge	Continuous through stay	Routine clinical recording; research abstraction	Record self-harm and heteroaggression events; extract standardized summary at discharge	Discharge summary of events and serious adverse events
Healthy controls: Baseline	School examination day	Same-day completion; brief administrative queries resolved promptly	In-person at school setting	Consent/assent; ASHRS; psychosocial battery; demographics	Consent/assent; ASHRS; demographics
Clinical cohort: 6-month follow-up	6 months post-discharge (T0+6 mo)	±6 weeks; remaining measures within 2 additional weeks; one 4-week phone extension for minimal dataset if needed	Phone, video, or in-person (blood only in-person)	C-SSRS; ASHRS; recurrence of self-harm; psychosocial measures; health service use; optional venous blood sampling (if in-person)	Minimal dataset: C-SSRS current ideation/behavior; occurrence of self-harm since last contact; serious adverse events; hospitalizations

Clinical cohort: 18-month follow-up (study completion)	18 months post-discharge (T0+18 mo)	±6 weeks; remaining measures within 2 additional weeks; one 4-week phone extension for minimal dataset if needed	Phone, video, or in-person (blood only in-person)	As at 6 months; confirm study completion and contact preferences for dissemination	Same as 6-month minimal dataset

Data integrity and analysis considerations linked to timing

- Timestamping: All assessments are timestamped (date, start/stop times, modality) to allow precise calculation of assessment intervals and to inform sensitivity analyses on timing effects, per STROBE/SPIRIT principles [1,7].
- Window adherence in analysis: Primary analyses use data collected within prespecified windows; out-of-window data are incorporated with timing indicators to adjust for potential bias and variability in exposure-outcome intervals [1,7].
- Confidentiality in operations: Scheduling communications and contact logs are stored separately from de-identified research data with role-based access and audit trails, in compliance with GDPR [4].

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7.2 Behavioural assessments

Overview of behavioural constructs and their linkage to objectives

The behavioural assessment battery targets core domains implicated in adolescent self-harm to address the primary objectives of characterizing occurrence, persistence, and risk and of developing/validating the Adolescent Self-Harm Risk Scale (ASHRS). Constructs include: current and historical suicidal and self-injurious thoughts/acts; non-suicidal self-injury (NSSI) topography, frequency, and functions; short- and medium-term risk of self-harm (ASHRS); dynamic inpatient risk (self-harm and heteroaggression); and psychosocial correlates spanning emotion regulation, personality functioning and borderline features, attachment/relationships, trauma exposure/symptoms, anxiety/depression, social support, and substance use. Instruments were selected for adolescent applicability, brevity where feasible, and evidence of reliability/validity, consistent with COSMIN-aligned good measurement practice [4]. Together, these assessments provide criterion and construct

anchors for ASHRS validation and supply predictors and outcomes for longitudinal modelling of self-harm trajectories.

Primary behavioural outcomes and risk assessment tools

- Suicidal ideation and behaviour: Columbia–Suicide Severity Rating Scale (C-SSRS). The C-SSRS classifies ideation severity and documents behaviours/attempts with established reliability and predictive validity for self-harm outcomes in adolescents [1]. It provides safety-critical screening at every contact and anchors primary outcomes (occurrence of self-harm, attempts) and convergent validity for ASHRS.

- Non-suicidal self-injury (NSSI) history and characteristics: Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT). This structured tool captures lifetime and recent NSSI frequency, methods, medical severity, and contextual features, supporting standardized phenotyping of NSSI and discriminant validity relative to suicidal behaviours [2]. It informs baseline characterization and longitudinal change.

- NSSI functions and reinforcement processes: Inventory of Statements About Self-Injury (ISAS). The ISAS assesses intrapersonal and interpersonal functions of NSSI, aiding theory-driven analyses of mechanisms and providing convergent validity targets for ASHRS subdomains related to urges, affect regulation, and social drivers [3].

- Short- and medium-term self-harm risk: Adolescent Self-Harm Risk Scale (ASHRS). The ASHRS is the study's novel, brief risk instrument designed for rapid use during/after hospitalization. Psychometric evaluation will include internal consistency, dimensionality, test–retest reliability where feasible, construct and criterion validity against C-SSRS, B-NSSI-AT/ISAS, and prospective self-harm, and prognostic performance (discrimination/calibration) for 6- and 18-month outcomes, aligned with COSMIN guidance for validation studies [4,15].

Dynamic inpatient behavioural risk monitoring

- Routine clinical recording of self-harm and heteroaggression during admission is abstracted into standardized variables (event type, timing, severity, antecedents, interventions). These data quantify acute behavioural risk states and serve as proximal outcomes and ecological validity anchors for ASHRS during hospitalization [13].

- Heteroaggression risk (clinical utility indicator): Dynamic Appraisal of Situational Aggression—Youth Version (DASA-YV). The youth adaptation of the brief dynamic checklist is used operationally to flag short-term risk for inpatient aggression. In this study it provides a contextual behavioural indicator for convergent validity with acute risk states; claims are made conservatively given variability in validation across settings [14].

Psychosocial and developmental correlates

- Emotion regulation/self-control: Difficulties in Emotion Regulation Scale (DERS) assesses nonacceptance, impulse control, and access to strategies, constructs linked to self-harm maintenance and targeted in explanatory models of recurrence [8].

- Personality functioning: Levels of Personality Functioning Questionnaire for Adolescents (LoPF-Q 12–18) indexes self/interpersonal functioning consistent with ICD-11/DSM-5-AMPD, enabling examination of structural vulnerabilities associated with persistent self-harm [6].

- Borderline personality features: Borderline Personality Features Scale for Children (BPFS-C or brief variant) captures affective instability, identity disturbance, and impulsivity, supporting risk stratification and ASHRS convergent validity [7].

- Attachment/relationships: Inventory of Parent and Peer Attachment (IPPA) evaluates trust, communication, and alienation in key relationships relevant to protection/risk for self-harm [5].

- Trauma exposure/symptoms: Childhood Trauma Questionnaire–Short Form (CTQ-SF) provides standardized assessment of maltreatment types and severity; trauma load is analysed as a distal risk/contextual moderator [10].

- Anxiety and depressive symptoms: Revised Child Anxiety and Depression Scale (RCADS) yields DSM-aligned anxiety/depression indices for modeling affective comorbidity as a correlate and mediator of risk [12].

- Social support: Multidimensional Scale of Perceived Social Support (MSPSS) quantifies perceived support from family, friends, and significant others as a protective factor [9].

- Substance use risk: CRAFFT screening assesses alcohol/drug risk behaviours that may elevate near-term self-harm risk and complicate discharge planning [11].

These measures collectively provide theoretically grounded predictors and validators for ASHRS constructs, and covariates for multivariable models examining self-harm occurrence and persistence.

Methods, administration, and language versions

- Mode and respondent: All behavioural instruments are adolescent self-report or clinician-administered (C-SSRS, DASA-YV) as per manuals. Slovenian/Slovene versions will be used where available; where linguistic adaptation is necessary, forward–backward translation, cognitive debriefing with adolescents, and documentation of measurement properties will follow COSMIN-aligned best practice to support validity and comparability [4].

- Scoring and data quality: Instruments will be scored per published guidelines; completeness and internal consistency (e.g., alpha, omega) will be monitored at interim checks. For ASHRS, iterative refinement will be guided by item analysis and factor/IRT methods, with prespecified rules for item retention to minimize respondent burden while preserving reliability and validity [4,15].

Timing and frequency of assessments

- Baseline (all participants): C-SSRS (current/lifetime as indicated), B-NSSI-AT, ISAS, ASHRS, and psychosocial battery (DERS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT). For clinical participants, baseline occurs during hospitalization after stabilization; for healthy controls, at the school-based encounter.

- Inpatient period (clinical cohort): Continuous clinical recording of self-harm/heteroaggression with abstraction at discharge; DASA-YV ratings per unit practice inform dynamic risk context.

- Follow-up (clinical cohort only): At 6 and 18 months post-discharge, reassessment includes C-SSRS (current and since last contact), ASHRS, recurrence of self-harm (behavioural outcome since last contact), and selected psychosocial measures (DERS, RCADS, MSPSS, and brief indices of relationship/functional status) to capture change in proximal risk/protection. B-NSSI-AT and ISAS are re-administered at 18 months to update NSSI characteristics/functions.

This schedule aligns with the study's longitudinal objectives: safety-critical surveillance at every contact; repeated ASHRS to model short- and medium-term risk; and targeted psychosocial reassessment to evaluate dynamic correlates and mediators of self-harm trajectories.

Participant safety and burden minimization

- The C-SSRS is administered first at each contact to ensure immediate safety appraisal; any indication of imminent risk triggers predefined clinical escalation before proceeding. Measures are sequenced from brief/high-yield to longer instruments, with options to split sessions to reduce fatigue, consistent with adolescent research ethics and measurement best practice [1,4,13].

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7.3 Digital/remote data capture

Platforms and modalities

- Electronic data capture (EDC): Study data are collected in a secure, on-premises, Slovenian-hosted REDCap instance (Research Electronic Data Capture), configured with role-based access, audit trails, branching logic, range checks, and instrument version control [1,2]. Paper data collection is not planned.
- Electronic consent/assent: Adolescents and, where applicable, parents/guardians complete electronic informed consent/assent via REDCap's e-consent framework with integrated signature capture, time/date stamps, versioning, and automated PDF archiving. Re-consent at the age of majority is supported electronically [3].
- Remote follow-up: At 6 and 18 months, assessments are completed via:

- Secure video call (preferred) with screen-sharing of self-report instruments and interviewer-administered measures entered directly into REDCap by trained staff.
- Telephone call for the minimal safety dataset when video is not feasible; staff enter responses contemporaneously in REDCap.
- Participant self-completion of selected questionnaires through a personalized, single-use REDCap survey link sent after identity verification.

- Inpatient/school baseline: During hospitalization and school encounters, participants complete surveys on study-provisioned tablets using the same REDCap instruments to ensure measurement equivalence across modes [4,5].

Data types and capture cadence

- Electronic consent/assent: Captured once at enrolment; re-consent at majority if reached during follow-up.
- Safety and self-harm outcomes (clinical cohort): C-SSRS current status and since-last-contact items administered at baseline and at 6 and 18 months via video/phone; interviewer entries in REDCap [6]. Inpatient self-harm and heteroaggression events are abstracted at discharge from clinical records into standardized REDCap forms.
- Self-harm risk and characteristics: ASHRS, B-NSSI-AT, and ISAS at baseline (all participants); ASHRS at 6 and 18 months; B-NSSI-AT and ISAS repeated at 18 months (clinical cohort).
- Psychosocial measures: DERS, RCADS, MSPSS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, CRAFFT at baseline; brief reassessments of proximal domains (e.g., DERS, RCADS, MSPSS, brief relationship/function indices) at 6 and 18 months (clinical cohort).
- Contact preferences and logistics: Participant-selected contact mode(s) and privacy preferences recorded at enrolment and updated as needed; automated, content-neutral reminders (SMS/email) are logged in REDCap.
- Biospecimen metadata: Consent choices and laboratory tracking fields (collection date/time, tube ID, processing status) are entered into REDCap; no genetic/epigenetic results are stored in the EDC.

All survey instruments use standardized Slovene language versions where available; mode-migration principles and usability checks are applied to preserve measurement properties across web, tablet, and interviewer-administered formats [4,5].

Participant requirements, usability, and support

- Access: Participants require a phone (mobile or landline) for scheduled calls; a smartphone, tablet, or computer with internet is recommended for optional video and web surveys. Study tablets are provided during inpatient and school assessments.
- Usability: Surveys use adolescent-appropriate plain language, responsive design, large fonts, and progressive disclosure to minimize burden. Progress is auto-saved; sessions can be split in alignment with the visit windows.
- Identity verification: Before any remote assessment, staff confirm two identifiers (e.g., initials, date of birth) and a prearranged contact method; for minors, parent/guardian identity is verified for consent-related communications.
- Training and support: Brief orientation is provided at enrolment. Participants and parents/guardians receive a study contact line and email for technical assistance. Staff are trained in tele-assessment, remote suicide risk protocols, and data entry procedures [3,6].

Remote safety procedures

- Safety-first workflow: At each remote contact, the C-SSRS is administered before other measures. If acute risk is identified, data collection pauses and predefined escalation steps are followed (e.g., maintaining contact, alerting on-call clinicians/emergency services, notifying guardians per consent), consistent with international guidance for suicide research and tele-assessment [3,6].
- Privacy during calls: Participants are asked to confirm they are in a private space; if not, sensitive items are deferred or conducted by telephone without others present.

Data security, privacy, and storage

- Governance and GDPR compliance: Data processing follows GDPR principles (lawfulness, fairness, transparency; purpose limitation; data minimization; accuracy; storage limitation; integrity/confidentiality; accountability). Consent materials specify processing purposes, recipients, retention, and rights (access, rectification, erasure where applicable), with a designated contact for data protection queries [7].
- Pseudonymization: Research data are stored under study IDs; the re-identification key and contact log are held in a physically and logically separate access-restricted repository.
- Encryption and transmission: All web traffic uses TLS 1.2+; data at rest on the REDCap server and backups are encrypted (AES-256 or equivalent). Survey links are single-use and time-limited. Email/SMS reminders avoid sensitive content.
- Access control and audit: Role-based access, least-privilege permissions, unique user credentials with two-factor authentication, automatic session timeouts, and full audit logs are enforced. Periodic access reviews are conducted.
- Hosting and backups: The REDCap server is hosted within the Republic of Slovenia on secure institutional infrastructure, with daily incremental and routine full backups to encrypted, access-controlled storage; backup restoration is tested periodically. Business continuity and disaster recovery plans are maintained.
- Data quality: Real-time validations (required fields for safety items, range/logic checks), timestamping of start/stop times, and automated query flags support data completeness and integrity. Mode and timing metadata are captured to inform analysis.

Equity and inclusion in remote participation

- Alternative arrangements: For participants with limited connectivity or device access, telephone administration of the minimal dataset and mailed or clinic-based completion of

extended measures are offered. Reasonable accommodations (e.g., larger fonts, extended time) are available.
- Burden minimization: Scheduling honors privacy preferences and daily routines; opt-out from electronic reminders is supported without loss of study contact.

Rationale and standards

The mixed-mode approach integrates eConsent, ePROs, and tele-assessments to reduce burden, enhance retention, and preserve measurement consistency. REDCap provides a validated, widely adopted platform for secure academic data capture with features suited to longitudinal behavioral research [1,2]. ISPOR/ePRO guidance supports measurement equivalence across electronic and interviewer-administered formats when usability and migration principles are followed [4,5]. Remote administration of suicide risk assessments is feasible with appropriate safety protocols and trained personnel [6]. All processing aligns with CIOMS ethical guidance for electronic consent and the GDPR framework for sensitive health data [3,7].

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7.4 Training and standardization of personnel

Overview and staffing

- Study personnel include: principal investigator (PI) and co-investigators; clinical assessors/interviewers (psychiatrists/psychologists); research coordinators and data managers; school-site assessors; inpatient chart abstractors; and phlebotomy/laboratory staff.
- All personnel complete pre-study training and role-specific competency checks before engaging with participants or data. Training emphasizes standardized administration/scoring of behavioral instruments, suicide risk safety procedures, adolescent-appropriate and trauma-informed communication, data protection under GDPR, and use of the electronic data capture system.

Pre-study training curriculum (all roles)

- Research ethics and safeguarding: CIOMS guidance for research with minors and vulnerable populations; confidentiality, assent/consent, distress management and escalation; documentation of adverse events and reportable concerns [1,2].
- Participant interaction: adolescent-appropriate communication, privacy protection (in person and remote), cultural and gender sensitivity, and handling of sensitive topics (self-harm, trauma, sexual identity) in a trauma-informed manner [2].
- Protocol and SOPs: study overview; eligibility; schedule and visit windows; minimal safety dataset workflow; deviation reporting; version control and change-management procedures aligned with SPIRIT/STROBE principles [10,11].
- Data protection and privacy: GDPR principles, role-based access, pseudonymization, contact log separation, incident response for data breaches, and secure communications [12].
- Electronic data capture: REDCap user training (role-based permissions, eConsent, instrument versioning, range/logic checks, audit trails); tele-assessment workflows and documentation standards [13,14].
- Safety-first workflow: recognition of imminent risk; remote and in-person escalation procedures; coordination with treating teams/emergency services; documentation requirements per WHO guidance for suicide research [2].

Role-specific training and competency requirements

- C-SSRS interviewers:
  - Complete standardized C-SSRS training modules and supervised practice interviews (minimum 5 observed or co-rated administrations) [6].
  - Demonstrate inter-rater agreement with a qualified trainer on recorded or live co-rated cases before independent administration; target agreement: weighted kappa ≥0.70 for ideation severity and behavior classification, interpreted using established benchmarks [8,9].
  - Annual refresher focused on updates, drift correction, and safety scenarios.

- DASA-YV raters (inpatient units):
  - Training in DASA-YV indicators, scoring anchors, and unit-specific integration; supervised ratings on at least 5 shifts with a credentialed rater [7].
  - Initial and semiannual calibration sessions using recent de-identified case vignettes; target inter-rater ICC ≥0.75 for total score [8].

- Self-report instrument facilitators (ASHRS, B-NSSI-AT, ISAS, DERS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT):
  - Instruction on standardized scripts, neutral probes for missing responses, handling of participant queries without coaching, and management of sensitive disclosures consistent with safety SOPs.
  - Training on use of validated Slovene versions and procedures for any forward–backward translations and cognitive debriefings, aligned with COSMIN principles to preserve measurement properties [3].
  - ePRO administration equivalence procedures across tablet/web/interviewer-administered modes following ISPOR guidance (usability checks, consistent layout, response option parity) [4,5].

- Chart abstractors (inpatient events):
  - Orientation to standardized abstraction forms for self-harm and heteroaggression events (event taxonomy, timing, severity, antecedents, interventions).
  - Double-abstraction of the first 10 charts with reconciliation; quarterly 5% random re-abstraction for drift monitoring.

- School-site assessors:
  - Training on consent/assent in educational settings, privacy during survey administration, and rapid referral pathways if acute risk is disclosed.
  - Telemetry for on-site issues escalation to the clinical team per safety SOPs.

- Phlebotomy and laboratory personnel:

- Certification in venipuncture for adolescents; study-specific SOPs for identification, labeling, chain-of-custody, and biospecimen metadata entry in REDCap; safe-handling and incident reporting procedures.

Standardization materials and SOPs

- Study Manual of Operations (MoO) with instrument-specific administration guides, standardized scripts, scoring rules, and examples of common pitfalls.
- Safety SOPs covering in-person and remote contacts, including a stepwise escalation algorithm, after-hours coverage, and documentation templates, aligned with WHO guidance [2].
- Data management SOPs detailing eConsent procedures, instrument version control, range/logic checks, query resolution, and audit trail reviews.
- Translation and instrument adaptation SOPs (when applicable), consistent with COSMIN recommendations [3].
- School-site SOPs for room setup, privacy checks, and emergency referral.

Competency assessment, calibration, and drift control

- Qualification prior to participant contact:

- Knowledge checks (minimum passing score 85%) on protocol/SOPs and GDPR.
- Observed practice: two satisfactory observed or co-rated administrations per interviewer per key instrument (C-SSRS; ASHRS block), documented on competency checklists.

- Inter-rater reliability (IRR) and calibration:

- C-SSRS: quarterly calibration meetings using de-identified vignettes or live co-ratings; maintain kappa ≥0.70; corrective coaching if below threshold [8,9].
- DASA-YV: semiannual IRR sessions with target ICC ≥0.75; action plans for raters falling below threshold [8].
- Chart abstraction: quarterly dual-review of a random 5% sample; discrepancy rate target ≤10% on critical fields; remediation if exceeded.

- Ongoing refresher and updates:

- Semiannual refresher covering safety events, protocol amendments, and frequent data queries; ad hoc micro-trainings when instruments or SOPs are updated.
- New personnel onboarding mirrors pre-study curriculum; shadowing and competency sign-off required before independent work.

Tele-assessment competencies

- Role-play exercises for remote identity verification, privacy confirmation, and administration of the minimal safety dataset by phone/video.
- Simulation of acute-risk scenarios in tele-contexts with evaluation of response time, documentation quality, and adherence to escalation pathways [2].
- Verification of ePRO usability with adolescents and parents/guardians; adherence to ISPOR mode-equivalence practices [4,5].

Documentation of training and oversight

- Training master file maintained by the coordinator, including:

- Individual training logs (modules completed, dates, scores).
- Certificates (e.g., C-SSRS), competency checklists, IRR summaries with targets and outcomes.

- Attendance and minutes from calibration/refresher meetings; corrective action plans where applicable.

- Version-controlled repository for MoO/SOPs with acknowledgment logs confirming staff review of each new version.
- Monitoring:

- Monthly data quality dashboards (missingness on core outcomes, timing flags, query rates).
- Triggered retraining if thresholds are exceeded (e.g., core outcome missingness >5% in a month, repeated safety documentation gaps).

Quality thresholds and corrective actions

- Instruments and interviews:

- Maintain ≥95% completeness for the minimal safety dataset within visit windows; investigate causes and retrain if recurrent.
- For PROs, item-level missingness ≤3% per instrument per quarter; address usability or procedural issues if exceeded.

- Safety procedures:

- 100% documentation of safety screening order and escalation steps when indicated; any lapse prompts immediate review and remediation.

- Data management:

- Zero tolerance for shared accounts; role-based access reviewed quarterly; audit logs sampled monthly to verify compliance.

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7.5 Fidelity monitoring for behavioural components

Overview and scope

Given the observational design and absence of an experimental behavioural intervention, fidelity monitoring focuses on the consistency, completeness, and quality of behavioural assessments and safety procedures across settings (inpatient, school, and remote). Procedures are aligned with behavioural fidelity frameworks (planning/training, delivery, receipt/participant responsiveness, enactment) adapted to assessment processes rather than treatment delivery [1,2], and with SPIRIT/STROBE principles for prespecification, monitoring, and transparent reporting of protocol adherence [3,4].

Fidelity domains and indicators

Fidelity is operationalized through prespecified indicators mapped to the behavioural procedures:

- Protocol adherence (delivery):
  - Correct sequencing of measures with safety-first order (C-SSRS administered before any other assessments at each contact).
  - Use of approved Slovene instrument versions and current instrument build in the EDC.
  - Administration mode per SOP (video preferred; telephone permitted only for minimal dataset) and identity verification for remote contacts.
  - Visit timing within defined windows; application of minimal dataset rules when constrained.

- Dose/exposure:
  - Completion of core instruments at each time point; item-level missingness thresholds.

- Quality of delivery:
  - Interviewer competence and inter-rater reliability for clinician-administered tools (C-SSRS; DASA-YV where applicable), and adherence to standardized scripts for self-report facilitation.

- Participant responsiveness/feasibility:
  - Session duration, need for splitting, interruptions, and participant-reported burden flags captured in session logs.

- Data integrity:
  - Real-time range/logic checks, timestamping, and audit trails in the EDC.

Monitoring methods and frequency

- Structured fidelity checklists:
  - At every contact, assessors complete a brief REDCap fidelity checklist documenting safety-first order, mode, identity verification (remote), instrument versions used, deviations from scripts, and whether minimal dataset rules were applied.

- EDC-based surveillance:
  - Automated dashboards track core indicators (e.g., completion of C-SSRS prior to other instruments, within-window completion, core outcome completeness, item-level missingness, duration outliers, instrument version drift). Dashboards are reviewed monthly by the coordinator and PI [5].

- Inter-rater reliability and supervision:
  - C-SSRS: quarterly calibration using de-identified vignettes or live co-ratings; target weighted kappa ≥0.70 for ideation severity/behaviour classifications, with corrective coaching if below threshold [6,7].

- DASA-YV (inpatient context): semiannual calibration with target ICC ≥0.75 for total scores; remediation plans for raters below threshold [8].
- Supervisory review: random 10% sample of clinician-administered sessions per quarter are co-rated or reviewed via contemporaneous notes for scoring/anchoring consistency when recording is not feasible due to sensitivity.

- Chart abstraction fidelity (inpatient events):
- Double-abstraction of the first 10 charts and quarterly 5% random re-abstraction; discrepancy rate threshold ≤10% on critical fields, with reconciliation and retraining if exceeded.

- Participant responsiveness monitoring:
- Session logs capture pauses, need for breaks, and reasons for early termination; trends inform procedural refinements to minimize burden.

Identification, documentation, and management of deviations

- Definitions:
- Minor deviations: e.g., brief departure from scripts without safety impact, isolated item omissions below thresholds.
- Major deviations: e.g., failure to administer C-SSRS first, missed minimal safety dataset within the allowed extension, use of incorrect instrument version, administration outside visit windows without permitted extension, or lapses in identity verification.

- Capture and classification:
- Deviations are logged in a REDCap deviation form with date, description, root-cause classification (personnel, system, participant, contextual), and preliminary impact assessment on data completeness/validity.

- Corrective and preventive actions (CAPA):
- For major deviations or recurrent minor deviations, the PI reviews cases within 10 working days, issues CAPA (e.g., targeted retraining, SOP clarification, EDC form edit checks), and schedules follow-up verification in the subsequent month’s dashboard review.

- Safety precedence:
- Any deviation arising from urgent safety escalation is recorded as justified; documentation of the safety-first workflow steps is required per WHO guidance [9].

Thresholds and triggers for action

- Minimal safety dataset completeness ≥95% within windows; trigger investigation and retraining if missed in two or more cases in a month.
- Core instrument item-level missingness ≤3% per instrument per quarter; trigger usability or process review if exceeded.
- C-SSRS inter-rater agreement maintained at kappa ≥0.70; DASA-YV ICC ≥0.75; any shortfall prompts immediate calibration and supervised practice [6–8].
- Instrument version drift rate 0% (no administrations on deprecated versions); any occurrence triggers immediate lock of outdated instruments and assessor notification.

Use of fidelity findings

- Internal quality assurance:
- Fidelity metrics are used for continuous quality improvement, staff feedback, and targeted retraining; summaries are reviewed in monthly operations meetings.

- Transparency in reporting:

- Prespecified fidelity outcomes (e.g., proportions of visits with safety-first order adhered to, within-window completion rates, core outcome completeness, IRR metrics) will be reported descriptively in study publications to inform interpretability and potential biases, consistent with STROBE and good practice for behavioural fidelity reporting [2,4].
- Sensitivity analyses may incorporate timing and mode indicators to assess potential impacts of out-of-window or modality-constrained assessments on key outcomes.

Roles, responsibilities, and data governance

- The research coordinator maintains the fidelity monitoring plan, dashboards, and deviation/CAPA logs; the PI oversees adjudication of major deviations and approves CAPA.
- Site assessors are responsible for real-time checklist completion and immediate reporting of major deviations.
- All fidelity data are stored in the secure REDCap environment with role-based access, full audit trails, and linkage to session metadata only via study IDs to preserve confidentiality [5].

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8 MEASURES AND INSTRUMENTS

8.1 Primary and secondary measures with scoring and interpretation

Primary outcome domain, measures, scoring, and interpretation

The primary outcome domain is self-harm occurrence and severity over time among high-risk adolescents. This domain is operationalized using:

- Self-harm and suicidal behavior (index admission, 6 and 18 months): Columbia–Suicide Severity Rating Scale (C-SSRS), administered by trained interviewers. Primary variables are:

- Suicidal ideation severity (SIS) ordinal classification (0–5) reflecting worst ideation since last contact; higher categories indicate more severe ideation and greater risk [1].
- Suicidal behaviors: presence/absence and counts of actual, aborted, and interrupted attempts; preparatory acts/behavior; lethality/medical damage ratings when applicable [1].

- Recency and since-last-contact occurrence are captured to support time-to-event analyses [1].

Interpretation: SIS categories and behavior classifications follow the C-SSRS manual; any suicidal behavior since last contact is coded as positive for the binary “any suicidal behavior” endpoint. Ordinal ideation categories will be summarized as distributions and modeled as ordered outcomes; shifts toward lower categories indicate improvement. Change in SIS is interpreted cautiously because minimally important change thresholds are not established; we will report distribution-based standardized change metrics.

- Inpatient self-harm events (proximal outcome): Prospective abstraction of clinically documented events during hospitalization (self-injurious acts with or without suicidal intent, severity/medical intervention required, antecedents, and staff response). Variables include event counts, time stamp, and severity tier.

Interpretation: Event burden is summarized as counts and rates per 100 patient-days; severity distribution provides clinical context for proximal risk.

- Short- and medium-term risk of self-harm: Adolescent Self-Harm Risk Scale (ASHRS), a brief, study-developed risk tool administered at baseline, 6, and 18 months. Scoring will be finalized through item analysis and factor/IRT modeling:

- Provisional scoring: summed or IRT-based theta total and subdomain scores, scaled to a common metric (e.g., 0–100).
- Risk stratification: prespecified approach to derive low/moderate/high risk bands using outcome-oriented cut-points selected by maximizing clinical utility (e.g., Youden’s J) and targeting sensitivity for near-term events; calibration to 6- and 18-month outcomes will produce predicted risk probabilities and calibration plots.

Interpretation: Higher ASHRS scores reflect greater near-term risk. Until cross-validated cut-points are established, interpretation will emphasize continuous risk estimates and decision-curve analyses. Validation will follow COSMIN-aligned methods for reliability, validity, and responsiveness [2,3].

Secondary outcome domains, instruments, scoring, and interpretation

- Non-suicidal self-injury (NSSI) history and characteristics: Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT). This structured assessment yields:

- NSSI frequency indices (lifetime, past year, past month), number of methods, medical severity (e.g., need for medical care), contextual features (triggers, setting), and cessation efforts [4].

Scoring/interpretation: Frequency and method count are summarized as counts and categorical bands; severity as ordinal categories. Derived composites (e.g., past-year frequency × method diversity) index NSSI burden.

- NSSI functions: Inventory of Statements About Self-Injury (ISAS). Part I records NSSI frequency, methods, and pain. Part II rates 13 functional domains on 0–2 scales (0 = not relevant; 1 = somewhat; 2 = very relevant); subscale scores are the mean of two items per function; higher scores indicate stronger endorsement [5].

Interpretation: Intrapersonal (e.g., affect regulation) and interpersonal functions are examined as correlates/predictors of persistence and as convergent validators for ASHRS subdomains.

- Dynamic inpatient aggression risk: Dynamic Appraisal of Situational Aggression—Youth Version (DASA-YV). Seven dynamic indicators scored 0/1 yield a 0–7 total; higher scores indicate greater imminent risk of aggression [6].

Interpretation: Descriptive context for acute ward milieu; used for convergent validity with acute risk states. Claims about predictive accuracy are conservative given setting variability.

- Emotion regulation: Difficulties in Emotion Regulation Scale (DERS). Thirty-six items rated 1–5 (reversed as needed) yield a total score (36–180) and six subscales; higher scores indicate greater dysregulation [7].

Interpretation: Continuous totals/subscales; change scores across follow-up indicate shifts in proximal risk mechanisms.

- Personality functioning: Levels of Personality Functioning Questionnaire for Adolescents (LoPF-Q 12–18). Items rated on a 1–5 Likert scale produce total and domain scores (identity, self-direction, empathy, intimacy); higher scores reflect more impairment [8].

Interpretation: Continuous scores as distal vulnerability markers.

- Borderline personality features: Borderline Personality Features Scale for Children (BPFS-C or brief). Items rated on a Likert scale (typically 1–5) summed to a total; higher scores reflect more features [9].

Interpretation: Continuous total; exploratory clinical bands applied cautiously where supported.

- Attachment/relationships: Inventory of Parent and Peer Attachment (IPPA). Subscales for trust, communication, and alienation are scored by summing Likert items (reverse-scored where specified); higher trust/communication and lower alienation reflect more secure attachment [10].

- Childhood trauma exposure: Childhood Trauma Questionnaire–Short Form (CTQ-SF). Five subscales (emotional/physical/sexual abuse; emotional/physical neglect) scored 5–25 each; cut-points classify none/minimal, low to moderate, moderate to severe, and severe to extreme [11].

Interpretation: Subscale totals and severity categories; a total trauma load index may be reported.

- Anxiety/depression: Revised Child Anxiety and Depression Scale (RCADS-47). Raw scores converted to age/sex-normed T-scores for subscales and total anxiety/depression indices; higher T-scores indicate greater symptom burden. T ≥65 (borderline) and ≥70 (clinical) guide interpretive bands [12].

Interpretation: Continuous T-scores with categorical bands for descriptive reporting.

- Social support: Multidimensional Scale of Perceived Social Support (MSPSS). Twelve items rated 1–7; mean total and subscale scores (family, friends, significant other); 1.0–2.9 low, 3.0–5.0 moderate, 5.1–7.0 high perceived support [13].

Interpretation: Protective factor; higher scores hypothesized to attenuate risk.

- Substance use risk: CRAFFT. Six yes/no items summed 0–6; scores ≥2 indicate elevated risk warranting further assessment [14].

Summary measures and analytic representations

- Primary outcomes for analysis:

- Any suicidal behavior since last contact (binary; C-SSRS).
- Time-to-first suicidal behavior post-discharge (days; C-SSRS plus clinical records).
- Inpatient self-harm rate (events per 100 patient-days) and severity distribution.
- C-SSRS ideation severity (ordinal 0–5) and change (baseline to 6/18 months).
- ASHRS total/subdomain scores (continuous), predicted risk probabilities (0–1), and provisional risk bands.

- Secondary outcomes for analysis:

- NSSI frequency (counts; categorical bands: none, 1–4, 5–19, ≥20 in past year), number of methods (count), and medical severity (ordinal).
- ISAS function subscales (continuous 0–2) and function profiles.
- DERS, LoPF-Q, BPFS-C, IPPA, CTQ-SF (subscales and totals as continuous), RCADS T-scores (continuous with banded descriptors), MSPSS mean scores (continuous with low/moderate/high categories), CRAFFT total (continuous; dichotomized at ≥2).

- Change metrics:

- Continuous scales: mean change with 95% CIs and standardized effect sizes; mixed-effects models for repeated measures.
- Categorical outcomes: transitions across RCADS bands and MSPSS support categories; McNemar

or multinomial models where appropriate.
- Responsiveness: For ASHRS and proximal psychosocial measures, distribution-based indices (e.g., 0.5 SD) will be used cautiously; no a priori minimal important difference is assumed.

- Score handling:

- Missing items handled per instrument manuals (e.g., prorating when ≤20% items missing; otherwise set to missing). Scale reliability (alpha/omega) reported per wave. ASHRS scoring parameters (weights, cut-points) pre-specified and locked before validation testing.

Validation status and alignment with objectives

All secondary instruments are established, adolescent-appropriate measures with published evidence of reliability and validity in relevant populations (C-SSRS, ISAS, DERS, LoPF-Q 12–18, BPFS-C, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT, DASA-YV) [1,4–14]. Their selection provides criterion, convergent, and discriminant anchors for ASHRS validation and covariates for modeling occurrence and persistence of self-harm. ASHRS is novel; its scoring, dimensionality, reliability, construct validity, and prognostic performance will be evaluated against C-SSRS outcomes, NSSI indices (B-NSSI-AT, ISAS), inpatient events, and 6-/18-month recurrence, consistent with COSMIN principles for measurement development and validation [2,3].

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8.2 Psychometric properties and validation approach

Overview and instruments requiring validation

Psychometric evaluation will follow COSMIN guidance for development, reliability, validity, and responsiveness of patient-reported and clinician-rated measures, with an a priori analysis plan aligned to best practices in scale development [1–3]. Measurement equivalence across electronic and interviewer-administered modes will be addressed per ISPOR ePRO recommendations [4,5].

- Newly developed instrument: Adolescent Self-Harm Risk Scale (ASHRS). Full validation is required in Slovene-speaking adolescents and across modes.
- Adapted/translated instruments: Slovene versions of established tools (e.g., B-NSSI-AT, ISAS, DERS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT) will have their internal structure and reliability re-examined in this population, acknowledging prior validation evidence internationally [6–15].
- Clinician-administered tools requiring rater agreement: C-SSRS and DASA-YV will undergo inter-rater reliability assessment in this setting [6,7].

Reliability

- Internal consistency:

- ASHRS and multi-item self-report scales: Cronbach's alpha and McDonald's omega (hierarchical and total) with 95% CIs at each wave; target ≥0.70 for group-level comparisons, recognizing alpha's assumptions and complementing with omega where congeneric models fit better [16–19].

- Test–retest reliability:

- A subsample of clinically stable participants (e.g., healthy controls and stabilized inpatients pre-discharge) will re-complete ASHRS and brief psychosocial indices within 7–14 days. Intraclass correlation coefficients (two-way mixed, absolute agreement) will be estimated; targets: ICC ≥0.70 for total scores [16].

- Inter-rater reliability:

- C-SSRS: quarterly co-ratings or vignette ratings; weighted kappa for ideation severity and behavior classifications with 95% CIs; threshold ≥0.70 [6,17].
- DASA-YV: periodic paired ratings; ICC for total scores; target ≥0.75 [7,16].

- Score precision:

- For ASHRS IRT models, conditional reliability/information functions will be reported to characterize precision across the latent risk continuum [21,22].

Validity

- Content validity (ASHRS):

- Multistep process per COSMIN: domain mapping to the theoretical framework; expert panel review (child/adolescent psychiatry, psychology, nursing, lived experience) to rate relevance, comprehensiveness, and comprehensibility; cognitive debriefing interviews with Slovene adolescents (clinical and school-based) to optimize wording and response options; iterative item refinement with documentation of decision rules [2].

- Structural validity:

- ASHRS: split-sample or cross-validation approach with exploratory factor analysis (polychoric correlations) followed by confirmatory factor analysis (CFA) using robust estimators; model fit indices (CFI/TLI ≥0.90–0.95; RMSEA/SRMR ≤0.08/0.08) [20].
- Item response theory: graded response modeling to evaluate item discrimination and threshold ordering; item fit and local dependence checks; test information curves to guide item reduction while preserving precision in clinically relevant ranges [21,22].
- Established scales: CFAs to verify expected factor structures in the Slovene sample (e.g., DERS six-factor model; ISAS function subscales; LoPF-Q domains), with modifications only when theoretically justified [8–11,20].

- Measurement invariance and differential item functioning (DIF):

- Multi-group CFA across clinical vs healthy controls, sex, and age bands (13–15 vs 16–19) to assess configural, metric, and scalar invariance; ΔCFI ≤0.01 as primary criterion [23].
- ASHRS DIF analyses by group and administration mode using ordinal logistic regression/IRT-based methods; items with meaningful DIF will be revised or modeled with group-specific parameters [23,24].

- Convergent and discriminant validity:

- Hypothesized correlations (direction/magnitude prespecified) between ASHRS and:
- Convergent: C-SSRS ideation severity/behaviors, NSSI indices (B-NSSI-AT frequency/methods; ISAS intrapersonal functions), DERS, RCADS depression/anxiety (moderate-to-strong positive) [6–12].
- Discriminant: MSPSS (negative), select IPPA dimensions (trust/communication positive, alienation negative), with weaker magnitudes than convergent relations [10,12,13].
- Known-groups validity: higher ASHRS and self-harm severity among inpatients vs healthy controls; within-clinical gradients by index-event severity (e.g., recent attempt vs ideation only).

- Criterion-related and predictive validity:

- Short- and medium-term prognostic performance of ASHRS for:
- Any suicidal behavior (C-SSRS since-last-contact) and time-to-first event at 6 and 18 months.
- NSSI recurrence and inpatient self-harm events.
- Discrimination (AUC with 95% CIs), calibration (calibration plots, intercept/slope), and overall performance (Brier score). Internal validation via bootstrapping; optimism-corrected estimates reported [25].
- Clinical utility: decision curve analysis to quantify net benefit across thresholds; sensitivity prioritized to minimize missed high-risk cases, with transparent trade-offs [26].

- Responsiveness:

- For ASHRS and proximal psychosocial measures reassessed longitudinally, standardized response means and mixed-effects estimates will index change. Anchor-based interpretation will reference shifts in C-SSRS ideation categories and occurrence/non-occurrence of self-harm; minimally important change will not be assumed a priori given limited evidence in this domain [6].

Feasibility and acceptability

- Indicators:

- Completion rates and item-level missingness per instrument and wave; administration time (automatically timestamped); need for breaks; participant-flagged burden or distress; mode-related issues.

- Methods:

- Embedded post-assessment acceptability items (brief ratings on clarity, relevance, burden), free-text feedback, and assessor usability notes. Cross-mode comparability checks (distributional and item-level) will inform whether additional migration evidence is required beyond minimal changes, per ISPOR guidance [4,5].

- Thresholds triggering review:

- Item missingness >3%, systematic floor/ceiling effects, or recurrent burden flags will initiate content review and potential refinement before locking final ASHRS scoring.

Implications for analysis, interpretation, and reporting

- Scoring finalization and version control:

- ASHRS item set, dimensionality, and scoring (summed vs IRT-based) will be finalized and locked prior to confirmatory validation and outcome modeling; any item reductions will be documented with rationale. Deprecated versions will be quarantined and excluded from primary analyses.

- Handling measurement error and invariance:

- Reliability estimates (alpha/omega/ICC) and structural fit indices will be reported alongside outcome analyses each wave to contextualize precision. Sensitivity analyses will examine robustness to administration mode and, if scalar invariance is not supported, will rely on latent variable models or group-specific calibrations.

- Use of predictive metrics:

- Discrimination, calibration, and decision-curve results will guide whether ASHRS is interpreted as a continuous risk index or with provisional bands; any cut-points will be labeled exploratory and accompanied by predicted probabilities and uncertainty intervals [25,26].

- Transparency:

- Psychometric findings (content validity evidence, factor/IRT results, invariance/DIF, reliability, responsiveness, feasibility) will be pre-specified in the statistical analysis plan, summarized in manuscripts, and used to qualify conclusions about group differences, longitudinal change, and prognostic associations, in line with COSMIN-aligned reporting standards [1,2].

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8.3 Cultural and linguistic adaptation plan

Scope and guiding principles

This plan ensures that all participant-facing and clinician-administered materials are linguistically accurate and culturally appropriate for Slovene-speaking adolescents (13–19 years) in inpatient and school settings in Slovenia. Adaptation follows established guidance for translation and cultural adaptation of patient-reported outcomes and clinician-rated tools, with emphasis on conceptual equivalence, comprehensibility, and preservation of measurement properties [1–4]. Mode equivalence procedures are applied for electronic administration [6,7].

Materials requiring cultural/linguistic adaptation

- Participant-facing documents:

- Assent and consent forms (adolescent and parent/guardian versions), information sheets, re-contact materials, risk-and-support resource sheets, and debrief texts.
- eConsent and ePRO on-screen instructions, help texts, and standardized administration scripts.

- Study instruments and procedures:

- Self-report scales/questionnaires: ASHRS (new), B-NSSI-AT, ISAS, DERS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT.
- Clinician-rated tools: C-SSRS; DASA-YV (for inpatient contexts).
- Chart abstraction forms and event taxonomies (self-harm and heteroaggression).

- Site procedures with participant interaction:

- Standardized safety scripts (e.g., minimal safety dataset), privacy checks for remote contacts, and referral/helpline scripts.

Where validated Slovene versions exist and are appropriate for the target age range, these will be used without modification. Where not available or where content requires contextualization for Slovenian adolescent settings, the translation and adaptation procedures below will be applied.

Translation and cultural adaptation process

- Preparation

- Define concepts of interest and item intent; create an adaptation brief and a term-by-term glossary (including sensitive terminology for self-harm, suicidality, gender identity/sexual orientation, substance use, and trauma) to guide translators and reviewers [1–3].
- Confirm copyright/permissions for translation and adaptation with instrument owners.

- Forward translation

- Two independent native Slovene translators (fluent in English) produce forward translations, with at least one having clinical/psychological terminology expertise and one with plain-language expertise

focused on adolescent readability [1–3].

- Reconciliation

- A reconciliation linguist synthesizes a single Slovene version, documenting rationale for choices, especially for concepts with no direct lexical equivalents (e.g., “aborted attempt,” “urge,” “affect regulation”) [1–3].

- Back-translation

- A native English-speaking translator blinded to the source text back-translates the reconciled Slovene version to English [1–3].

- Expert review and harmonization

- Multidisciplinary panel (child/adolescent psychiatry, clinical psychology, nursing, linguistics, and lived-experience youth advisor) reviews forward/back translations and resolves discrepancies, focusing on conceptual equivalence, appropriateness for clinical and school contexts, and potential stigma or ambiguity [2–5].
- Cross-instrument harmonization aligns overlapping constructs and response scales across tools (e.g., frequency anchors, time frames) to reduce respondent confusion without altering validated content [1–3].

- Readability and plain language

- Target B1–B2 reading level for adolescents and B2–C1 for guardian materials; minimize idioms; prefer gender-neutral phrasing where grammatically feasible in Slovene; ensure examples relevant to Slovenian school and family contexts [2–4].

- Formatting for ePRO

- Apply mode-migration minimal-change principles: preserve item order, stems, response options, and instructions; ensure consistent layout, navigation, and visual analogs of response scales; implement accessibility features (font size adjustability) [6,7].

Cognitive interviewing and pre-testing

- Cognitive interviewing

- Conduct semi-structured cognitive interviews with 8–12 adolescents in the clinical sample and 8–12 in the school sample for each newly translated or adapted instrument, covering think-aloud and targeted probes on comprehension, retrieval, judgment, and response mapping [5].
- Particular focus on sensitive/self-harm terminology, time frames (e.g., “past month,” “since last contact”), and response scales; refine wording iteratively with documented decision logs.

- Pilot testing

- Field a pilot ePRO bundle in 30–50 participants (balanced across settings) to assess clarity, administration time, item-level missingness, and usability; predefined thresholds for action include item missingness >3% or recurring clarification requests [4,6,7].
- Clinician-administered tools undergo pilot administrations to confirm that Slovene prompts and probes maintain intended scoring anchors; minor wording refinements are made without altering scoring rules.

- Finalization and version control

- Lock versions after resolving cognitive/pilot findings; archive all source files, translator notes, back-translations, and harmonization records in the translation master file with version numbering and effective dates.

Maintenance of cultural relevance and linguistic accuracy during conduct

- Ongoing monitoring

- Monthly review of item-level missingness, free-text feedback, and assessor usability notes; triggers for review include systematic misunderstandings, elevated missingness, or participant distress linked to wording [4].

- Standing language review group meets quarterly to evaluate flagged items and propose controlled corrections; any mid-study changes follow version-control SOPs with impact assessment.

- Rater and facilitator support

- Provide glossaries and standardized Slovene scripts for neutral probes and explanations that preserve item intent; prohibit ad hoc rewording that could alter meaning.
- Refresher briefings incorporate observed linguistic issues and updates to scripts.

- Equity and inclusion

- Offer interpreter support case-by-case for non-native Slovene speakers to ensure ethical communication in consent and safety discussions; data collection in languages other than Slovene will not proceed unless full linguistic validation is completed per this plan.
- Monitor for unintended cultural bias via differential item performance indicators; items demonstrating meaningful differential item functioning will be prioritized for review and, where necessary, analytic adjustment rather than ad hoc wording changes midstream [4].

- Documentation and auditability

- Maintain a complete audit trail of all translation decisions, cognitive interview summaries, pilot findings, and any approved amendments; ensure alignment between ePRO builds and the locked linguistic versions across sites and time points [6,7].

Instrument-specific notes

- ASHRS (new tool)

- Developed in Slovene from inception; content validity established through expert panel ratings and adolescent cognitive debriefings; iterative item refinement precedes psychometric validation and scoring lock [4,5].

- Established measures

- Use existing Slovene versions where verified as conceptually equivalent and age-appropriate; otherwise, apply full forward–back translation and harmonization. No changes to item content or scoring beyond permitted linguistic adaptation.

- Clinician-administered tools

- C-SSRS and DASA-YV administration scripts and probes undergo targeted linguistic verification to maintain anchor integrity. Any clarifying statements used by interviewers are standardized and documented to avoid rater drift attributable to language variation.

Participant information and consent/assent materials

- Adolescent materials prioritize clarity, confidentiality statements, and help-seeking instructions in adolescent-appropriate Slovene; guardian materials elaborate procedures, risks, and data privacy while preserving readability.
- All materials include locally relevant crisis contacts and service pathways, reviewed by clinicians and youth advisors for acceptability and cultural fit [2–4].

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9 DATA MANAGEMENT AND QUALITY

9.1 Data capture systems, source data, CRFs, audit trails

Data capture systems

Study data are captured primarily via a validated, access-controlled electronic data capture (EDC) platform hosted on secure servers within the Republic of Slovenia under the University Psychiatric Clinic Ljubljana (UPKL). The system supports role-based access, configurable eCRFs, real-time edit checks, programmable skip logic, electronic signatures, and a complete, immutable audit trail, in accordance with ICH E6(R2) Good Clinical Practice and EU expectations for computerized systems and electronic data in clinical research [1,2]. Data are encrypted in transit and at rest, with nightly backups, disaster-recovery procedures, and environment change control.

Electronic patient-reported outcome (ePRO) instruments are administered on clinic tablets or secure web links using mode-consistent layouts following ISPOR ePRO migration guidance to preserve measurement properties [3]. Where temporary system or connectivity constraints arise, paper source forms approved for contingency use are deployed; data are subsequently transcribed into the EDC by trained staff within 5 working days, with dual-data entry and adjudication for critical variables to minimize transcription error [1,2]. Remote follow-up contacts (telephone/video) are documented contemporaneously in the EDC; any audio recordings made for rater reliability or qualitative notes (if applicable and consented) are stored on encrypted institutional drives and indexed in the EDC as source files.

Laboratory, genetic, and epigenetic data and associated sample metadata are managed in a laboratory information management system (LIMS) compliant with biobanking best practices (unique barcodes, chain-of-custody, processing timestamps, storage location, and freeze–thaw tracking), with controlled interfaces for pseudonymized linkage to the EDC [2,4].

All processing of personal data complies with the EU General Data Protection Regulation (GDPR); identifiers are limited to a site-held participant identification log separated from research data, with pseudonymized study IDs used for all analyses and transfers [5].

Source data definition

Source data comprise original records and certified copies that first capture participant information, including:

- Signed consent/assent and HIP-like privacy documentation, where applicable to GDPR-aligned institutional practice [5].
- Clinician-administered assessments and structured interviews: C-SSRS, DASA-YV, and chart abstraction of inpatient self-harm/heteroaggression events (clinical notes, incident reports, observation flow sheets).
- Self-report instruments administered as ePRO or paper: ASHRS, B-NSSI-AT, ISAS, DERS, LoPF-Q 12–18, BPFS-C/brief, IPPA, CTQ-SF, RCADS, MSPSS, CRAFFT.

- Hospital records relevant to eligibility and outcomes (admission/discharge summaries, diagnoses, medications, emergency interventions).
- Digital records generated by the EDC/ePRO (timestamps, administration logs), and, where applicable, audio files/transcripts of interviews or co-ratings explicitly consented for reliability/quality assurance.
- Laboratory and biobanking records: phlebotomy logs, barcoded tube labels, shipment receipts, LIMS entries (sample receipt, processing steps, QC metrics), and results files (e.g., genotyping/methylation raw and processed outputs) [4].

Paper documents are considered source when they are the first place where data are recorded. Scanned certified copies stored in the regulated content management system may serve as source if they preserve legibility, content, and metadata per data integrity principles [2].

Case report forms (CRFs) and data collection instruments

CRFs and eCRFs are derived from the protocol and instrument manuals, with standardized administration scripts, item-by-item completion instructions, and built-in logic to enforce valid ranges, required fields, permitted units, and skip patterns. Instruments maintain original item wording and response options; any culturally adapted Slovene versions are locked prior to production build, aligned with the cultural/linguistic adaptation plan.

- Design and version control:

- Each CRF has a unique form ID, version number, effective date, and change history. Proposed revisions undergo controlled impact assessment and are approved by the Principal Investigator (PI) and data management before release; deprecated versions remain archived and are not used prospectively [2].

- Completion:

- Trained assessors complete clinician-rated eCRFs contemporaneously. Participants complete ePROs privately with on-screen guidance; assistance is limited to neutral clarifications per script. For paper contingencies, black ink and legible print are required; unanswered items are discouraged unless allowed by instrument rules.

- Review and verification:

- Site staff perform same-day checks for completeness and plausibility. The data management team runs automated edit checks and weekly data listings to identify outliers, inconsistencies, and missingness patterns. Discrepancies trigger queries routed to sites for resolution within defined timelines (typically 10 working days), with all actions documented in the audit trail [1,2].

- Transcription from paper:

- Two independent data entry operators enter paper source for prespecified critical fields (eligibility criteria, primary/secondary outcomes, event dates/severity). Discrepancies are reconciled by a third reviewer; non-critical fields undergo single entry with targeted verification.

Data reconciliation and source data verification (SDV)

A risk-based monitoring and SDV approach is applied consistent with ICH E6(R2) [1]:

- Critical data (eligibility, consent, cohort assignment, C-SSRS ideation severity and suicidal behaviors, inpatient self-harm events and severity, ASHRS scores at prespecified time points, serious adverse clinical events relevant to safety referrals, sample ID and chain-of-custody) undergo 100% SDV against source.
- Non-critical data undergo targeted SDV sampling informed by centralized review (e.g., unusual score distributions, date inconsistencies).
- Reconciliation:

- Event reconciliation aligns eCRF event logs with ward incident reports and clinical notes monthly.

- Biobank reconciliation aligns EDC specimen records with LIMS inventories (IDs, volumes, storage locations) quarterly, with discrepancies resolved via documented chain-of-custody review [2,4].

Audit trails and data integrity controls

Data integrity follows ALCOA+ principles (Attributable, Legible, Contemporaneous, Original, Accurate,

plus Complete, Consistent, Enduring, and Available) and EU/UK regulator expectations for computerized systems [2,6]:

- System-level audit trails automatically capture user ID, date/time stamp (synchronized with server time), data field, previous value, new value, reason for change (free-text or coded), and electronic signature status. Audit trails are immutable, retained with the study record, and available for inspection.
- Data corrections:

- Electronic: authorized users enter corrections via the EDC “change” function with mandatory reason-for-change. Direct database edits are prohibited outside validated data-fix utilities subject to change control.
- Paper: original entries are not obliterated; a single line strike-through, dated and initialed, with the corrected value and reason documented in the margin or designated correction log.

- User access and segregation of duties:

- Role-based permissions (e.g., data entry, assessor, monitor, data manager, statistician, PI) are provisioned on the principle of least privilege, reviewed quarterly, and revoked upon role change or departure. Developers and system administrators do not have permission to modify production data records.

- Data lifecycle controls:

- Time-bound data entry windows, form status flags (in progress, completed, verified, frozen, locked), and database freeze/lock procedures are enforced prior to interim/final analyses. Exports for analysis are checksum-verified and documented; only pseudonymized datasets are released to analysts [2].

- Computerized system validation and change control:

- The EDC/ePRO and LIMS environments are validated for intended use with documented user requirements, risk assessment, testing (IQ/OQ/PQ or fit-for-purpose equivalents), and periodic revalidation following significant updates. Configuration and code changes follow SOP-governed change control with impact analysis and approval prior to deployment [2].

Data quality oversight and issue management

- Edit checks and listings:

- Real-time hard checks prevent impossible entries (e.g., dates in the future, out-of-range scale scores), while soft checks generate queries for confirmation (e.g., extreme but plausible values). Centralized surveillance flags protocol deviations, missing assessments, and unusual patterns (heaping, straight-lining).

- Query management:

- All queries are tracked within the EDC with open/close dates, responsible role, and resolution text. Repeated issues inform targeted retraining and, if systemic, CRF or process refinement.

- Rater agreement and mode consistency:

- Periodic co-ratings and vignette exercises for clinician-rated tools are logged as quality records; any recalibrations are documented without retroactive score alteration. Mode-related issues for ePROs are monitored; changes to presentation follow ISPOR minimal-change principles and undergo impact assessment prior to implementation [3].

Data protection, retention, and records management

- Confidentiality and security:

- Pseudonymization is applied at capture; direct identifiers are stored only in the site-restricted linkage file. Data transfers use encrypted channels; portable media are prohibited. Access logs and intrusion detection are monitored by institutional IT per policy [2,5].

- Record retention:

- Essential documents, source data, audit trails, and analysis data are retained in durable, retrievable form for the period required by Slovenian law, GDPR, and institutional policy. Destruction, when permitted, follows SOPs with certificates of destruction [2,5].

- Participant rights:

- GDPR rights (access, rectification, restriction, and, where applicable, erasure) are operationalized through institutional processes that balance research integrity and lawful bases for processing;

requests and outcomes are documented in the study records [5].

Biologic sample data and chain-of-custody

- Unique, pseudonymized specimen IDs and barcodes are assigned at draw; phlebotomy time, processing intervals, and storage conditions are recorded in real time. Any aliquoting, shipment, or analysis events are logged in the LIMS with responsible personnel, date/time, and location to maintain full traceability [2,4].
- Data generated from biospecimens (raw and processed) are stored with metadata, versioned pipelines, and checksum-validated files. Linkage to phenotypic data uses the pseudonymized study ID; re-identification is restricted to designated custodians for safety or legal requirements only.

Paper records and contingency procedures

- Paper source and CRFs are stored in locked, access-controlled cabinets within the clinical unit; removal is prohibited except for scanning in secure areas. A paper records log documents creation, movement, and archiving.
- In contingency use, pre-numbered paper forms mirror eCRF structure. Upon transcription, a verification stamp records the transcriber, date, and verification status. Paper and electronic record counts are reconciled weekly until all forms are entered and verified.

Data lock and archival

- Prior to interim and final analyses, the database is frozen; outstanding queries are resolved; programmed data derivations are re-run under version-controlled code; and quality checklists are signed by data management and the PI. After lock, no changes are permitted without formal unlock authorization and full audit trail documentation [2].
- Upon study closeout, all electronic records (EDC, ePRO, LIMS, audit trails), certified copies of paper records, and system validation documentation are archived in compliant repositories to ensure long-term readability and accessibility.

References

1. International Council for Harmonisation. ICH E6(R2) Guideline for Good Clinical Practice. Geneva: ICH; 2016.
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9.2 Data integrity, monitoring, and inspections

Quality management framework and governance

Data integrity is managed under a risk-based quality management system consistent with ICH E6(R2) Good Clinical Practice and ICH E8(R1) principles of quality by design and risk-based quality management [1,2]. Critical-to-quality (CtQ) factors for this observational, high-risk adolescent study include: informed consent/assent documentation; eligibility confirmation; accurate capture of C-SSRS assessments and suicidal/self-harm events; completeness and timing of prespecified instruments (including ASHRS); chain-of-custody for biospecimens and derived data; and protection of personal data. Computerized systems and electronic records comply with EMA guidance on computerised systems (including validated audit trails) and ALCOA+ expectations for data integrity [3,4]. GDPR obligations are embedded throughout data handling and monitoring activities [5].

A study-level Data Quality and Monitoring Plan (DQMP) prespecifies CtQ data fields, monitoring methods and frequency, roles/responsibilities, query and deviation workflows, escalation thresholds, and documentation standards. The Principal Investigator (PI) has overall responsibility; a designated monitor, independent of day-to-day data entry, executes monitoring. The data manager oversees centralized surveillance, issue trending, and CAPA coordination; statisticians advise on risk indicators and missing-data patterns.

Monitoring approach and scope

A combined centralized and targeted on-site/remote monitoring strategy is implemented, aligned to ICH E6(R2)/E8(R1) risk-based monitoring (RBM) principles [1,2]:

- Centralized monitoring (primary modality):
  - Ongoing review of data flows, instrument completion, time-stamps, range/consistency checks, and outlier detection through programmed listings and dashboards.
  - Key risk indicators (KRIs) include overdue assessments, atypical score distributions (e.g., heaping/straight-lining), inconsistent C-SSRS categorizations across visits, implausible dates/intervals (e.g., events outside hospitalization), discordance between inpatient incident logs and eCRF events, unusual biospecimen reconciliation discrepancies, and elevated missingness by instrument or rater.
  - Monthly data review meetings triage findings, assign actions, and document outcomes.

- Remote monitoring:
  - Source data verification (SDV) performed via secure access to redacted source or certified copies, focusing on CtQ data. Remote review of consent/assent documentation, eligibility verification, C-SSRS co-ratings, and specimen logs is conducted at least quarterly.

- On-site monitoring:
  - Scheduled at study initiation and then risk-triggered (e.g., systemic query backlogs, repeated protocol deviations, KRI excursions). On-site visits include direct SDV, review of investigator site files, training records, privacy safeguards for adolescent assessments, and physical inspection of paper records and sample storage.

SDV is 100% for CtQ variables (consent/assent, eligibility, C-SSRS ideation severity and suicidal behaviors, inpatient self-harm events with timestamps/severity, ASHRS time-point identifiers/scores, serious safety referrals, and biospecimen chain-of-custody) and risk-based sampling for non-critical fields, as defined in the DQMP [1].

Detection, documentation, and resolution of discrepancies

- Data discrepancies:
  - Automated edit checks flag impossible or improbable values at entry; centralized listings identify cross-form inconsistencies. Monitors and data managers raise electronic queries with clear issue descriptions and required actions. Sites respond within defined timelines; all actions are recorded in an immutable audit trail with user/time stamps and reasons for change per EMA expectations [3].

- Reconciliation:

- Monthly reconciliation aligns inpatient event eCRFs with ward incident reports and clinical notes; quarterly reconciliation aligns EDC biospecimen records with LIMS inventories. Discrepancies trigger documented investigations and corrective entries, preserving original values per ALCOA+ [4].

- Rater calibration issues:

- Divergences identified via co-ratings/vignettes lead to targeted retraining; prospective scoring is recalibrated but prior verified scores are not retroactively altered. Trends inform preventive actions and, if needed, enhanced guidance in administration scripts.

- Escalation and CAPA:

- Recurrent or material issues (e.g., misclassification of C-SSRS behaviors, repeated late entries, specimen mislabeling) are escalated to the PI. Root-cause analysis is performed; CAPA plans define containment, corrective steps, effectiveness checks, and timelines. Completion and effectiveness are tracked centrally.

Missing data and protocol deviations related to data collection

- Missing data management (operational):

- Real-time prompts discourage item/scale omissions unless permitted by instrument rules; daily site-level checks and weekly centralized listings identify partial forms and overdue visits. Participants are promptly re-contacted within allowable visit windows. For paper contingencies, dual data entry for CtQ fields minimizes transcription-related missingness.
- Item-level missingness thresholds (e.g., >3% for any item; >10% for any instrument at a timepoint) trigger review and potential retraining or process adjustment.

- Protocol deviations (PDs):

- PDs related to data (e.g., assessments outside window, use of non-approved instrument versions, incomplete consent elements, unblinded co-rating outside SOP, late entry beyond defined windows without contemporaneous justification) are documented on PD forms with classification (major/minor), root cause, participant impact, and CAPA. Major PDs affecting CtQ data are reported to the sponsor/oversight per institutional policy and, where required, to the ethics committee.

- Retention of transparency:

- No undocumented data deletion or overwriting is permitted. All corrections require a reason-for-change. Late data entry requires contemporaneous source and explanation; the audit trail must show original and corrected states [3,4].

Preservation of data integrity across the data lifecycle

- Attributable and contemporaneous capture:

- All entries are linked to unique user IDs; time on device is synchronized to server time. Clinician-rated tools are completed contemporaneously; delayed entries must reference dated source notes.

- Consistency and completeness:

- Controlled eCRF versions and locked instrument translations prevent drift. Database freezes/locks precede interim/final analyses; post-lock changes require formal unlock authorization with full audit traceability [3,4].

- Enduring and available records:

- Electronic records, audit trails, and certified copies are retained per legal/institutional retention periods; accessibility for oversight is ensured through validated repositories and documented retrieval procedures [3–5].

Inspection and audit readiness

The study maintains inspection-ready documentation to facilitate audits/inspections by the sponsor,

UPKL quality unit, ethics committees, or competent authorities:

- Essential documents:
  - Current/archived protocol and amendments; DQMP; SOPs; training logs; delegation logs; investigator site files; consent/assent templates and signed forms; instrument licenses/permissions; cultural/linguistic adaptation records; monitoring reports and follow-up letters; PD and CAPA logs; risk assessments; data protection impact assessment (DPIA); GDPR legal bases and privacy notices; and computerized system validation packages (user requirements, risk assessments, IQ/OQ/PQ/fit-for-purpose testing, change control).

- System access and demonstrations:
  - Read-only access for inspectors to EDC audit trails, role/permission matrices, data correction logs, and LIMS chain-of-custody is provided under supervision, preserving participant confidentiality in line with GDPR [3,5].

- Staff readiness:
  - Key personnel are trained to describe processes for consent verification, assessment administration, query management, SDV, reconciliation, and CAPA. Interview scripts and rater calibration materials are available for review.

- Pre-inspection checks:
  - Prior to scheduled inspections, targeted internal audits verify completeness of essential files, reconciliation status of CtQ datasets, closure of outstanding queries, and alignment between source and eCRF for sampled records. Any gaps are addressed with documented corrective actions.

Roles and responsibilities

- Principal Investigator:
  - Overall accountability for data integrity, protocol adherence, and timely resolution of CtQ issues; approves CAPA and database locks.

- Monitor:
  - Executes RBM activities (centralized, remote, on-site), conducts SDV and reconciliation checks, verifies consent/eligibility, issues/triages queries, documents findings, and confirms CAPA effectiveness.

- Data Manager:
  - Designs edit checks and listings, oversees centralized surveillance and trend analysis, manages query workflows, controls CRF versions, coordinates freezes/locks, and maintains export traceability.

- Site Assessors/Coordinators:
  - Ensure contemporaneous, accurate source documentation and eCRF entries; respond to queries; implement CAPA; maintain site files; and support inspections.

- Statistician:
  - Advises on KRIs, missing-data surveillance, and data fitness-for-purpose prior to analysis; confirms dataset provenance and lock conditions.

- IT/System Administrator (institutional):
  - Maintains validated environments, access controls, backups, and disaster recovery; provides audit trail exports; implements change control per approval [3].

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9.3 Privacy, coding, GDPR/local regulations, data breach procedures

Roles, responsibilities, and governance

- Data controller and oversight: University Psychiatric Clinic Ljubljana (UPKL) is the data controller for all study processing activities carried out in Slovenia. The Principal Investigator (PI) is responsible for protocol compliance and ensures that privacy-by-design and data minimisation are embedded in all procedures. The institutional Data Protection Officer (DPO) provides independent oversight, advises on lawful bases and safeguards, reviews and approves the Data Protection Impact Assessment (DPIA), and is the point of contact with the supervisory authority.
- Processors and third parties: Any external service providers (e.g., electronic data capture [EDC]/hosting vendors, certified laboratories) act as processors under written data processing agreements (DPAs) aligned with GDPR Article 28, with clear instructions, confidentiality, security, subprocessor control, and audit rights [1,2].
- Staff responsibilities: Access to identifiable data is strictly role-based and limited to staff who need it for consent verification, safety follow-up, or legally mandated reporting. All personnel complete mandatory training on confidentiality, secure handling of special-category data, and breach reporting procedures before accessing systems.

Lawful basis, special-category data, and participant rights

- Lawful basis: Given the public-mission context and the scientific objectives, the primary lawful basis anticipated for personal data is performance of a task carried out in the public interest (GDPR Art. 6(1)(e)) or legitimate interests where appropriate, with special-category data processed under the scientific-research derogation with appropriate safeguards (GDPR Art. 9(2)(j), Art. 89(1)), as permitted by Slovenian law (ZVOP-2) [1,3]. Where explicit consent is used for specific optional elements (e.g., audio recording for rater reliability), it will meet GDPR standards (freely given, specific, informed, unambiguous, and withdrawable without detriment) [4].
- Children and guardians: For minors, assent is sought from adolescents; parental/guardian consent is obtained as required by Slovenian law and ethics approval. Privacy notices use clear, age-appropriate language.
- Research safeguards and possible derogations: The study applies appropriate safeguards (pseudonymisation, data minimisation, access controls, and independent oversight) to enable, where lawfully applicable, limited derogations from certain data subject rights strictly for scientific research integrity (e.g., restrictions on erasure or portability after data are irreversibly pseudonymised and analyses are underway), consistent with GDPR Art. 89 and ZVOP-2. All rights requests (access, rectification, restriction, objection where applicable, erasure where applicable) are handled via institutional procedures with DPO oversight and documented outcomes [1,3].

Confidentiality protections, coding, and separation of identifiers

- Coding/pseudonymisation:

- At enrolment, each participant is assigned a unique study ID. Direct identifiers (name, national ID, full address, personal contact details) are recorded only on a site-held participant identification log

stored separately from research data in an access-restricted location.
- All research data, including clinical scales (e.g., C-SSRS, B-NSSI-AT, ISAS), ePROs, hospitalization event logs, and biospecimen metadata/results, are captured and stored under the study ID without direct identifiers. Linkage for re-identification is permitted only for defined purposes (safety escalation, clinically indicated referrals, rights requests, withdrawal, and legal obligations) by designated custodians approved by the PI and DPO.

- Separation of functions:

- Consent/assent forms and re-contact details are retained in a restricted repository distinct from the analytical dataset. Personnel involved in statistical analysis receive only pseudonymised datasets. Any publications or data sharing use de-identified, aggregation-limited outputs to minimise re-identification risk [2,5,6].

- Minimisation and purpose limitation:

- Only data necessary to meet prespecified objectives are collected. Free-text fields are discouraged; when used, they are reviewed to remove inadvertent identifiers before analysis.

- Privacy during assessments:

- Interviews and ePRO completion occur in private settings. Participants are informed of confidentiality limits related to imminent risk of harm; disclosures triggering duty-of-care responses are documented minimally and handled through predefined clinical pathways.

Storage, security, and access controls

- Hosting and localization: Primary EDC/ePRO systems and institutional storage are hosted on secure servers located in the Republic of Slovenia. No identifiable or pseudonymised data are transferred outside the EU/EEA unless lawfully justified and safeguarded (e.g., Standard Contractual Clauses and transfer risk assessment), with DPO approval [1,2].
- Technical and organisational measures:

- Encryption in transit and at rest; strong authentication and least-privilege role-based access; quarterly access reviews; immutable audit trails; regular backups and disaster recovery; vulnerability management and change control consistent with recognised information security standards (e.g., ISO/IEC 27001-aligned controls) [2,7].

- Pseudonymised linkage of biospecimens via barcoded IDs; chain-of-custody in a validated LIMS; segregation of raw genetic/epigenetic data from any direct identifiers.

- Data retention and deletion:

- Records are retained only for the period approved by the ethics committee and required by Slovenian law and institutional policy for scientific research and auditability. When permissible, secure destruction or irreversible anonymisation is performed under SOPs with documented certificates.

DPIA, records of processing, and documentation

- DPIA: Prior to initiation, a DPIA assesses risks inherent in processing special-category data from minors, genetic/epigenetic data, and high-risk clinical information, and defines mitigations (pseudonymisation, access controls, encryption, minimisation, retention limits, breach response). The DPIA is approved and periodically reviewed by the DPO, and updated upon material changes in processing [1,3].
- Records of processing: Article 30 records describe purposes, categories of data/subjects, recipients, retention, transfers, and safeguards, and are maintained by the controller with DPO oversight [1].
- Transparency materials: Participant-facing privacy notices specify the controller, DPO contact, purposes, lawful bases, categories of recipients, retention, rights, and the limited conditions under which confidentiality may be overridden for safety/legal reasons.

Data sharing and secondary use

- External sharing for validation or secondary analysis occurs only in pseudonymised form under data sharing agreements that prohibit re-identification, restrict onward transfers, specify purposes compatible with the original research, require equivalent security, and mandate

breach notification and return/destruction at end of use. Any new purposes undergo ethics/DPO review to confirm compatibility with research exemptions and safeguards under GDPR and ZVOP-2 [1,3].

Data breach identification, containment, and notification

- Definition and scope: A personal data breach is any security incident leading to accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored, or otherwise processed, including pseudonymised data where re-identification risk exists [1,2].
- Detection and internal reporting:

- All staff must immediately report suspected breaches (e.g., lost device, misdirected email, unauthorised access, ransomware, corrupted files) to the PI and institutional Information Security function via the designated incident channel and notify the DPO without delay. Initial facts (what, when, systems/users involved, data types, volume, containment steps) are logged in the breach register.

- Containment and assessment:

- The incident response team (PI, DPO, IT security, data manager, and relevant leads) promptly contains exposure (e.g., revoke access, isolate systems, reset credentials, retrieve or remotely wipe devices, disable links), preserves forensic evidence, and assesses the likelihood and severity of risk to rights and freedoms considering data sensitivity (e.g., self-harm, mental health, trauma, sexual identity), identifiability, volume, and potential for misuse [2].

- Notification:

- Where a breach is likely to result in a risk to the rights and freedoms of natural persons, the controller notifies the Slovenian supervisory authority (Information Commissioner) without undue delay and, where feasible, not later than 72 hours after becoming aware, including the information required by GDPR Art. 33(3) (nature of breach, categories/approximate number of data subjects/records, likely consequences, measures taken/proposed) [1,2].

- Where the risk is high, affected data subjects are informed without undue delay in clear language per GDPR Art. 34, including guidance to mitigate harm (e.g., vigilance for phishing, available support), unless an exemption applies (e.g., subsequent measures ensure no high risk, or notification would involve disproportionate effort and public communication is used) [1,2].

- Processors must notify the controller without undue delay after becoming aware of a breach, per DPA obligations [1].

- Post-incident actions:

- Root-cause analysis and corrective/preventive actions (technical, organisational, training) are documented and tracked to completion; effectiveness is verified. All breaches and justifications for notification/no notification are recorded in the breach register to demonstrate accountability [1,2].

- Special considerations for sensitive cohorts:

- Given the extreme sensitivity of adolescent mental health and genetic data, the threshold for “likely high risk” is interpreted conservatively; even pseudonymised data exposures are evaluated for re-identification vectors (small cohorts, rare event combinations). Communications are coordinated with clinical teams to avoid distress and to offer support resources.

Limits to confidentiality and safety overrides

- Participants are informed that confidentiality may be lawfully and ethically overridden in narrowly defined situations to protect life or prevent serious harm (e.g., imminent risk of suicide or violence). Any such disclosures are minimised to what is necessary, directed to appropriate care providers or authorities, documented, and reviewed under institutional safeguarding policies.

International transfers and cross-border collaboration

- No routine international transfers of identifiable or pseudonymised data are planned. If collaboration requires transfers outside the EU/EEA, GDPR Chapter V mechanisms are applied (e.g., European Commission adequacy decision or Standard Contractual Clauses with supplementary measures following a transfer risk assessment), with prior DPO and ethics approval and explicit description in the privacy notice [1,2].

Audits, inspections, and continual compliance

- Compliance with GDPR, ZVOP-2, and institutional policies is reviewed through internal audits and is inspection-ready. Privacy controls are tested periodically; material findings inform updates to SOPs, training, and the DPIA. Changes in processing (e.g., new instruments, new processors, additional data linkage) trigger re-assessment for privacy impacts and, where applicable, amendments to ethics approvals and transparency materials.

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9.4 Record keeping, retention, and archiving

Scope of records and essential documents

The study maintains a complete, contemporaneous, and auditable record of all activities and data generated, applying ALCOA+ principles and GDPR accountability. Records include, at minimum:

- Governance and approvals: ethics committee approvals and correspondence; protocol and amendments; Data Quality and Monitoring Plan; SOPs; Data Protection Impact Assessment; data processing agreements; investigator and staff curricula vitae; delegation and training logs; rater calibration records; cultural/linguistic adaptation files (translation certificates, decision logs, version histories).
- Participant-level source documents: signed consent/assent and privacy notices; eligibility confirmations; C-SSRS, B-NSSI-AT, ISAS, ASHRS and other instrument source (ePRO administration logs, certified paper copies where used); hospitalization records supporting self-harm/heteroaggression events; safety referrals and outcomes; adverse clinical events relevant to duty-of-care; withdrawal/retention communications and outcomes.
- Case report forms (CRFs/eCRFs): all finalized entries with audit trails, data queries and resolutions, protocol deviation forms, reconciliation logs (clinical events and biospecimens).
- Biobanking and laboratory documentation: specimen logs (collection, processing, storage, shipments), LIMS chain-of-custody, QC reports, certificates of analysis, raw and processed genetic/epigenetic data with analysis metadata/pipeline versions.

- Monitoring and quality records: centralized/on-site/remote monitoring reports and follow-up letters; issue logs; corrective and preventive actions (CAPA); risk indicator outputs; internal audit reports.
- System records: computerized system validation documentation (user requirements, risk assessments, IQ/OQ/PQ or fit-for-purpose testing), change-control records, access control reviews, backup and disaster-recovery verification, system audit trail exports.
- Correspondence: substantive communications with sites, laboratories, vendors, and regulators/oversight (including breach notifications, if any); meeting minutes and decisions affecting conduct or data.

A Study Master File (SMF) maintained by the sponsor/institution and Investigator Site Files (ISFs) at each site collectively comprise the essential documents archive, following ICH E6(R2) expectations by analogy and the EMA TMF guidance adapted to non-interventional research [1,2,6].

Formats, filing, and version control

- Electronic records are stored in validated systems (EDC/ePRO, LIMS, regulated e-archive) with immutable audit trails, role-based access, and time-stamped versioning per EMA computerized systems guidance [2].
- Paper records (e.g., signed consents, contingency paper source) are filed in pre-indexed ISF binders; certified copies are created for electronic archiving where permitted. Scanning procedures ensure completeness, legibility, and metadata capture; certified copies may serve as source if they meet data integrity criteria [1,2,5].
- All instruments, CRFs, and participant-facing documents carry unique identifiers, version numbers, and effective dates; superseded versions are withdrawn from use and archived.

Storage, security, and custody

- Primary electronic repositories are hosted on secure UPKL servers located in Slovenia with encryption at rest and in transit, routine backups, and disaster-recovery capabilities aligned to ISO/IEC 27001 controls [5]. Write-once or functionally immutable backups are maintained for audit trails and final datasets.
- Paper records are stored in locked, access-controlled areas within UPKL; movement off-site is prohibited except for secure scanning/archiving under chain-of-custody.
- Custodianship:

- The Principal Investigator (PI) is accountable for the integrity and completeness of site records; the institutional data manager and archivist oversee electronic archiving and retrieval.
- Access is granted on the principle of least privilege and reviewed quarterly; read-only supervised access is provided to monitors, auditors, or inspectors, preserving GDPR safeguards [2,3].

Archiving procedures at study closeout

At closeout, the database is locked; final exports, code, and outputs are checksum-verified and indexed. The SMF and each ISF are reconciled against a predefined essential documents index; missing items are obtained or deviations documented. Archival packages include:

- Final protocol and amendments; analysis plans; locked datasets and derivation specifications; statistical code and logs; result listings; final reports and publications.
- Complete audit trails (EDC/ePRO, LIMS), query histories, monitoring reports, CAPA closures.
- Certified copies of signed consent/assent; participant identification logs retained separately with restricted access.
- System validation and change-control dossiers; user/permission matrices at lock; backup/DR test attestations.

Electronic archives are stored in a validated e-archive ensuring long-term readability and migration planning; integrity checks (hash verification) are performed at ingest and periodically thereafter. Paper

archives are boxed, labeled, and logged; environmental conditions minimize degradation.

Retention periods

- Essential documents (SMF/ISF), source data, audit trails, and analysis records will be retained for at least 10 years after study closeout or last publication, whichever is later, unless a longer period is required by institutional policy or funder/oversight, and provided retention remains compatible with GDPR storage limitation and research safeguards [1,3,6].
- Genetic/epigenetic raw data and associated metadata will be retained for at least 15 years to enable verification and secondary analyses under approved governance, reflecting biobanking best practice; retention beyond this window will be reviewed by the DPO and ethics committee for continued necessity and proportionality [4].
- Biospecimens: retention in the UPKL biobank follows consent terms, ISO 20387-aligned procedures, and ethics approvals; when retention is no longer justified or permitted, specimens are logged and destroyed under controlled conditions with certificates retained [4].

Any stricter legal or contractual requirement (e.g., funder mandate) supersedes the above minima. Retention schedules are documented in the Records Retention Schedule and reviewed periodically.

Access, retrieval, and audits/inspections

Archived records remain readily retrievable within a reasonable timeframe (typically 10 working days for standard requests; expedited for inspections). A documented request and release log records who accessed what, when, and why. Inspectors/auditors may review archives on-site or via supervised read-only electronic access, with participant confidentiality preserved per GDPR [2,3].

Record transfer, relocation, and business continuity

If records are transferred (e.g., change of PI, institutional reorganization, or vendor transition):

- A transfer plan defines scope, media, indexing, integrity checks, encryption, and responsibilities; both sender and receiver sign a transfer/receipt log.
- For international transfers of personal data, GDPR Chapter V mechanisms and DPO approval are required; identifiable records are not transferred outside the EU/EEA unless lawfully justified and safeguarded [3].
- Disaster events trigger institutional business-continuity procedures; backups are restored to validated environments with documented reconciliation to pre-event states [2,5].

Destruction and anonymisation

At the end of the approved retention period, and where further retention is not required or justified, records are securely destroyed or irreversibly anonymised:

- Paper: cross-cut shredding or certified destruction services with chain-of-custody; certificates of destruction filed.
- Electronic: cryptographic erasure or secure overwrite aligned to institutional policy; destruction logs retained.
- Exceptions: records necessary to demonstrate research integrity or to fulfill legal/accountability obligations may be retained longer, subject to documented justification and DPO oversight; truly anonymised datasets may be retained for scientific purposes consistent with GDPR recital 26 [3].

Participant withdrawals are handled per consent and GDPR: identifiable data are removed from active datasets where feasible; data already processed for research integrity may be retained under Art. 89 safeguards, with actions documented [3].

Responsibilities and oversight

- PI: ensures completeness, accuracy, and timely archiving of ISF; approves destruction/transfer; maintains readiness for inspection.
- Data Manager/Archivist: prepares archival packages; validates electronic archives; maintains indexes and retrieval processes; oversees retention schedules and migrations.
- DPO: oversees GDPR-compliant retention, transfers, and destruction; reviews derogations for scientific research; audits compliance.
- Monitor/Quality Unit: verifies presence and quality of essential documents at closeout; confirms archiving and retention controls are in place and effective.

References

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10 STATISTICAL ANALYSIS

10.1 Analysis populations and protocol deviation handling

Analysis populations

- Full analysis set (FAS; intention-to-observe): All enrolled, consented/assented participants who meet eligibility criteria and provide at least one post-enrolment measurement relevant to any primary or secondary objective. For the high-risk inpatient cohort, this includes participants with baseline assessments and/or documented inpatient self-harm/heteroaggression events. For healthy controls, this includes participants with baseline assessments. The FAS is the primary analysis population for all efficacy/associational and prognostic objectives, consistent with transparent, minimally biased reporting for observational research [1,2].

- Longitudinal follow-up analysis set (LFAS): Subset of the high-risk cohort with at least one post-discharge follow-up (6 or 18 months) contributing to longitudinal models of trajectories, relapse, or time-to-event outcomes. Analyses that require repeated measures will be primarily conducted in the LFAS, with modeling approaches that accommodate intermittent missingness without listwise deletion where appropriate [5,6].

- Measurement evaluation set (MES): Participants with valid administration of the ASHRS and prespecified comparator instruments at the same visit (e.g., ASHRS with C-SSRS and B-NSSI-AT at baseline), used for psychometric evaluation (dimensionality, reliability, construct validity) and predictive performance analyses. Where specific analyses require additional data (e.g., inpatient events for short-term predictive validity, or 6-/18-month

outcomes for medium-term predictive validity), corresponding MES subsets will be defined a priori per analysis plan, in line with COSMIN/psychometric reporting standards [3].

- Per-protocol set (PP): Subset of the FAS excluding participants with major protocol deviations that are expected to materially affect the interpretability of primary outcomes (see classification below). The PP is used for sensitivity analyses only, recognizing the observational design and prioritizing the FAS for primary inference [1,2].

- Biospecimen analysis sets: Defined per assay (genetic/epigenetic) as participants with analyzable samples meeting pre-established quality control thresholds and linkable phenotypic data at the relevant timepoint(s). Primary phenotypic inferences remain anchored in the FAS/LFAS; omics-specific analyses will transparently report denominators and missingness patterns [2].

Protocol deviations: identification and classification

Protocol deviations (PDs) are captured prospectively via dedicated eCRF forms and centralized monitoring. PDs are categorized as minor or major based on expected impact on consent/eligibility integrity, primary endpoint validity, or key risk-of-bias domains, guided by ICH E6(R2)/E9 principles adapted to non-interventional research [1,4]:

- Major PDs (examples):
  - Ineligibility identified post-enrolment that contradicts prespecified criteria (e.g., age outside 13–19 years; excluded conditions such as acute psychosis or intellectual disability).
  - Deficient or incorrect consent/assent that cannot be remediated per ethics guidance.
  - Use of a non-approved instrument version/translation for CtQ measures (C-SSRS, B-NSSI-AT, ASHRS) or administration outside standardized procedures likely to alter scores.
  - Missed or grossly out-of-window administration for time-critical assessments used in primary outcomes (e.g., baseline ASHRS administered after inpatient sentinel events without contemporaneous documentation).
  - Systemic failure to monitor/record inpatient self-harm/heteroaggression events during the specified observation period.
  - Data integrity concerns (fabrication, unresolvable discordance between source and eCRF) affecting CtQ variables.
  - Biospecimen mislabeling or chain-of-custody breaks preventing valid linkage of omics data to phenotype.

- Minor PDs (examples):
  - Modest visit-window deviations unlikely to affect outcome classification.
  - Partial missing items within allowable scoring rules of instruments.
  - Administrative timing issues (late entry with adequate source) without evidence of recall bias.

Each PD record specifies participant ID, description, date, root cause, impacted endpoints, classification (major/minor), and corrective/preventive actions. Classification is reviewed by the PI and data management; disagreements are adjudicated before database lock [4].

Handling of protocol deviations in analyses

- Primary analyses:
  - The FAS is used for all primary and secondary endpoints, applying an intention-to-observe approach appropriate for observational cohorts [1,2]. Participants with major PDs remain in the FAS unless consent/eligibility is invalid; their affected data points may be censored or excluded for specific endpoint calculations where the PD compromises the measurement (e.g., exclude a non-standard ASHRS administration from ASHRS-based models while retaining unaffected measures).
  - Time-to-event, longitudinal mixed-effects, or generalized estimating equation models will include available observations, leveraging methods robust to data missing at random and unequal

observation counts, as detailed in the Statistical Analysis section [5,6].

- Per-protocol sensitivity:
  - The PP excludes participants with major PDs impacting the relevant endpoint(s). Endpoint-specific PP datasets will be constructed (e.g., PP-AS HRS for ASHRS-based analyses; PP-events for inpatient event analyses). Effect estimates (associations, discrimination, calibration where applicable) will be compared between FAS and PP to assess robustness.

- Endpoint-specific rules:
  - Inpatient event analyses: If inpatient surveillance is substantially incomplete (major PD), event-based endpoints for that participant are set to missing for the affected interval; other endpoints remain analyzable if unaffected.
  - Instrument-based endpoints: If a CtQ instrument was administered with a non-approved version or outside standardized procedures, that instrument score is excluded from analyses requiring valid scoring; other instruments from the same visit may be retained if valid.
  - Consent/eligibility deficiencies: Participants with non-remediable consent/assent or confirmed ineligibility are excluded from all inferential analyses and flagged in accountability reports.

- Biospecimens:
  - Samples failing QC or with linkage uncertainties are excluded from omics analyses only; corresponding phenotypic data remain in FAS/LFAS analyses.

Sensitivity analyses for impact of deviations and missingness

Planned sensitivity analyses, pre-specified by endpoint and population, will probe the influence of PDs and plausible missing-data mechanisms, consistent with ICH E9 and contemporary recommendations for handling missing data [1,5,6]:

- Population sensitivity: Compare primary FAS results with PP results for key endpoints (e.g., associations predicting inpatient/self-reported self-harm, ASHRS predictive models, suicidality outcomes).

- Window adherence sensitivity: Re-estimate models restricting to assessments within protocol-defined visit windows versus allowing prespecified grace periods.

- Measurement sensitivity:
  - Re-run analyses excluding assessments with any administration irregularities (minor+major) versus excluding only major deviations.
  - For ambiguous event classifications, conduct analyses using alternative coding (e.g., inclusive versus strict definitions of self-harm) and report the range of estimates.

- Missing-data sensitivity:
  - Apply multiple imputation under missing-at-random assumptions for covariates and outcomes where appropriate; compare with mixed-model analyses using all observed data.
  - Conduct tipping-point or delta-adjustment analyses to assess the robustness of conclusions under plausible missing-not-at-random departures, focusing on outcomes with differential loss to follow-up [5,6].

- Influence diagnostics: Evaluate the impact of high-leverage observations and sites/raters associated with PD clusters; report whether exclusion materially shifts inferences.

Results of sensitivity analyses will be summarized alongside primary findings to inform the credibility and transportability of conclusions per STROBE-aligned reporting [2].

Documentation and reporting

- All PDs and analysis population derivations will be finalized before database lock and archived with programming specifications, logs, and annotated consort-style flow diagrams adapted for observational cohorts [2].
- Statistical outputs will clearly state denominators, PD-related exclusions by endpoint, and rationale. Any post hoc reclassification of PDs will be documented and justified, with audit trails preserved in accordance with study governance [4].

References

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10.2 Descriptive and inferential methods for outcomes

Descriptive summaries

- Baseline characteristics will be summarized separately for the high-risk inpatient cohort and healthy controls using appropriate descriptive statistics: means and standard deviations or medians and interquartile ranges for continuous variables; counts and percentages for categorical variables. Distributions will be displayed using histograms/violin plots and assessed for normality and outliers.
- Between-group contrasts at baseline (high-risk vs controls) will be described using standardized mean differences (SMDs) with 95% confidence intervals to avoid misinterpretation of significance testing in observational settings and to aid interpretability and transportability [1].
- For inpatient observation, exposure time will be summarized (patient-days), and event rates will be presented as incidents per 100 patient-days with exact Poisson confidence intervals.
- Longitudinal completeness, timing, and reasons for missingness at 6- and 18-month follow-up will be tabulated. Graphical overviews (e.g., spaghetti plots, trajectory plots) will depict repeated measures (e.g., ASHRS) and time-to-event accrual.

Primary outcome analysis

The primary inferential focus is the association between ASHRS risk scores (index assessment) and subsequent self-harm outcomes at prespecified horizons:

- Inpatient horizon (during index hospitalization):

- Any-event outcome: a log-link Poisson or negative binomial regression with a log(patient-days) offset will estimate incidence rate ratios (IRRs) for ASHRS, selecting negative binomial if overdispersion is detected (likelihood ratio test; examination of Pearson residuals) [2]. Robust (sandwich) standard errors will account for within-patient dependence when modeling counts [3].
- Recurrent-event sensitivity: a Cox model with Andersen–Gill formolation will estimate hazard ratios

(HRs) for recurrent self-harm events, using robust variance to account for event dependence; proportional hazards (PH) will be checked via Schoenfeld residuals and time-by-covariate tests [4,5].

- Short-term post-discharge horizon (within 6 months):

- Primary specification: a Cox proportional hazards model for time to first self-harm post-discharge (any self-injurious act with or without suicidal intent, per prespecified definitions) with censoring at last contact or 6 months [5]. PH assumptions will be evaluated; if violated, time-varying effects or flexible parametric models will be considered.
- Complementary binary outcome at 6 months (any self-harm yes/no) will be modeled with logistic regression; for more interpretable risk ratios in frequent outcomes, a modified Poisson model with robust errors may be used [3].

- Predictive performance of ASHRS:

- Discrimination will be quantified using Harrell's C-index/AUC with optimism-corrected estimates via bootstrapping (≥1000 resamples) or nested cross-validation depending on sample size [6–8].
- Calibration will be assessed with calibration intercept and slope, smooth calibration curves, calibration-in-the-large, and Brier score; internal validation will correct for overfitting [6–8].
- Decision-curve analysis will quantify net benefit across threshold probabilities to inform clinical utility without requiring fixed cut-points [9]. Any cut-point exploration (e.g., Youden index) will be clearly labeled exploratory, with emphasis on reporting continuous risk.

ASHRS will be analyzed as a continuous predictor; nonlinearity will be examined with restricted cubic splines, favoring parsimonious transformations supported by likelihood ratio tests and visual inspection [6,7].

Secondary and exploratory outcome analyses

- Severity of suicidality (C-SSRS):

- Ordinal outcomes (e.g., ideation severity categories) will be modeled with proportional odds ordinal regression; proportional odds will be tested (e.g., score test). If violated, partial proportional odds or adjacent-category models will be used [10].

- NSSI characteristics (B-NSSI-AT, ISAS):

- Counts/frequencies: Poisson/negative binomial (or zero-inflated variants if excess zeros) with appropriate exposure terms when relevant [2].
- Functions/subscales (continuous): linear models or linear mixed-effects models (LMMs) for repeated measures, with random intercepts (and slopes when supported), unstructured or appropriate covariance structures, and robust standard errors if residual assumptions are tenuous [11].

- Heteroaggression risk (DASA-YV):

- Short-term prediction of inpatient aggression events will parallel self-harm models (rate-based or time-to-event) with IRRs or HRs as effect measures.

- Longitudinal trajectories (6 and 18 months in high-risk cohort):

- Repeated measures of ASHRS and related psychosocial scales will be analyzed using LMMs or generalized linear mixed models (GLMMs) as dictated by outcome type, including fixed effects for time (categorical and/or continuous with splines) and key covariates; participant-level random intercepts will accommodate within-subject correlation [11].
- Marginal models via generalized estimating equations (GEEs) with robust variance will be used for population-averaged inferences when random-effects assumptions are not desired; working correlation structures will be compared by QIC [12].

- Genetic/epigenetic exploratory analyses:

- Candidate-variant or methylation-site associations with primary outcomes will use multivariable regression appropriate to outcome type with penalization as needed to prevent overfitting; multiple-testing control will be by false discovery rate (FDR) procedures with transparent reporting of tested hypotheses and effective numbers of tests [13]. Integrative models will be treated as hypothesis-generating and reported with internal validation where feasible.

Covariates, confounding, and model building

63. Prespecified covariates for adjustment reflect domain knowledge and directed acyclic graph (DAG)-informed selection to reduce confounding without overadjustment: age, sex, index presentation (suicidal vs NSSI), prior self-harm attempts, baseline depression/anxiety

severity, trauma exposure, substance use, relevant psychiatric diagnosis, family/peer relationship indices, and length of stay for inpatient models. Treatment exposures during usual care (e.g., psychotropics) will be summarized descriptively and included as covariates in sensitivity analyses to address confounding by indication without implying causal effects.

64. For longitudinal/time-to-event analyses, time-varying covariates (e.g., repeated ASHRS, clinical state changes) may be incorporated using extended Cox models or mixed-effects frameworks, contingent on data availability and prespecified analysis plans [5,11].
65. Variable functional forms will be checked (component-plus-residual plots; splines); molticollinearity will be assessed (variance inflation factors), with dimension reduction or penalization (e.g., ridge) applied if indicated, prioritizing model stability and interpretability [6,7].
66. Clustering and rater/unit effects will be handled using random effects or cluster-robust standard errors; although single-center, analyses will account for ward/unit and rater where they plausibly induce correlation.

Subgroup and interaction analyses

- Prespecified subgroups: sex (female/male), age band (13–15 vs 16–19), index presentation (suicidal vs NSSI), prior attempt (yes/no), and high vs low trauma exposure. Subgroup effects will be evaluated using interaction terms between ASHRS (or exposure of interest) and subgroup indicator within the primary models; forest plots will present interaction estimates with 95% CIs. Subgroup findings will be considered exploratory unless strong a priori justification exists, and interpretation will emphasize consistency and plausibility rather than isolated p-values.

Model diagnostics and assumption checks

- Goodness-of-fit and residual diagnostics will be performed for all models: deviance and Pearson residuals for GLMs; influence/leverage diagnostics; assessment of overdispersion and zero inflation for count models; evaluation of PH for Cox models; calibration/discrimination for predictive specifications [2,5–8,10–11].
- Internal validation and optimism correction will be undertaken for prediction models (bootstrap or cross-validation). Where applicable, shrinkage (e.g., penalized likelihood) will reduce overfitting [6–8].

Handling of missing data in analyses

- Mixed-effects, GEE, and survival models inherently accommodate unbalanced longitudinal data under missing-at-random assumptions. For covariates with missingness, multiple imputation by chained equations (MICE) will be employed with imputation models including outcomes, predictors, and auxiliaries; estimates will be combined using Rubin's rules. Outcome missingness will not be imputed for time-to-event endpoints; sensitivity analyses will assess departures from MAR using delta-adjustment or pattern-mixture approaches [14,15].

Multiplicity and statistical threshold

- Two-sided alpha of 0.05 defines statistical significance for the primary analyses. Secondary and exploratory analyses will control for multiple comparisons using the Benjamini–Hochberg false discovery rate at q=0.10 unless otherwise justified by domain-specific constraints; families of hypotheses will be prespecified (e.g., secondary clinical outcomes; omics panels) [13].

- For prediction model performance metrics (e.g., AUC, calibration slope), 95% confidence intervals with bootstrap-based uncertainty will be reported; emphasis will be on effect sizes, uncertainty, and clinical relevance rather than dichotomous significance [6–9].

Reporting standards

- Analyses and reporting will align with STROBE for observational cohorts and TRIPOD for prognostic/predictive modeling, including clear specification of outcomes, predictors, time origins/horizons, handling of missing data, and internal validation procedures [1,7].

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10.3 Longitudinal/repeated-measures plans

Analytical framework for repeated measures

Longitudinal data arise from repeated administration of ASHRS and other psychosocial instruments at baseline, 6 months, and 18 months in the high-risk cohort, and from prospective inpatient event monitoring with irregular timing. Analyses will use likelihood-based mixed-effects models for subject-specific inference and generalized estimating equations (GEE) for population-averaged effects, chosen according to outcome type and inferential target [1–4]. Mixed-effects approaches provide unbiased estimates under missing at random (MAR) given correctly specified models, accommodate unequal observation counts and irregular spacing, and explicitly model within-participant correlation via random effects and structured residual covariance [1–3]. GEE will be used when marginal effects are preferred and when robust inference is prioritized over subject-level variance decomposition; working correlation structures will be compared using quasi-likelihood under the independence model criterion (QIC) [4,5].

Healthy controls contribute a single baseline assessment and are included in cross-sectional contrasts and baseline-adjusted models but not in within-subject longitudinal analyses.

Modeling plans by outcome type

- Continuous repeated measures (e.g., ASHRS total score; dimensional subscales):

 - Linear mixed-effects models (LMMs) with fixed effects for time (categorical and/or continuous with restricted cubic splines), prespecified covariates, and interactions of interest; random intercepts for participants and random slopes for time when supported by likelihood ratio tests and diagnostics [1–3].
 - Residual covariance structures evaluated include unstructured, autoregressive AR(1), and heterogeneous compound symmetry; selection will balance fit and parsimony [1,2].
 - Nonlinearity over time will be accommodated with spline terms; heteroskedasticity will be addressed using variance functions or robust (sandwich) standard errors.

- Binary/ordinal repeated outcomes (e.g., C-SSRS category; any self-harm in a recall window):

 - Generalized linear mixed models (GLMMs) with logit or complementary log-log link and random intercepts (and slopes for time if indicated); proportional odds or partial proportional odds for ordinal endpoints, with assessment of proportionality assumptions [2,3].
 - As a marginal alternative, GEE with logit or log links, robust standard errors, and exchangeable, independent, or AR(1) working correlations, selected by QIC [4,5].

- Count outcomes (e.g., number of NSSI acts in a recall period):

 - Mixed-effects Poisson or negative binomial models with log link; a log-exposure offset will be included when applicable (e.g., days at risk). Zero-inflated or hurdle variants will be considered if excess zeros are evident by Vuong-type or information-criterion comparisons and residual diagnostics [2,6].

- Inpatient recurrent events:

 - Rates over patient-days will be modeled as specified in the primary analysis, with robust standard errors to accommodate within-participant dependence. Sensitivity models may use frailty terms to capture unobserved heterogeneity across participants [7].

Correlation structures, clustering, and rater effects

Within-participant correlation is handled by:

- Participant-level random intercepts (minimum) and random time slopes where supported.
- Structured residual correlation (e.g., AR(1)) when random slopes do not fully capture serial dependence.
- For GEE, exchangeable or AR(1) working correlation with robust variance for valid inference under misspecification.

Potential clustering by inpatient unit/ward and rater effects for clinician-rated instruments will be addressed using crossed or nested random effects where feasible, or cluster-robust (Huber–White) standard errors at the rater/unit level when random-effects estimation is unstable due to small cluster counts [2,3].

Time-varying covariates and dynamic prediction

Time-varying clinical and psychosocial covariates (including repeated ASHRS) will be incorporated in longitudinal GLMM/LMMs and in extended Cox models for post-discharge outcomes, with careful alignment of measurement times to avoid immortal-time bias [7]. For prognostic use of evolving ASHRS, landmarking will be applied at prespecified times (e.g., discharge, 6 months) to update risk for subsequent intervals, and joint models of longitudinal ASHRS and time-to-self-harm with shared random effects will be explored to address informative dropout and to generate individualized dynamic predictions with internal validation [7–9].

Irregular timing, exposure, and scale

Models naturally accommodate unequal spacing. When recall windows or exposure durations vary (e.g., patient-days at risk), appropriate offsets and at-risk indicators will be included. Time may be modeled as categorical (baseline, 6, 18 months) for robust mean contrasts and as continuous with splines to estimate trajectories and rates of change [1–3].

Missing data in longitudinal contexts

- Primary approach:

- LMM/GLMM likelihood-based estimation under MAR uses all available observations without listwise deletion and yields unbiased estimates if the missingness mechanism depends on observed data included in the model [1–3].
- For marginal GEE analyses with intermittent missingness, estimates remain consistent under missing completely at random; when MAR is plausible, inverse probability weighting (IPW) augmented GEE will be used with stabilized weights derived from models of visit/nonresponse conditional on observed history [4,10].

- Multiple imputation (MI):

- For partially missing baseline or time-varying covariates, multiple imputation by chained equations with two-level (multilevel) specifications will be used so that imputation models reflect within- and between-participant variability; outcomes, predictors, and auxiliary variables predictive of missingness (e.g., prior engagement, hospitalization length, baseline severity) will be included, and estimates combined with Rubin's rules [11–13].
- Repeated outcome imputation will be avoided when likelihood-based mixed models are primary; if needed for secondary complete-data methods, two-level MI compatible with the analysis model will be applied [11–13].

- MNAR sensitivity:

- Pattern-mixture or delta-adjustment analyses will assess departures from MAR by progressively shifting imputed values for those with missing follow-up based on clinically plausible ranges; conclusions will be examined for tipping points [12,13].
- For potentially informative dropout linked to self-harm events or rehospitalization, shared-parameter joint models (longitudinal ASHRS with time-to-dropout/self-harm) will be used as sensitivity analyses to evaluate bias from nonrandom attrition [8,9,12].

Model selection, checking, and reporting for repeated measures

67. Selection will be guided by likelihood ratio tests for nested mixed models, AIC/BIC for non-nested comparisons, and QIC for GEE; parsimony will be favored when fit is similar [1,4,5].
68. Assumptions will be checked via residual diagnostics (conditional and marginal), assessment of overdispersion and zero inflation for counts, evaluation of link function adequacy, inspection of random-effects distributions, and influence diagnostics. When assumptions are marginal, robust standard errors and transformation or alternative links will be considered [1–3,6].
69. Estimates will be presented as marginal means/contrasts over time (with 95% CIs) alongside subject-specific effects where relevant. Graphical displays will include observed and model-based trajectory plots with uncertainty ribbons and spaghetti plots to illustrate heterogeneity. For dynamic prediction exercises, time-updated performance (calibration and discrimination) will be reported with internal validation [7–9].

Alignment with analysis populations

Repeated-measures analyses will be conducted in the Longitudinal Follow-up Analysis Set (LFAS), with FAS-based sensitivity analyses including participants who contribute only baseline or inpatient observations, using methods that permit unbalanced data. Endpoint- and instrument-specific per-

protocol sensitivity sets will be applied where administration deviations could bias longitudinal inferences.

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10.4 Subgroup and sensitivity analyses

Prespecified subgroup analyses

Subgroup analyses will explore heterogeneity of associations and predictive performance relevant to adolescent self-harm risk and the Slovenian inpatient context. All subgroup analyses are exploratory unless otherwise stated and will be evaluated by including interaction terms between the exposure/predictor of interest (e.g., continuous ASHRS score) and the subgroup indicator within the primary model, with results presented as subgroup-specific estimates and interaction contrasts with 95% CIs. Interpretation will prioritize consistency, biological/clinical plausibility, and coherence across related outcomes rather than isolated p-values, following best-practice guidance for credible subgroup inferences [1–3].

- Sex: female vs male. Rationale: sex differences are consistently reported for NSSI prevalence, suicidal ideation, and methods/lethality; testing effect modification informs tailoring of risk assessment and safety planning.
- Age band: 13–15 vs 16–19 years. Rationale: developmental stage may influence self-regulatory capacity, impulsivity, and help-seeking.
- Index presentation: suicidal self-harm vs NSSI at admission. Rationale: baseline intent may modify proximal and post-discharge event risk and ASHRS performance.
- Prior self-harm attempt: yes vs no. Rationale: recurrence risk and threshold for re-injury differ by history.
- Trauma exposure: high vs low (prespecified binary cut anchored to instrument norms). Rationale: trauma-related dysregulation may modify pathways to self-harm.
- Psychiatric diagnosis group: internalizing predominant vs externalizing/behavioral predominant. Rationale: symptom clusters may interact with risk indicators.
- Substance use at baseline: any vs none. Rationale: acute disinhibition may alter short-term risk.
- Ward/unit during admission: Intensive Child and Adolescent Psychiatry Unit vs Unit for Adolescent Psychiatry. Rationale: unit milieu and surveillance intensity may affect observed inpatient events and predictive gradients.

For each subgroup, we will report:

- Association models: subgroup-specific incidence rate ratios or hazard ratios for inpatient/post-discharge outcomes with an interaction p-value; nonlinearity in continuous predictors will be assessed uniformly (e.g., restricted cubic splines) across subgroups to avoid differential model misspecification.
- Prediction models: discrimination (C-index/AUC) with bootstrap-based CIs and calibration (intercept, slope, smooth curves) estimated within subgroups; differences will be appraised with interaction terms and stratified net benefit via decision-curve analysis when sample size permits [4,5].
- Psychometrics: measurement invariance of ASHRS across sex and age bands (configural, metric, scalar) will be evaluated to support fair comparisons; subgroup contrasts will not be interpreted if scalar invariance is untenable, and partial invariance strategies will be applied cautiously [6,7].

Multiplicity will be addressed by controlling the false discovery rate within the family of subgroup interaction tests (q=0.10) and by emphasizing effect sizes and uncertainty intervals in line with STROBE/TRIPOD recommendations [4,8].

Additional stratified descriptions

For context, descriptive stratifications (not inferential subgroup testing) will summarize baseline characteristics and crude inpatient event rates by:

- Length of stay tertiles (exposure opportunity)
- Baseline ASHRS score bands (e.g., quartiles) alongside continuous analyses
- Family/peer relationship indices (high vs low support)

These summaries are intended to aid interpretation of main-model estimates and to inform subsequent hypothesis generation without formal claims.

Sensitivity analyses

Sensitivity analyses will assess robustness of primary and secondary findings to alternative assumptions, outcome definitions, and analytic specifications, aligned with ICH E9 and contemporary missing-data/prediction-model guidance [4,9–12].

- Population definitions:

- Full analysis set vs endpoint-specific per-protocol sets excluding major protocol deviations affecting the endpoint measurement.
- Longitudinal follow-up analysis set vs augmented sets including participants contributing only baseline/inpatient data using methods that accommodate unbalanced panels.

- Outcome definitions and coding:

- Self-harm classification: analyze with inclusive (any self-injurious act irrespective of intent) vs strict (suicidal intent required for “suicidal” outcome; NSSI analyzed separately) definitions; report the range of estimates.
- Inpatient events: include vs exclude “prevented”/aborted acts; examine alternative recurrence frameworks (rate models vs Andersen–Gill).
- Post-discharge horizon: primary 6-month window vs extended sensitivity to 3 and 9 months if data density allows; check proportional hazards and apply time-varying effects when violated.

- Model specification:

- Link and distribution: Poisson vs negative binomial for counts (with overdispersion checks); zero-inflated/hurdle variants if excess zeros are supported by diagnostics.
- Functional form: linear vs spline-transformed ASHRS and continuous covariates; report whether nonlinear terms materially change inferences.
- Dependence structure: robust (sandwich) SEs vs random-effects/frailty terms for within-person clustering of events; GEE vs mixed-effects for repeated binary/ordinal outcomes.
- Predictor scaling: continuous ASHRS as primary; exploratory cut-points evaluated only for communication, with primary inference remaining on the continuous scale.

- Missing data:

- Primary likelihood-based mixed models (MAR) compared with multiple imputation by chained equations for covariates; estimates combined with Rubin's rules.
- MNAR departures: delta-adjusted/pattern-mixture tipping-point analyses for outcomes with differential attrition; joint models of longitudinal ASHRS and time-to-self-harm to evaluate informative dropout.
- Inverse probability weighting for visit nonresponse in marginal models, using stabilized weights derived from observed history.

- Confounding and covariate sets:

- Prespecified adjustment set vs parsimonious sets informed by directed acyclic graphs; alternative inclusion of usual-care treatment exposures to probe confounding by indication without causal interpretation.
- Collinearity handling: re-estimate with penalization (ridge) when variance inflation suggests instability; compare with standard estimates.

- Rater/unit effects and clustering:

- Cluster-robust SEs at rater/unit level vs crossed random effects to assess influence of local clustering on standard errors and effect sizes.

- Measurement and psychometrics:

- Exclude assessments with any administration irregularities vs excluding only major deviations; verify that ASHRS reliability (omega) remains stable across sensitivity sets.
- If full scalar invariance for ASHRS is not supported, re-estimate subgroup associations using latent variable scores from partial-invariance models.

- Predictive performance robustness:

- Internal validation via bootstrapping vs k-fold cross-validation; evaluate optimism-corrected discrimination/calibration.
- Shrinkage/penalization: compare unpenalized models with penalized likelihood (e.g., ridge) to assess overfitting; report calibration slope differences.

- Biospecimen-related analyses:

- Genomic/epigenetic models adjusted vs unadjusted for estimated leukocyte cell-type composition and batch; FDR thresholds varied (q=0.05 vs q=0.10) to examine stability of signals.

Interpretation and reporting of subgroup and sensitivity results

- Subgroup findings will be integrated with the main analyses by:

- Prioritizing interaction estimates over within-subgroup significance testing, avoiding spurious inference from underpowered comparisons [1–3].
- Considering credibility factors (a priori specification, consistency across related endpoints/time horizons, biological plausibility, and independence from multiple testing artifacts) and applying the ICEMAN framework to any seemingly large subgroup effects before highlighting them in conclusions [2,3].

- Sensitivity analyses will be summarized alongside primaries, indicating whether conclusions are unchanged, attenuated, or reversed, and which assumptions drive differences. Where multiple reasonable specifications yield similar inferences, we will emphasize the stability of effect direction and magnitude; where results are sensitive, we will present qualified interpretations and recommend cautious application in practice, consistent with STROBE/TRIPOD reporting [4,8,10–12].

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10.5 Missing data strategy

Overview and principles

Missing data are anticipated due to item nonresponse on questionnaires, intermittent missed assessments during admission, incomplete surveillance of inpatient events, and attrition at 6- and 18-month follow-up. Strategies prioritize prevention, rigorous documentation of reasons, transparent description of extent/patterns, and prespecified analyses that are valid under plausible missing-data mechanisms with sensitivity analyses for departures from those assumptions, consistent with STROBE and authoritative guidance on prevention and treatment of missing data [1–4].

Prevention, documentation, and monitoring

- Prevention:

- Minimize burden by streamlining assessments, using validated Slovene translations, training staff in standardized administration, and enabling flexible windows for follow-ups consistent with the SoA.
- Real-time edit checks in the eCRF/app identify omitted critical fields; prompts are used to complete key items when clinically appropriate.

- Documentation:

- For each missed visit or incomplete instrument, the proximate reason is coded using standardized categories (e.g., participant refusal, clinical instability, administrative error, lost to follow-up, relocation, consent withdrawal, data entry delay, biospecimen QC failure).
- Inpatient event surveillance completeness (patient-days observed vs expected) is logged per participant and ward.

- Monitoring:

- Monthly dashboards summarize missingness by domain, rater/unit, and timepoint; signals of differential missingness by group (high-risk vs controls; sex; age band) trigger corrective actions.
- A Missing Data Working Log records protocol adaptations that do not compromise scientific integrity.

Quantifying extent and patterns; exploring reasons

- Extent:

- Item-level, instrument-level, visit-level, and domain-specific missingness will be summarized as counts and percentages with 95% CIs.
- For longitudinal measures (e.g., ASHRS, C-SSRS, ISAS), completeness matrices and trajectory plots display observation patterns across baseline, 6, and 18 months.

- Patterns:

- Compare baseline characteristics of responders vs nonresponders using standardized mean differences.
- Examine predictors of missingness with logistic models for visit attendance and ordinal models for partial completion, including observed history (prior scores, events), length of stay, and sociodemographics.
- Assess clustering of missingness by rater/unit.

- Reasons:

- Tabulate coded reasons by timepoint and domain to inform the plausibility of MCAR/MAR/MNAR mechanisms and to guide sensitivity scenarios [2–4].

Item-level missingness and scoring rules

- Standardized scoring rules are applied for validated instruments:

- Where instrument manuals permit prorating with maximum allowable missingness (e.g., ≤20% of items within a multi-item scale), prorated scores will be computed; otherwise, the scale is set to missing for that timepoint, and item-level data retained [5,6].
- For ASHRS development, item-level missingness will be minimized; exploratory and confirmatory factor analyses will use full-information maximum likelihood (FIML) when appropriate, avoiding listwise deletion and aligning estimation with the assumed missingness mechanism [6,7].

- Free-text/rare items not essential to primary scores are not imputed and are analyzed as observed.

Primary analytical approach

- Longitudinal and repeated-measures outcomes:

- Likelihood-based mixed-effects models (LMM/GLMM) will serve as the primary approach, which provide unbiased estimates under missing at random (MAR) conditional on included observed data and correct model specification; these models use all available observations without listwise deletion [3,8].
- For marginal inferences via GEE, when intermittent nonresponse is associated with observed history (MAR), inverse probability weighting with stabilized weights derived from visit-attendance models will be used; robust (sandwich) variance ensures valid inference under working-correlation misspecification [9].

- Time-to-event outcomes:

- Survival models (e.g., Cox) will analyze observed event/censoring times without imputing primary event times; censoring occurs at last confirmed contact. Sensitivity analyses will evaluate potential informative censoring (see below) [2,4,10].

- Cross-sectional comparisons and prediction models:

- Analyses will include all participants with observed outcomes; missing covariates will be addressed via multiple imputation as detailed below. Internal validation for prediction models will be integrated with the imputation process [11].

Multiple imputation (MI) for covariates and nonprimary outcomes

- Scope:

- MI is used for partially missing baseline and time-varying covariates and, where needed for secondary analyses requiring complete data (e.g., certain psychometric evaluations), selected nonprimary outcomes.

- Method:

- Multiple imputation by chained equations (MICE) with multilevel specifications will reflect within-person clustering over time; appropriate univariate models will be used for each variable type:

predictive mean matching for approximately continuous scales, logistic for binary, multinomial for nominal, and proportional odds for ordinal variables; truncation/bounds will preserve feasible score ranges [4,12,13].
- Passive imputation will maintain consistency of derived variables (e.g., total scores from items when items are imputed).

- Imputation model content:

- Include all variables in the corresponding analysis models, observed outcomes (where justified), prior measurements of the variable being imputed, indicators of visit timing, ward/unit, length of stay, baseline severity (e.g., C-SSRS levels, ASHRS), prior self-harm history, key psychosocial constructs (depression/anxiety, trauma, family/peer support), and auxiliary variables predictive of missingness (e.g., engagement indicators, contact modality).

- Number of imputations and diagnostics:

- Generate a number of imputations at least equal to the approximate percentage of incomplete cases, with a minimum of 30 datasets and increased as needed based on the fraction of missing information; convergence and Monte Carlo error will be monitored, and between-imputation variability reported [4,12].

- Estimation and pooling:

- Fit analysis models within each imputed dataset and combine estimates and standard errors using Rubin's rules, ensuring congeniality between imputation and analysis models [4,12].

Outcome-specific handling

- Inpatient event counts and rates:

- Missing surveillance intervals (e.g., unobserved patient-days) are treated as missing exposure time and excluded from rate denominators; outcomes are not imputed for these intervals. Models include exposure offsets and use robust variance [8].

- Post-discharge binary outcomes (any self-harm within a window):

- Primary analysis uses mixed models/survival without imputing missing outcomes; MI may be used for secondary complete-data logistic models to permit comparability across methods under MAR, with sensitivity analyses for MNAR (below) [2,4,10,12].

- Psychometrics (ASHRS and comparators):

- Factor-analytic models will use FIML or WLSMV with pairwise present as appropriate; where MI is employed for items, imputation models will be compatible with the latent structure and item types to avoid biasing loadings and reliability estimates [6,7,12].

Sensitivity analyses for departures from MAR

- Pattern-mixture/delta-adjustment:

- Implement controlled MI with post-imputation shifts (delta adjustments) applied to outcomes among those missing at follow-up, exploring scenarios where missing outcomes are systematically worse or better than predicted under MAR (e.g., ±0.2 to ±0.6 SD for continuous scales; log-odds shifts for binary outcomes). Tipping-point analyses will identify the magnitude of departure required to alter conclusions [4,12,13].

- Informative dropout and event dependence:

- Joint models of longitudinal ASHRS and time-to-self-harm with shared random effects will assess the impact of informative dropout; comparisons to standard Cox/LMM estimates will be reported [8,11].

- Inverse probability of censoring weighting (IPCW):

- For survival analyses with differential loss to follow-up, IPCW based on models of follow-up probability given observed history will be applied to test robustness to informative censoring; stabilized weights and truncation will control variance inflation [9,10].

- Best/worst-case bounds:

- For key binary outcomes at fixed horizons, conservative bounding analyses will be presented (e.g., coding all missing as events vs nonevents) to contextualize plausible ranges without overinterpretation.

Diagnostics, transparency, and reporting

- Assumption checks:

- Compare observed vs imputed distributions; evaluate imputation model fit, convergence, and compatibility with analysis models; inspect weight distributions for IPW/IPCW and apply truncation if extreme values unduly influence variance [4,9,12].

- Missingness mechanism appraisal:

- Findings from missingness predictor models and reason codes will be integrated to justify MAR assumptions or highlight where MNAR is plausible, guiding emphasis on sensitivity results.

- Accountability and reproducibility:

- A prespecified Statistical Analysis Plan addendum will detail variable-wise imputation methods, bounds, and code lists for reasons; all programming scripts and seeds will be archived.

- Reporting:

- Analytic outputs will state denominators, missingness by endpoint and timepoint, imputation details (variables, number of datasets, diagnostics), and results of sensitivity analyses, adhering to STROBE and specific guidance for prediction model reporting [1,11].

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10.6 Qualitative methods (e.g., thematic analysis, interpretive description)

Overview and qualitative components

To complement quantitative assessments and elucidate the lived experience and contextual drivers of adolescent self-harm in the Slovenian inpatient setting, the study includes two qualitative strands aligned with SRQR/COREQ standards for design, conduct, and reporting [1,2]:

- Interpretive description interviews: in-depth, semi-structured interviews with a purposive subsample of high-risk inpatients (and, where feasible, at 6-month follow-up) to understand antecedents, functions, contexts, perceived risk/protection, help-seeking, and experiences of inpatient care. Interpretive Description is chosen to generate clinically applicable insights that can inform practice and risk assessment without imposing a priori theory [3–5].

- Cognitive interviewing for ASHRS development: iterative think-aloud and verbal probing interviews to optimize item comprehension, relevance, recall period, response options, and cultural/linguistic clarity of the ASHRS for adolescents in Slovenia [6,7].

Qualitative strands run in parallel with quantitative data collection, with planned integration points for interpretation and instrument refinement.

Sampling and participant selection

- Sampling frame: enrolled adolescents in the high-risk cohort meeting study eligibility and who are clinically and ethically appropriate for qualitative participation per treating team.
- Sampling strategy: purposive maximum-variation sampling to capture heterogeneity in factors anticipated to shape experiences and meanings of self-harm: sex, age band (13–15; 16–19 years), index presentation (suicidal vs NSSI), prior self-harm attempts (yes/no), trauma exposure (higher vs lower), psychiatric presentation (internalizing vs externalizing predominant), and inpatient unit (Intensive Child and Adolescent Psychiatry Unit; Unit for Adolescent Psychiatry). Recruitment will proceed iteratively, monitoring sample composition against these strata [4,5,8].
- Sample size: target approximately 30–40 interpretive interviews inpatients across baseline/discharge (with up to 15 re-interviewed at 6 months to explore change and continuity) and 2–3 iterative cognitive interviewing rounds of 8–12 participants each (total 16–30) for ASHRS item testing. Final numbers will be guided by information power and saturation of meaning (sufficiency), assessed through ongoing analytic review of redundancy, diversity of accounts, and adequacy to address study objectives [8–10].
- Healthy controls: a small comparator subset (approximately 10–12) may be invited to cognitive interviews only to probe clarity and age-appropriateness of ASHRS wording without eliciting narratives of self-harm.

Recruitment, consent/assent, and safety

- Approach: clinicians introduce the qualitative substudies after initial stabilization; research staff then provide study information and obtain written consent/assent. For participants under 15, parental consent and adolescent assent are required; for those 15–17, procedures follow local regulations and ethics approvals; 18–19-year-olds provide their own consent.
- Safety procedures: interviews are conducted by trained clinicians/researchers experienced with adolescents at risk. A brief pre-interview risk screen confirms appropriateness to proceed. A standardized distress and safety protocol includes options to pause/stop, on-call clinician availability, and same-day clinical debrief if indicated. Any acute risk disclosed triggers immediate referral per clinical pathways; participation is voluntary and may be discontinued without consequence to care [11].

Data collection procedures

- Mode and timing:

- Interpretive interviews: 45–75 minutes, in Slovene, audio-recorded, conducted in a private space during late inpatient stay or near discharge; optional follow-up interview (~30–60 minutes) at 6 months (in person or secure video/phone per participant preference).
- Cognitive interviews (ASHRS): 30–60 minutes, think-aloud completion of the draft scale with concurrent and retrospective probing on comprehension, retrieval, judgment, and response mapping; rapid iteration between rounds [6,7].

- Topic guides:

- Interpretive interviews: flexible guides covering pathways to self-harm (precipitants, functions, ambivalence), emotion regulation and interpersonal contexts (family/peers/school/social media), experiences of risk assessment and inpatient care, perceived helpful/unhelpful elements, barriers/facilitators to safety and help-seeking post-discharge, and views on risk communication.

Guides are refined after pilot interviews.
- Cognitive interviews: probes target clarity of instructions, item wording, time frames, examples of terms (e.g., “urge,” “intent”), response scales, and perceived sensitivity or redundancy; comprehension problems are categorized (lexical, syntactic, conceptual, cultural) to inform revisions [6,7].

- Field notes and reflexive memos: interviewers maintain contemporaneous notes and post-interview memos on contextual factors, emergent insights, and reflexive observations to support analytic rigor [4,5].

Data handling and management

Audio files are transcribed verbatim in Slovene by trained personnel, with identifiers removed at transcription. Anonymized transcripts and memos are stored on secure, access-controlled servers in Slovenia in accordance with GDPR-compliant procedures already described in the protocol. For dissemination, selected quotations may be translated into English using a translate–review–reconcile process to preserve meaning; back-translation will be used if conceptual fidelity is uncertain [12].

Analytical framework and procedures

- Interpretive description with reflexive thematic analysis:

- Analytic orientation: inductive–deductive, clinically oriented, privileging participants’ meanings while attending to practice relevance [3–5].
- Coding: two analysts independently familiarize with data, generate initial codes line-by-line, and iteratively refine a shared codebook through discussion and memoing. Codes are organized into candidate themes that capture patterned meaning relevant to risk, protection, and care experiences; themes are reviewed against coded extracts and the full dataset, defined, and named [4,5,13].
- Managing diversity and nuance: within-theme matrices contrast experiences by prespecified strata (e.g., index presentation, sex, unit) to explore variation without overstating subgroup differences.

- Cognitive interviewing analysis:

- Rapid matrix-based analysis catalogs item-level issues (type, frequency, severity), exemplar verbatim, and proposed revisions. Decision logs document item modifications, retention, or deletion, with priority to comprehension and relevance for 13–19-year-olds [6,7].

- Software: qualitative data will be managed and coded in NVivo or MAXQDA; version and libraries will be archived to support reproducibility.

Ensuring rigor, credibility, and consistency

- Methodological coherence and reporting: the qualitative plan adheres to COREQ/SRQR for transparency in sampling, context, researcher roles, and analysis [1,2].
- Reflexivity: analysts document positionality, assumptions, and evolving interpretations in reflexive journals; periodic peer debriefs examine alternative explanations and challenge early closure [4,5,13].
- Team-based analysis and dependability: dual coding of an initial subset (20–25%) establishes shared application of codes; discrepancies are resolved by negotiated consensus. An audit trail preserves codebook evolution, analytic memos, and theme development decisions [9,13].
- Credibility checks: member reflections will be sought opportunistically at 6-month follow-up (where participants re-enroll) to gauge resonance of preliminary interpretations, recognizing that “validation” is interpretive rather than confirmatory. Thick description and verbatim exemplars will support transferability judgments [9,13].
- Saturation/information power: sampling continues until additional interviews yield diminishing novel insights relative to objectives, sample specificity, and analytic focus; stopping is justified using contemporaneous saturation tables and information power criteria [8–10].

Integration with quantitative components

- Design-level integration: a convergent mixed-methods approach is used. Qualitative interviews run in parallel with quantitative assessments to contextualize statistical associations and trajectories; explanatory follow-up interviews may be prioritized for subgroups with discrepant or unexpected quantitative patterns (e.g., high ASHRS but no events; low ASHRS with events) [14,15].
- Analysis-level integration:

- Joint displays weave qualitative themes (e.g., functions of self-harm, perceived triggers, safety strategies) with quantitative indicators (e.g., ASHRS domains, C-SSRS levels, inpatient events) to elucidate mechanisms and boundary conditions [14,15].
- Qualitative insights inform covariate selection and interpretation of nonlinearity or interactions observed quantitatively (e.g., trauma by support).

- Instrument development: cognitive interviewing findings directly feed ASHRS item refinement; interpretive themes inform content coverage and wording of items/domains, supporting content validity and comprehensibility in the target population per best-practice guidance [6,7].
- Interpretation and recommendations: integrated narratives will inform practice-oriented recommendations on assessment, communication, and safety planning that are sensitive to adolescents' perspectives.

Data protection and confidentiality in qualitative materials

All qualitative materials are coded with study IDs and stored separately from any contact information. Consent forms specify use of anonymized quotations, with participants able to decline quotation without foregoing participation. Any potentially identifying details within quotes are masked or altered while maintaining meaning.

Reporting

Qualitative methods and findings will be reported with sufficient detail for appraisal and replication, including sampling frames and characteristics, interviewer background/training, topic guides, coding framework, theme structure, and integration products (e.g., joint displays), consistent with COREQ/SRQR [1,2].

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11 DISCUSSION

11.1 Anticipated Contributions

Anticipated contributions to knowledge and theory

- Advance understanding of near-term and longer-term self-harm risk in adolescents by integrating inpatient event surveillance with longitudinal psychosocial trajectories, addressing persistent limitations of traditional risk-factor lists that show weak predictive utility when used in isolation [1].
- Elucidate mechanistic pathways linking emotion regulation, interpersonal context, and trauma exposure to self-harm occurrence and persistence within a high-risk inpatient population, including potential moderation by sex, age band, index presentation, and unit milieu. Mixed-methods integration will add explanatory depth by embedding adolescents' lived experiences alongside quantitative patterns, supporting theory refinement on functions and context-dependence of self-harm.
- Contribute region-specific evidence from Slovenia, a setting underrepresented in adolescent self-harm research, enabling cross-context comparisons and enhancing external validity of mechanisms derived largely from Anglophone cohorts.

Anticipated contributions to measurement and methodology

- Deliver the Adolescent Self-Harm Risk Scale (ASHRS), a brief, developmentally appropriate instrument with evidence on content validity (via cognitive interviewing), structural validity, reliability, and responsiveness aligned with COSMIN and ISPOR recommendations, and with transparent reporting per TRIPOD principles for predictive performance and calibration over time [2,3,4].
- Provide psychometric evidence on measurement invariance across key subgroups (e.g., sex, age bands), informing fair use of ASHRS in diverse adolescents and clarifying when latent-score approaches are preferable to raw score comparisons.
- Benchmark ASHRS against established tools (e.g., C-SSRS for suicidality; ISAS for NSSI functions), clarifying complementary roles of intent-focused and function-focused assessments and defining use-cases for rapid screening versus in-depth characterization [5,6].
- Demonstrate analytic strategies for dynamic risk estimation, including joint modeling and landmarking, to generate time-updated risk predictions during hospitalization and post-discharge—an approach responsive to the markedly elevated risk window following psychiatric discharge [1,7].

Anticipated practice and service contributions

- Equip clinicians with a rapid, scalable risk indicator (ASHRS) and empirically derived cut-free communication tools for discussing short-term and medium-term risk with adolescents and families, complementing clinical judgment and existing structured assessments (e.g., C-SSRS) without replacing individualized formulation [5].
- Inform safer care transitions by identifying modifiable psychosocial risk and protective factors that can be targeted in discharge and aftercare planning, where the burden of self-harm and suicide is concentrated in the weeks and months following discharge [7,8].
- Provide ward-level insights into antecedents and contexts of inpatient self-harm events, supporting local quality-improvement efforts on observation practices, milieu management, and safety planning.

Anticipated policy and community relevance

- Generate locally applicable evidence to guide adolescent self-harm prevention strategies in Slovenia, aligning with WHO priorities for strengthening surveillance, risk detection, and continuity of care for at-risk youths [8,9].
- Support resource allocation by identifying high-yield targets for screening in schools/primary care and by specifying which psychosocial domains most strongly inform risk stratification, thereby aiding stepped-care planning and referral pathways.

Anticipated contributions to future research

- Establish a well-characterized longitudinal cohort with linked biospecimens to enable subsequent analyses of genetic and epigenetic correlates in concert with psychosocial risk, contributing to increasingly integrative models of adolescent self-harm while avoiding deterministic interpretations [8].
- Provide open, reproducible reporting of model specifications, validation procedures, and sensitivity analyses to facilitate external validation and updating of ASHRS in other settings, in line with contemporary guidance for prediction model lifecycle management [2,4].
- Identify subgroup-specific evidence gaps (e.g., youth with discordant clinical presentation vs measured risk) to motivate targeted qualitative and intervention development work focused on tailoring assessment and aftercare.

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11.2 Limitations

Anticipated design and inference limitations

- Observational design and confounding: As a nonrandomized, prospective cohort, causal inference about determinants of self-harm and downstream outcomes is limited by residual and unmeasured confounding despite prespecified covariate adjustment and sensitivity analyses; associations will be interpreted cautiously and framed as noncausal in line with best practice for observational research [1,16].
- Single-country, two-unit clinical setting: Recruitment from specialized adolescent psychiatric units in Ljubljana enhances internal consistency but may limit generalisability to community samples, non-inpatient settings, other health systems, and cultural–linguistic contexts beyond Slovenia. Transportability to other countries and care pathways should be empirically verified before adoption [1,17].
- Healthy control design: Controls are assessed once at enrollment and recruited via school-based examinations, introducing potential selection and context differences (e.g., sociodemographic profile, care engagement) relative to inpatients. Between-group contrasts may therefore reflect both clinical status and recruitment context; we will prioritize within-cohort longitudinal inferences for risk estimation.
- Sample size and precision: The planned high-risk cohort (~200) supports the primary analyses but may yield wide uncertainty for subgroup interactions, complex longitudinal models, and multi-predictor genomic/epigenomic analyses. Subgroup findings will be considered exploratory given limited power and the recognized challenges in credible effect-modification inference [1,14].
- Follow-up windows: Outcomes are ascertained at 6 and 18 months; events occurring outside these windows or between contacts may be missed or dated imprecisely, potentially biasing incidence estimates and time-to-event analyses despite survival methods and sensitivity checks.

Recruitment, retention, and missing data

- Selection and participation biases: Inpatient enrollment may favor youths who are clinically stable enough to consent/assent, and school-based control recruitment may preferentially include more engaged students. These processes can induce selection effects that limit representativeness of the source populations [1].
- Attrition and intermittent missingness: Loss to follow-up at 6 and 18 months is likely in a highly mobile, vulnerable adolescent population, risking biased estimates if missingness depends on unobserved outcomes. Although we prespecify likelihood-based models under MAR, multiple imputation, IPCW, joint models, and tipping-point analyses, departures from MAR/MNAR cannot be ruled out and will temper interpretation [4,5].

Measurement and information biases

- Self-report and recall: Core constructs (self-harm history, functions, psychosocial factors) rely on adolescent self-report and clinician-administered scales, which are susceptible to recall error, social desirability, and context effects. While adolescent self-reports of risk behaviors show acceptable reliability on average, misclassification remains possible and may attenuate associations [9]. We will triangulate across instruments and clinical records where feasible.

- Outcome classification: Differentiating suicidal self-harm from NSSI is inherently challenging, and intent may vary within individuals over time; misclassification could bias comparisons between intent-defined outcomes. Use of standardized tools (e.g., C-SSRS) mitigates but does not eliminate this risk [7,8].
- Assessment reactivity and safety constraints: Although asking about suicide does not appear to increase suicidal ideation at the population level, transient reactivity or burden could influence responses and feasibility in acute phases, potentially creating informative missingness in the most severe cases [6]. Ethical imperatives may curtail data collection during crises, prioritizing safety over completeness.
- Rater and unit effects: Variability in administration fidelity, clinical observation intensity, and documentation practices across staff and units can introduce differential measurement error and surveillance bias for inpatient events. Planned training, fidelity monitoring, and cluster-robust analyses reduce but cannot fully remove these influences.

Prediction modeling and instrument-development constraints

- Risk of overfitting and optimism: The ASHRS is developed and internally validated within the same cohort; even with bootstrapping/cross-validation and shrinkage, performance estimates may be optimistic. External validation in independent samples, including non-inpatient and non-Slovenian contexts, will be required before clinical implementation, per TRIPOD guidance [2,3].
- Measurement invariance: Despite planned tests, full scalar invariance across sex, age bands, or clinical subgroups may not hold. If invariance is partial or absent, comparisons of mean levels and thresholds may be biased, and subgroup interpretations will require caution [1,18].

Biospecimen and omics-specific limitations

- Power and multiplicity: Genomic and epigenomic analyses face high dimensionality with modest sample size, increasing the risk of false positives and unstable effect estimates even with FDR control; findings will be considered hypothesis-generating until replicated [3,13].
- Tissue, batch, and cellular heterogeneity: Blood-derived methylation may not capture brain-relevant signatures; batch effects and leukocyte cell-type variation can confound associations if inadequately controlled. Although we will adjust for batch and estimated cell composition, residual confounding is possible [10–12].

Scope, feasibility, and integration limits

- Exclusions and clinical spectrum: Excluding youths with acute psychosis, intellectual disability, severe neurological illness, or acute poisoning enhances safety but narrows clinical heterogeneity, limiting applicability to these groups.
- Mixed-methods integration: Qualitative insights enhance contextual understanding but are not designed for causal adjudication; transferability may be constrained by purposive sampling within a single health system, and social desirability or interviewer–clinician role dynamics could influence narratives despite reflexive and safety procedures [1].
- Data protection and sharing: GDPR-compliant governance may limit the extent of individual-level data sharing outside Slovenia; deidentified derived data and code will be prioritized for transparency, but some replication activities may require controlled access.

Implications for interpretation and reporting

All limitations will be reported transparently with denominators, missingness profiles, precision estimates, and sensitivity analyses, adhering to STROBE/TRIPOD. Primary conclusions will

emphasize effect sizes, uncertainty, and robustness across prespecified analyses rather than isolated p-values; subgroup and omics findings will be framed as exploratory pending external validation and replication [1–3]. Where bias cannot be excluded, we will provide qualified interpretations and explicit recommendations for external validation prior to implementation.

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12 PARTICIPANT SAFETY AND RISK MANAGEMENT

12.1 Anticipated risks and mitigation; distress and safeguarding plans

Overview of potential risks

Participation involves discussing and reporting self-harm thoughts and behaviors, completing questionnaires/interviews on sensitive topics (e.g., trauma, relationships, sexuality/substance use), clinical risk assessments (e.g., C-SSRS), prospective monitoring of inpatient incidents, and provision

of a venous blood sample for genetic/epigenetic analyses. Anticipated risks fall into the following categories:

- Psychological/emotional distress: transient increases in sadness, anxiety, shame, or urges when discussing self-harm, trauma, or interpersonal stressors. Although asking about suicide does not appear to induce suicidal ideation at the population level, individual reactivity and short-lived distress can occur and require active monitoring and support [1].
- Safety risks due to disclosed acute intent or escalation: detection of near-term suicide risk or imminent self-harm during assessments necessitates immediate clinical response in line with best-practice care pathways [2,3,4].
- Privacy and confidentiality: inadvertent disclosure or re-identification of highly sensitive personal, clinical, and genetic data; misuse of information if accessed by unauthorized parties; inadvertent identification through verbatim quotations if not adequately de-identified [5,6].
- Physical risks: minor discomfort, bruising, vasovagal reaction, or infection risk from venipuncture; these are uncommon and typically mild when standard procedures are followed.
- Burden/fatigue: time demands, questionnaire load, repetition across visits, and potential perceived intrusiveness, especially during acute inpatient phases or follow-up contacts.
- Risks for healthy controls: unanticipated distress while reflecting on self-harm items; disclosure of risk requiring safeguarding in school/primary care settings.

Mitigation strategies for distress and burden

- Trauma-informed, participant-centred approach: staff use nonjudgmental, developmentally sensitive language; participants can pause, skip questions, or stop any activity without penalty to care or study participation in other components, consistent with ethical guidance for research with minors and high-risk populations [3,5].
- Timing and setting: inpatient assessments/interviews are scheduled only after initial stabilization and in coordination with the treating team; private, comfortable rooms are used to protect dignity and minimize triggers.
- Pre-assessment check-in and ongoing monitoring: a brief wellbeing/risk screen precedes sensitive procedures; interviewers and assessors monitor affect and arousal throughout and offer breaks, grounding strategies, or rescheduling when needed.
- Qualified personnel and training: all interviewers/assessors are clinicians or researchers trained in adolescent mental health, suicide risk assessment (including C-SSRS), safety planning, mandated reporting, and management of distress; procedures are standardized via SOPs and refreshed with periodic supervision [2–4].
- Burden reduction: measure sets are sequenced to start with less sensitive items; administration is modularized where feasible; total duration is capped per visit; repeat assessments avoid unnecessary duplication; follow-up contacts accommodate participant preference (in-person/secure telehealth) to reduce travel/time costs.
- Venipuncture safety: samples are collected by trained phlebotomists using aseptic technique; adolescents may decline or reschedule blood draw; observation is provided post-draw to manage vasovagal reactions.

Distress management during assessments

- Real-time support: if distress emerges, the session is paused; grounding and coping techniques are offered; involvement of the on-call clinician is available immediately on the inpatient units; for remote follow-ups, a same-day clinician is reachable and local emergency procedures are reviewed at the start of contact.
- Post-session debrief: a short debrief normalizes reactions, reinforces coping plans, and provides written resources (crisis lines, local services). Evidence-informed messages clarify that experiencing transient distress after discussing sensitive topics is common and typically subsides [1].

- Safety planning: when indicated, a brief collaborative safety plan is reviewed or updated, including personal warning signs, internal coping strategies, social supports, professional contacts, means-safety steps, and unit/family roles, aligned with current clinical guidance for self-harm care [4].

Safeguarding and escalation pathways

Safeguarding procedures are standardized and proportionate to the level of concern, with clear documentation, handovers, and follow-up:

- Recognition and initial appraisal:

- Any disclosure or observation suggesting acute risk (e.g., current suicidal intent, plan, recent attempt, inability to maintain safety, severe dissociation, homicidal ideation) triggers an immediate focused assessment using the C-SSRS and a brief mental state/risk appraisal by trained staff [2].

- Immediate actions for high/imminent risk:

- Inpatient participants: notify the responsible clinician/nurse in real time; initiate or adjust observation levels, environmental safety checks, and clinical interventions per unit protocol; ensure constant supervision if indicated; inform guardians as clinically and legally appropriate; document in the medical record and study notes [4].
- Follow-up (in-person or remote): maintain contact while summoning local emergency support if needed; facilitate direct linkage to crisis services; inform the treating clinician (with consent or under duty-of-care exceptions); notify guardians when required by safeguarding law and ethical guidance [3–5].
- Healthy controls in schools/clinics: if risk is identified, immediately connect the adolescent to the on-site clinician/school counselor or emergency services; inform guardians per safeguarding requirements; provide written and verbal information about urgent and ongoing care options; participation is stopped or deferred until safety is assured.

- Moderate but non-imminent risk:

- Develop or update a safety plan; arrange expedited clinical review (inpatient team, outpatient child and adolescent services, or school-based mental health); schedule a check-in within an agreed timeframe; reinforce means-safety steps and support mobilization [4].

- Abuse, neglect, or exploitation:

- Allegations or indicators of current abuse/neglect prompt mandatory reporting to child protection authorities according to Slovenian law and institutional policy; immediate safety needs are prioritized; disclosures are handled sensitively with clear, age-appropriate explanations of next steps, consistent with CIOMS and child safeguarding guidance [5].

- Heteroaggression risk:

- If credible risk to others is disclosed, take steps to warn/protect potential targets where legally required and clinically justified, engage the clinical team, and adjust risk management accordingly, with minimum necessary disclosure.

Confidentiality, limits, and participant communication

- Clear communication of limits: consent/assent materials and verbal explanations specify confidentiality protections and their limits (risk of harm to self/others; abuse/neglect; court orders), who may access data, and how safeguarding disclosures are handled. Adolescents are informed that choosing not to answer specific questions is acceptable and will not affect their clinical care.
- Use of quotations: participants can decline the use of quotations; any quoted material is de-identified to prevent recognition.
- Ongoing reminders: at each contact, staff reiterate the right to stop/skip, available support options, and how to request help during or after the session.

Data protection and privacy safeguards

- Data minimization and role-based access: only data necessary for protocol objectives are collected; access is restricted to authorized personnel according to study roles; identifiable data are stored separately from research data under coded IDs, in GDPR-compliant systems hosted in Slovenia [6].
- Secure transmission and storage: encryption is used for electronic data capture and transfer; physical records and biospecimens are stored in secure, access-controlled facilities; audit trails document data access and changes.
- Special category and genetic data: processing follows GDPR provisions for special category data with explicit consent; genetic/epigenetic data are coded and stored separately; no individual diagnostic feedback is returned unless required for immediate safety; any data sharing uses de-identified datasets under data-use agreements.
- Data breach response: suspected breaches are escalated within 24 hours to the Data Protection Officer; containment, assessment of risk to data subjects, and notification obligations are executed per GDPR and institutional SOPs, with documentation of corrective actions [6].

Monitoring, documentation, and oversight

- Safety logs: all distress events, escalations, safety-plan updates, and safeguarding referrals are logged with date/time, precipitating factors, actions taken, outcomes, and responsible personnel.
- Supervisory review: the clinical lead reviews safety events at regular intervals to identify patterns and improvement opportunities; protocol amendments are made if systematic risks are identified.
- Adverse event reporting: events attributable to study procedures (e.g., severe distress requiring medical intervention, vasovagal syncope from venipuncture) are reported per institutional ethics requirements; clinical events arising from underlying conditions are managed by the care team, with documentation of any study-related triggers.
- Stopping/deferral rules: assessments are deferred or terminated if a participant becomes acutely distressed or unsafe; re-approach occurs only after clinical stabilization and with participant assent.

Participant resources

At enrollment and each subsequent contact, adolescents receive age-appropriate written and verbal information on:

- Emergency contacts and crisis services available 24/7.
- Local outpatient mental health services and how to access them after discharge or from the community.
- Psychoeducation on coping with urges and where to seek immediate help.
- Study contact details for non-urgent questions or concerns.

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12.2 Adverse events reporting policy

Scope and guiding principles

This observational behavioural study does not introduce experimental treatments; nevertheless, systematic, proportionate identification and reporting of adverse events (AEs) is required to safeguard adolescents, ensure ethical oversight, and comply with institutional and regulatory obligations. AE procedures follow international ethics guidance for health-related research, adapted for non-interventional designs, and align with SPIRIT principles for prespecifying harms, with proportional emphasis on psychosocial and privacy-related risks relevant to self-harm research [1–3].

Definitions and reportable events

For this protocol, an AE is any untoward medical, psychological, social, or privacy-related occurrence in a participant temporally associated with participation in research procedures, whether or not considered causally related to those procedures [2]. In a behavioural study of high-risk adolescents, AEs include but are not limited to:

- Psychological/emotional events: marked distress, panic, dissociation, or escalation of self-harm urges during or immediately following assessments or interviews; persisting beyond the session or requiring clinical intervention.
- Safety events: emergent suicidal intent, suicide attempt, NSSI with medical consequences, or credible homicidal ideation identified during research contacts, irrespective of setting.
- Social harms: family, peer, school, or legal repercussions that are plausibly triggered by study participation or disclosures within study procedures.
- Physical events related to research procedures: vasovagal syncope, injury, infection, or other complications following venipuncture or study visits.
- Privacy and data-protection events: suspected or confirmed breaches of confidentiality, unauthorized data disclosure, reidentification, or security incidents involving personal/sensitive data (including genetic/epigenetic data).

A Serious Adverse Event (SAE) is any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent/significant disability/incapacity, or is an important medical or social event that may jeopardize participant safety or require intervention to prevent one of the foregoing outcomes [2]. Serious breaches of data protection (i.e., likely to result in a risk to the rights and freedoms of natural persons) are considered SAEs for reporting purposes under this protocol [5].

Unanticipated Problem (UP): an incident, experience, or outcome that is unexpected in nature, severity, or frequency; related or possibly related to participation; and suggests that the research places subjects or others at greater risk than previously recognized. UPs are reportable to oversight bodies even if they do not meet SAE criteria (e.g., a confidentiality lapse without demonstrated harm) [4].

Events that are outcomes of clinical care or the underlying condition but have no temporal or procedural link to study activities are not AEs for reporting (e.g., ward self-harm events that occur outside any study contact and are not plausibly triggered by research procedures). Such events remain captured as study outcomes via routine clinical surveillance per protocol and are managed by the clinical team. Any indication that study procedures contributed to an event (e.g., immediately after or during assessment) triggers AE evaluation.

Detection and identification

- Continuous surveillance during research contacts: trained staff monitor affect, risk signals, and wellbeing throughout all assessments/interviews; pre-session check-ins and post-session debriefs are standard.
- Passive and active reporting: participants, caregivers, clinicians, and school staff (for controls) may report concerns to the study team at any time via designated contact channels.
- Data-protection monitoring: the Data Manager monitors system alerts, access logs, and audit trails; all staff are trained to escalate suspected privacy/security incidents.

Documentation and assessment

All suspected AEs are documented on standardized AE forms within the electronic data capture system with audit trails, including:

- Event narrative, date/time of onset and detection, context (e.g., during C-SSRS administration; post-venipuncture; remote follow-up), and actions taken.
- Severity grading:

- Mild: transient/minimal symptoms; no intervention required.
- Moderate: discomfort or risk requiring brief intervention (e.g., session pause, grounding, first aid).
- Severe: marked distress or harm requiring clinical intervention, urgent risk management, or medical attention.
- Serious: meets SAE criteria above.

- Relatedness to study participation (one category):

- Not related: clear alternative cause; no temporal/procedural link.
- Unlikely related: temporal proximity but more likely due to underlying condition or context.
- Possibly related: reasonable possibility that procedures contributed.
- Probably related: likely contribution from procedures; alternative causes less plausible.
- Definitely related: clear causal link (e.g., vasovagal syncope immediately after blood draw).

- Expectedness: expected (pre-identified in protocol/consent) vs unexpected in nature, severity, or frequency [3,4].
- Outcome and resolution status; need for protocol modifications or additional safeguards.

Where privacy/data events are involved, the AE record cross-references the information security incident log while preserving minimum necessary linkage.

Immediate management and safeguarding interface

Participant safety actions (e.g., risk assessment, safety planning, clinical handover, emergency escalation) are initiated per safeguarding procedures described elsewhere in the protocol and occur independently of reporting timelines. Clinical care always takes precedence over documentation.

Reporting pathways, timelines, and responsibilities

- Internal notification:

- Any SAE or UP: notify the Principal Investigator (PI) and Clinical Safety Lead immediately and no later than 24 hours of awareness.
- Any suspected personal data breach: notify the Data Protection Officer (DPO) and PI within 24 hours.
- Non-serious AEs: enter in the AE log within 48 hours; flag to the site coordinator within 72 hours.

- External reporting to oversight bodies:

- Research Ethics Committee/Institutional Review Board (REC/IRB): report any SAE or UP that is related or possibly related to research procedures and is unexpected. Initial report within 7 calendar days of awareness; follow-up report with additional information within 15 calendar days or as requested by the REC/IRB [1,3,4].
- Institutional reporting: serious clinical incidents are reported per University Psychiatric Clinic Ljubljana (UPKL) incident policies within required institutional timelines.
- Data protection authority (Informacijski pooblaščenec): for personal data breaches likely to result in a risk to rights and freedoms, the DPO submits notification without undue delay and, where feasible,

not later than 72 hours after becoming aware, with content per GDPR Article 33; data subjects are informed without undue delay when the breach is likely to result in a high risk to their rights and freedoms (Article 34) [5].

- Periodic summaries:

- The PI provides aggregated AE/SAE/UP line listings and a narrative safety summary to the REC/IRB at least annually and at study closeout, including an assessment of any required protocol amendments or enhanced safeguards.

Responsibilities:

- Frontline assessors/interviewers: detect, stabilize, document preliminarily, and notify per timelines.
- Clinical Safety Lead: verify severity/relatedness, ensure clinical actions, and oversee SAE/UP submissions.
- PI: overall accountability; confirms final causality/expectedness, signs external reports, and implements corrective and preventive actions (CAPA).
- Data Manager: documents information-security incidents, supports DPO notifications, and coordinates data-containment steps.
- DPO: assesses breach risk, directs regulatory notifications, and monitors remediation [5].
- Steering/Safety oversight: reviews cumulative safety data quarterly to detect patterns and recommend modifications.

Special considerations

- Suicide attempts or severe NSSI occurring during or within 24 hours after a research contact are presumptively assessed as at least possibly related and reported accordingly, with final relatedness adjudicated by the Clinical Safety Lead and PI.
- For healthy controls in school/clinic settings, any identified acute risk is immediately transferred to on-site safeguarding pathways; reportability to the study REC/IRB follows the same relatedness and seriousness criteria.
- Qualitative interviews: any inclusion of personally identifying or potentially stigmatizing content in transcripts that could enable reidentification is treated as a privacy AE; corrective steps include redaction and access restriction, with reporting as required.

Record keeping, monitoring, and confidentiality

- AE/SAE/UP records are maintained in the study's secure electronic system with role-based access, coded participant identifiers, and complete audit trails; paper source notes, if any, are stored in locked cabinets in access-controlled areas.
- Identifiable clinical details are minimized; cross-references to medical records are stored separately from research data. Only the minimum necessary information is included in external reports to protect privacy while meeting regulatory requirements.
- The study team conducts periodic internal audits of AE documentation completeness and timeliness; the PI reviews concordance between clinical incident logs and AE records.
- All AE/SAE/UP documentation is retained per institutional policy and legal requirements for research records retention and is available for REC/IRB or regulatory inspection.

Corrective and preventive actions (CAPA)

Following any SAE or UP, the PI leads a root-cause analysis to determine contributory factors and implements CAPA (e.g., SOP updates, additional staff training, instrument sequencing changes, enhanced de-identification procedures, or modifications to contact modalities). Material protocol amendments prompted by safety findings are submitted to the REC/IRB prior to implementation,

unless immediate hazard elimination is required [1,3,4].

Participant communication

Participants and, where appropriate, parents/guardians are informed of any material harms or privacy incidents that affect them, the steps taken to mitigate risk, and available supports. Communications are developmentally tailored, minimize stigma, and document understanding and agreed next steps.

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
4. US Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): OHRP; 2007.
5. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.

12.3 Incident reporting and escalation pathways

Scope and principles

This section specifies procedures for identifying, reporting, escalating, investigating, and resolving reportable incidents that fall outside routine adverse event (AE) reporting. It applies to all study activities across inpatient units at UPKL and community/school settings for controls. Procedures are proportionate to risk, prioritize participant safety and data protection, and comply with CIOMS/ICH guidance, GDPR, and REC/IRB requirements [1–4].

Definitions and categories of reportable incidents (non-AE)

Reportable incidents include any unplanned occurrence that could compromise participant safety, rights, welfare, privacy, consent, or the integrity and credibility of study data/processes, whether or not an AE is present. Categories include:

- Data protection, privacy, and confidentiality incidents:
  - Suspected or confirmed personal data breach (loss, theft, unauthorized access/disclosure, ransomware), including genetic/epigenetic data or qualitative materials; misdirected emails, incomplete de-identification, re-identification risk; system outages leading to data loss [4,5].
- Significant protocol deviation/noncompliance:
  - Deviation that may increase risk to participants or materially affect primary outcomes, consent validity, eligibility, or key procedures (e.g., enrollment without valid consent/assent/parental permission; enrolling ineligible participants; failure to conduct mandated safeguarding assessment after risk disclosure; unapproved instrument changes; missed required follow-up with safety implications) [2,3].
- Minor protocol deviation:
  - Time-window misses without safety impact; administrative errors corrected without data loss (logged but not routinely escalated unless recurrent) [2].
- Informed consent irregularities:
  - Missing signatures, use of outdated documents, failure to provide required information or translators; concerns regarding voluntariness or undue influence [1,2].
- Safeguarding and professional conduct concerns unrelated to specific AEs:
  - Allegations of abuse/neglect by staff or others occurring within study interactions; boundary violations; discrimination; harassment; concerns about researcher competence or impairment; conflicts of interest not previously disclosed [1].

- Research misconduct and data integrity:
  - Fabrication, falsification, plagiarism, backdating, destruction of source data, intentional noncompliance, audit trail tampering [2].
- Specimen handling errors:
  - Mislabeling, mix-ups, chain-of-custody breaks, storage failures affecting biospecimens [2,5].
- Participant complaints/grievances:
  - Complaints about study burden, privacy, staff behavior, or perceived harms; media or social media issues that could expose participant identity or sensitive information [1,4].

Where an incident co-occurs with an AE/SAE/UP, both pathways are followed with cross-referenced documentation.

Immediate actions and containment

- Safety first: if participant welfare is at risk (e.g., safeguarding concern), initiate immediate clinical/safeguarding actions per site policy, independent of reporting timelines.
- Data containment: for suspected data breaches, isolate affected systems or records, preserve logs, prevent further disclosure, and contact the Data Manager/DPO within 24 hours [4,5].
- Procedure freeze: suspend the implicated procedure (e.g., recruitment using an invalid consent form) until risk is controlled and corrective steps are in place.

Reporting hierarchy and timelines

- Frontline staff (assessors/interviewers, coordinators):
  - Detect, stabilize, document preliminarily, and notify the Site Coordinator immediately and no later than 24 hours of awareness.
- Site Coordinator:
  - Triage within 24 hours; notify the Principal Investigator (PI). For personal data incidents, also notify the Data Manager and Data Protection Officer (DPO) within 24 hours [4].
- Principal Investigator:
  - Determines incident classification (minor deviation vs significant deviation/serious breach), oversees initial risk assessment, and directs escalation.
- Mandatory external notifications:
  - REC/IRB: report serious breaches or unanticipated problems that are related/possibly related and suggest greater risk than previously recognized. Initial notification within 7 calendar days; provide follow-up within 15 days or per REC instruction [1,3].
  - Institutional leadership/Quality and Risk Management (UPKL): per institutional incident policy timelines for clinical/safeguarding or integrity incidents.
  - Data Protection Authority via DPO: for notifiable personal data breaches, notify without undue delay and, where feasible, within 72 hours of awareness; notify affected data subjects without undue delay when high risk to rights/freedoms is likely, per GDPR Articles 33–34 [4].
  - Child protection/law enforcement: mandatory reporting of suspected abuse/neglect or credible risk to others per Slovenian law and institutional policy (immediate).
- Periodic reporting:
  - Summaries of incidents, trends, and CAPA are provided to the REC/IRB at least annually and at study closeout.

Documentation and investigation

- Incident log entry within 48 hours includes:
  - Category, date/time, discovery context, individuals and data/specimens involved, immediate actions, preliminary risk assessment, and initial classification (minor/significant/serious breach).
- Evidence preservation:
  - Retain source documents, correspondence, access logs, version histories, and chain-of-custody records. For digital events, export system logs and hash relevant files to preserve integrity [5].
- Root cause analysis (RCA):

- Led by the PI (and DPO for data breaches), using a structured method (e.g., 5-Whys/fishbone). Complete RCA for significant deviations/serious breaches within 10 business days or per REC/Institutional deadlines. Determine contributory factors: people, process, technology, environment, governance.

- Determinations:

- Impact on safety/rights, data integrity, and protocol objectives; relatedness to study processes; required CAPA; need for protocol/SOP amendments or re-consent.

Corrective and preventive actions (CAPA)

- Immediate corrective steps:

- Secure data; re-consent affected participants if required; retrain or suspend implicated procedures/personnel as appropriate.

- Preventive actions:

- SOP updates; system configuration changes (permissions, MFA, encryption at-rest/in-transit); revision of consent workflows; enhanced eligibility checks; labeling/custody enhancements for specimens; strengthened audit trails and monitoring frequency [2,4,5].

- Effectiveness checks:

- Define measurable indicators (e.g., zero recurrences over 3 months; 100% audit trail completeness); reassess within predefined intervals; escalate if ineffective.

Roles and responsibilities

- Frontline staff: recognize and report incidents; complete initial documentation; cooperate with investigations.
- Site Coordinator: triage; ensure timely entries; coordinate with clinical/unit leads and school partners for controls.
- PI: overall accountability; classifies seriousness; approves reports to REC/IRB; oversees RCA/CAPA; informs Steering/Safety oversight.
- Clinical Safety Lead: aligns safeguarding/clinical responses; ensures interface with AE/SAE procedures.
- Data Manager: initiates technical containment; compiles forensic logs; supports DPO notifications; validates data restoration.
- DPO: leads data breach risk assessment; determines notification obligations/content; advises on privacy CAPA and data subject communications [4].
- Institutional officials/Quality office: receive and review serious incidents; may initiate independent inquiries per policy.
- All personnel: complete mandatory training on incident recognition, GDPR, consent, and protocol compliance; maintain confidentiality throughout.

Communication with participants and stakeholders

- Participants and, where appropriate, parents/guardians are informed of incidents that materially affect their rights or welfare, with clear explanation of what occurred, risks, remedial steps, and available supports. Communications are documented and coordinated with the DPO for data matters and with clinical teams for safeguarding [1,4].
- External communications (media/social media) occur only through authorized institutional channels to protect confidentiality and integrity.

Monitoring and quality improvement

- Quarterly review of the incident register by the PI, DPO, Data Manager, and Clinical Safety Lead to identify patterns, persistent vulnerabilities, and training needs; findings inform protocol amendments or additional safeguards.
- Internal audits compare incident logs with AE/SAE records, consent documentation, eligibility checks, and system audit trails to verify completeness and timeliness; results are available for REC/IRB or regulatory inspection [2].

Incident categories, initial actions, and escalation timelines

Incident category	Examples	Immediate action	Internal notification	External notification
Data breach/privacy	Lost device, misdirected email, unauthorized access, re-identification risk	Contain, preserve logs, isolate systems	Data Manager/DPO within 24 h; PI same day	DPA via DPO within 72 h if notifiable; data subjects without undue delay [4]
Significant protocol deviation/serious breach	Invalid consent, ineligible enrollment, missed mandated safeguarding assessment	Stop implicated activity; secure records; initiate RCA	PI within 24 h; Clinical Safety Lead if safeguarding-related	REC/IRB within 7 days when related/possibly related and increases risk [1,3]
Minor protocol deviation	Visit outside window without safety impact	Correct and document	Site Coordinator within 72 h	Not routinely required; include in periodic summaries
Consent irregularity	Outdated forms, missing elements, language needs unmet	Re-consent with correct documents; pause procedures	PI within 24 h	REC/IRB if affecting rights/validity at scale
Specimen handling error	Mislabeling, storage failure	Quarantine, relabel if validated, document chain-of-custody	PI within 24 h; Data Manager if LIMS affected	As per REC/Institutional policy if impact is material
Safeguarding/pro conduct	Boundary violations, discrimination, harassment	Ensure safety; report per institutional safeguarding	PI and institutional safeguarding lead immediately	Child protection/law enforcement as mandated; REC/IRB if research-related [1]
Research misconduct	Fabrication, falsification, audit trail tampering	Preserve evidence; suspend implicated processes	PI and institutional research integrity office immediately	Per institutional policy; REC/IRB informed if protocol/data integrity affected [2]

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
3. US Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): OHRP; 2007.
4. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
5. International Organization for Standardization. ISO/IEC 27035-1:2016 Information technology—

Security techniques—Information security incident management—Part 1: Principles of incident management. Geneva: ISO; 2016.

13 ETHICAL AND REGULATORY ASPECTS

13.1 Ethics/IRB/IEC approval and ongoing reporting

Ethical oversight and approvals

Prior to any study activity, the full protocol and all supporting documents will be submitted for review and approval by a competent Research Ethics Committee/Institutional Review Board (REC/IRB) in Slovenia, with the University Psychiatric Clinic Ljubljana (UPKL) as the primary site. No recruitment, consent, data collection, or access to identifiable records will occur until formal written approval is obtained. The study will be conducted in accordance with the Declaration of Helsinki, CIOMS International Ethical Guidelines, and Good Clinical Practice principles adapted to non-interventional behavioral research; where these frameworks are designed for interventional trials, their core protections are applied by analogy to this observational design [1–3].

Submission package and pre-initiation conditions

The REC/IRB submission will include:

- Final protocol and lay summaries.
- Participant information sheets, consent/assent and parental permission forms in Slovene (and other approved languages if applicable), with versions tailored for inpatients and school-based controls.
- Recruitment materials and scripts for clinical units and schools.
- All questionnaires/interview guides, including the C-SSRS, B-NSSI-AT, ISAS, and measures used for the Adolescent Self-Harm Risk Scale (ASHRS) development and validation.
- Data management plan, privacy notices, coding/anonymization procedures, and data retention/archiving plans.
- Data Protection Impact Assessment (DPIA) covering special-category and genetic/epigenetic data, with confirmation of GDPR-compliant technical and organizational safeguards; consultation with the Data Protection Officer (DPO) will be documented where required by GDPR Articles 35–36 [5].
- Biospecimen procedures for venous blood collection, processing, storage, and any transfer; evidence of biobank or institutional approvals and material/data transfer agreements as applicable.
- Staff training plan (suicide risk assessment/safeguarding, consent with minors, confidentiality/GDPR).
- Site permissions from clinical units and participating schools/educational authorities, as required.

Conditions that must be met before study commencement:

- REC/IRB approval of the protocol and all participant-facing materials.
- Institutional authorization at UPKL (and partner sites/schools) to initiate the study.
- Completion of all required staff training and credentialing.
- DPO sign-off on the DPIA and data flows; execution of data processing/sharing agreements where relevant [5].
- Establishment and validation of secure data capture systems and audit trails, and readiness of incident/adverse event reporting pathways [2,5].

Consent, assent, and protections for minors

Consent/assent processes will follow REC/IRB-approved procedures and CIOMS guidance on research with children and adolescents, ensuring voluntariness, capacity-appropriate information, confidentiality, and clear explanation of safeguarding limits [1]. Parental permission is required for

participants under 15 years, with adolescent assent documented; consent from participants aged 15–19 years will follow applicable law and REC/IRB determinations. Any use of remote/telehealth contacts will employ consent verification procedures approved by the REC/IRB.

Continuing review and ongoing submissions

Throughout the study, the Principal Investigator (PI) will maintain active communication with the REC/IRB and:

- Submit and obtain approval for any protocol amendments or updates to consent/assent forms, instruments, recruitment materials, or data/biospecimen procedures before implementation, except when immediate changes are necessary to eliminate an apparent hazard to participants; in such cases, the REC/IRB will be notified promptly with a rationale and proposed revisions [2].
- Provide periodic progress reports at least annually, and more frequently if requested, summarizing enrollment, retention, deviations, adverse events/unanticipated problems, data protection incidents, safeguarding referrals, and any changes to risk–benefit assessments [1,3,4].
- Report any temporary holds, early stopping, or significant operational changes with justification and plans for participant communication.

Safety, unanticipated problems, and other reportables

The study will follow REC/IRB policies and applicable guidance for reporting serious adverse events (SAEs) and unanticipated problems involving risks to participants or others. Events that are related or possibly related to study procedures and are unexpected in nature, severity, or frequency will be reported to the REC/IRB within their specified timelines (typically initial report within 7 calendar days, with follow-up information as available), consistent with OHRP guidance and institutional policy [3,4]. Notifiable personal data breaches will be handled in line with GDPR, including supervisory authority notification within 72 hours when required and communication to affected data subjects where high risk is likely [5]. Aggregated safety and incident summaries will be provided in annual progress reports and at closeout.

Protocol deviations and noncompliance

All significant protocol deviations that may affect participant safety/rights, consent validity, or data integrity will be reported to the REC/IRB per policy, with a root-cause analysis and corrective and preventive actions (CAPA). Minor deviations will be logged and trended; recurrent patterns will be escalated with proposed mitigations [2–4].

Data protection governance and oversight

Processing of special-category personal data, including genetic/epigenetic information, will comply with GDPR principles of lawfulness, purpose limitation, data minimization, integrity/confidentiality, and accountability. The DPIA will be updated if data flows or risk profiles change materially. Any engagement of processors or cross-institutional data sharing will occur under written agreements specifying roles, safeguards, and data subject rights, as reviewed by the DPO and REC/IRB where applicable [5].

Roles and responsibilities for ethics communications

- Principal Investigator: overall accountability; serves as the primary point of contact with the REC/IRB; signs submissions; ensures timely reporting and implementation of REC/IRB determinations.
- Clinical Safety Lead: oversees safeguarding integration with research procedures; verifies reportable events; co-signs safety submissions as indicated.
- Site Coordinator: maintains the regulatory binder; tracks approvals, expirations, and training; coordinates amendment deployments and site communications.

- Data Protection Officer: advises on GDPR compliance and DPIA; leads assessment and external notifications for personal data breaches; coordinates participant communications for privacy incidents [5].
- Steering/Safety oversight (if convened): reviews cumulative progress, safety, and compliance metrics; advises on amendments and CAPA.

Study closeout and final reporting

Within timelines specified by the REC/IRB, a final report will be submitted upon study completion, including: enrollment and follow-up status, primary activities completed (including ASHRS development/validation milestones), summary of harms/unanticipated problems and resolutions, protocol deviations with CAPA, data protection outcomes, and dissemination plans. Publications will reflect ethical approvals and any material changes over time, in line with SPIRIT principles for transparent reporting adapted to observational behavioral research [3].

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
4. US Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): OHRP; 2007.
5. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.

13.2 Informed consent/assent, vulnerable groups, surrogate consent

Ethical basis and scope

Informed consent and assent procedures will adhere to the Declaration of Helsinki, CIOMS International Ethical Guidelines, and Good Clinical Practice principles adapted to non-interventional behavioral research, with additional safeguards for minors and individuals with diminished decisional capacity. Processing of special-category personal data, including genetic/epigenetic information, will comply with GDPR requirements for explicit consent and transparency [1–4]. Where national law or REC/IRB determinations provide more specific direction (e.g., age thresholds for consent), those requirements will prevail, consistent with the Council of Europe Oviedo Convention on human rights and biomedicine [5].

Consent pathways by age and capacity

- Adolescents under 15 years:

- Parental/guardian permission is required prior to any study procedures.
- The adolescent's affirmative assent is sought using developmentally appropriate materials and is required unless the REC/IRB approves a justified exception (e.g., minimal-risk record review). Lack of assent results in non-participation, even if parental permission is provided [1,6].

- Adolescents aged 15–19 years:

- Consent procedures will follow applicable Slovenian law and REC/IRB determinations regarding a minor's capacity to consent for health-related research. Where the REC/IRB requires parental/guardian permission in addition to adolescent consent for those under the age of majority, both will be obtained.
- Regardless of legal capacity, information is tailored to the adolescent's decisional maturity;

involvement of parents/guardians is encouraged where appropriate and consistent with confidentiality and safeguarding limits [1,5].

- Temporary or limited capacity at the time of enrollment:

- If an otherwise eligible inpatient has transiently diminished capacity (e.g., due to severe distress or sedation), enrollment is deferred until clinical stabilization permits a valid consent/assent process. In rare instances where enrollment timing is essential for minimal-risk data capture (e.g., baseline questionnaires integral to longitudinal validity) and allowed by law/REC, permission from a legally authorized representative (LAR; typically a parent/guardian) may be obtained with the adolescent's assent whenever feasible; full consent is re-sought from the adolescent at the earliest opportunity ("re-consent") [1,5,6].

Assent: content and process

Assent materials for 13–17-year-olds use clear, age-appropriate language, graphics where useful, and emphasize:

- The study purpose, procedures (including questionnaires/interviews and blood draw), expected time, and potential for emotional discomfort.
- Voluntariness, including the right to skip questions, pause, or stop without penalty to clinical care, school standing, or relationships with clinicians/teachers.
- Confidentiality protections and their limits (e.g., risk of serious harm to self/others, abuse/neglect) [1,2].
- Whom to contact with questions or concerns.

Assent is documented via a signature or verbal affirmation recorded on the consent form, per REC/IRB approval. If an adolescent expresses dissent at any time, participation in research procedures ceases, consistent with safeguarding obligations [1,6].

Surrogate consent and re-consent

- Legally authorized representative:

- For minors lacking legal capacity to consent or for participants who cannot consent due to temporary incapacity, consent is obtained from the LAR (parent or court-appointed guardian), in accordance with national law and REC/IRB determinations. The adolescent's views and preferences are solicited and respected to the extent possible [1,5,6].

- Re-consent:

- Re-consent is performed when capacity is regained, when a participant reaches the age at which they may legally consent for themselves, or when material protocol changes occur (e.g., new data uses). Participants can withdraw or modify permissions at re-consent without penalty [1–3,5].

Procedures to ensure comprehension and voluntariness

- Information delivery:

- Written Participant Information Sheets and consent/assent forms are provided in Slovene; other languages are supplied with certified translations if needed. Verbal explanations use plain, non-stigmatizing language and avoid technical jargon. Interpreters are engaged when language barriers exist [1–3].

- Time for consideration:

- Adolescents and parents/guardians are given sufficient time to review materials and ask questions. In inpatient settings, approach occurs only after initial stabilization in coordination with the treating team to minimize therapeutic misconception and undue pressure.

- Comprehension checks:

- Staff use brief teach-back questions (e.g., "Can you tell me what will happen if you decide not to take part?") to confirm understanding of purpose, procedures, risks, benefits, confidentiality limits, voluntariness, and withdrawal options. Misunderstandings are corrected before consent is finalized [1,2].

- Minimizing undue influence:

- Consent is obtained by trained research personnel who are not the primary decision-makers for the participant's clinical care or school grading. No financial or academic inducements are offered. For

school-based controls, teachers do not collect consent and are not present during consent discussions; participation or refusal has no effect on grades or access to school services [1,6].

- Ongoing consent:

- At each contact, staff reaffirm voluntariness, right to skip items, and avenues for support. New information affecting willingness to continue is communicated promptly, with re-consent if warranted [1,2].

Additional protections for vulnerable groups

- High-risk inpatients:

- Recruitment and consent occur in private settings; sessions are scheduled to avoid periods of acute crisis. Participants may opt out of sensitive modules (e.g., trauma, sexuality) or the blood draw while remaining in the study for other components, when methodologically feasible, reducing all-or-nothing pressure [1].

- Adolescents with trauma histories, minority stress, or stigmatized identities:

- A trauma-informed approach is used; examples and questions are framed sensitively; participants can decline use of direct quotations in any qualitative materials. Privacy is prioritized to reduce social harms [1,2].

- Healthy school-based controls:

- Parental involvement follows REC/IRB-approved requirements by age; privacy is ensured during assent/consent and data collection. School staff are briefed on safeguarding boundaries and do not access individual responses [1].

- Safeguarding interface:

- Limits of confidentiality are explained clearly at consent/assent. If imminent risk is disclosed, safety procedures take precedence; any necessary disclosures are limited to the minimum required and are explained to the adolescent and guardian, consistent with law and ethics [1,2].

Consent for genetic/epigenetic components and biospecimens

- Explicit consent:

- Separate, clearly delineated consent sections address venous blood collection, genetic/epigenetic analyses, data storage, and future use. Participation in behavioral assessments is not contingent on agreeing to biospecimen collection; participants may decline or withdraw biospecimen consent independently (“tiered consent”), where scientifically feasible [1–3].

- Data handling and feedback:

- Materials explain coding, storage, sharing of de-identified data under agreements, and that no individual clinical results will be returned unless required for immediate safety. On withdrawal, participants may request destruction of stored identifiable biospecimens not yet irreversibly de-identified, consistent with GDPR and REC/IRB-approved procedures [3].

Who may obtain consent/assent and training

Consent/assent is obtained by investigators, clinicians, or research coordinators who:

- Are trained in adolescent communication, suicide risk/safeguarding, confidentiality/GDPR, and consent with minors.
- Are delegated in the site delegation log and have completed protocol-specific training and competency checks.
- Can recognize and manage potential undue influence or therapeutic misconception, and can pause or defer consent when conditions for valid consent are not met [1,2].

Modality, documentation, and records

- Modality:

- In-person written consent/assent is standard. For remote follow-up activities, REC/IRB-approved electronic or teleconsent procedures may be used, including verified identity checks and secure delivery of consent documents, with documentation of date/time and personnel [2].

- Documentation:

- Signed consent/assent and parental permission forms include version/date, participant and LAR names/signatures, name/signature of the person obtaining consent, and any language assistance used. Each party receives a copy; the original is filed in the regulatory binder or secure electronic repository with audit trails.

- Record retention:

- Consent records are retained per institutional policy and law, separate from research data, with access restricted to authorized personnel and availability for REC/IRB inspection [2,3].

Withdrawal, partial participation, and data use

- Participants may withdraw at any time without consequences to care or schooling. Where feasible, they may opt for partial participation (e.g., questionnaires without blood draw).
- Upon withdrawal:

- No further data are collected. Participants may request destruction of biospecimens not yet de-identified. Data already analyzed or included in aggregated datasets may not be retractable; this limitation is explained during consent [1–3].

Documentation of decisional capacity and exceptions

- Capacity assessment is proportionate and documented (brief mental status and understanding of key consent elements). If capacity is unclear, consent is deferred or obtained from the LAR with the adolescent's assent, followed by re-consent when feasible.
- Any exception to standard consent procedures requires prior REC/IRB approval and is documented with justification; emergency waivers are not applicable to this non-therapeutic observational study [1,2].

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
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5. Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention). Oviedo: Council of Europe; 1997.
6. US Department of Health and Human Services. 45 CFR 46, Subpart D—Additional protections for children involved as subjects in research. Washington (DC): HHS; 2009.

13.3 Protocol deviations/violations and amendments

Definitions and scope

- Protocol deviation: any departure from prespecified procedures, requirements, or time windows in the approved protocol, SOPs, or REC/IRB determinations, whether or not it affects participant safety, rights, consent validity, or data integrity (e.g., minor scheduling windows exceeded without impact on outcomes or safety) [1,2].

- Protocol violation (significant deviation/serious breach): noncompliance that may increase risk to participants or others, compromise consent or eligibility, or materially affect the integrity or reliability of key study outcomes (e.g., use of outdated consent documents; enrollment of ineligible participants; failure to perform a mandated safeguarding assessment after risk disclosure; unapproved alteration of primary measures or their sequencing) [1–3].
- Noncompliance: failure to adhere to applicable regulatory/ethical requirements, REC/IRB determinations, or institutional policies. Serious noncompliance is a subset that results in, or poses, significant risk to participants' rights, safety, or welfare, or to data integrity [1–3].

These definitions are applied proportionately to this prospective observational behavioral study conducted under Good Clinical Practice principles adapted for non-interventional designs [1,2].

Identification and detection

- Real-time controls:

- Pre-visit checklists (eligibility, current approved consent/assent versions, required safeguarding procedures).
- Electronic case report form (eCRF) edit checks and mandatory fields for primary measures (e.g., C-SSRS, B-NSSI-AT, ISAS; ASHRS modules).

- Ongoing surveillance:

- Routine data quality reviews by the Data Manager and Site Coordinator; automated audit trails to detect backdating or out-of-window entries.
- Source data verification (proportionate sampling) of consent records, eligibility determinations, and key outcomes (self-harm events during hospitalization; ASHRS scores).

- Staff reporting:

- All personnel are required to self-report suspected deviations immediately upon discovery to the Site Coordinator, without fear of reprisal, consistent with a just culture approach [1,2].

Documentation and initial assessment

- Log and classify within 48 hours of awareness:

- Description, date/time, personnel involved, affected participants/data/specimens, root-cause hypothesis, immediate containment, and preliminary classification (minor deviation vs protocol violation/serious breach).

- Impact assessment (PI or delegate within 72 hours):

- Safety/rights: whether rights, welfare, or data protection were affected.
- Scientific integrity: whether primary/secondary outcomes, analysis populations, or psychometric evaluations (e.g., ASHRS validation) were compromised.
- Regulatory/ethics: whether the event constitutes serious noncompliance or an unanticipated problem requiring REC/IRB notification [1,3].

- Cross-reference:

- If the occurrence coexists with an adverse event or data breach, documentation links to the AE or information-security incident logs, preserving minimum necessary identifiers [1–3].

Review, management, and CAPA

- Triage and investigation:

- The PI leads or delegates a proportionate root-cause analysis (RCA) for all protocol violations and for recurrent minor deviations, using a structured method (e.g., 5-Whys). Complete RCA typically within 10 business days or per REC/Institutional timelines [1,2].

- Corrective actions:

- Immediate steps to eliminate/mitigate risk (e.g., suspend implicated procedures; re-consent; re-verify eligibility; repeat or replace invalid assessments when feasible and unbiased).

- Preventive actions:

- SOP revision; retraining; additional decision aids for eligibility; consent version control checks; enhanced eCRF edit checks; sequencing locks for key instruments; strengthened safeguarding prompts in the workflow [1,2].

- Effectiveness verification:

- Define objective indicators (e.g., zero recurrences over one quarter; 100% use of current consent versions; on-time completion of mandated risk assessments) and reassess on a predefined schedule; escalate if ineffective.

Reporting criteria and timelines

- Report to REC/IRB:

- Any protocol violation/serious noncompliance that is related or possibly related to study conduct and increases risk to participants or others, compromises consent validity, or materially affects data integrity, including unanticipated problems. Initial report within 7 calendar days of awareness; submit follow-up information within 15 days or as requested [1,3].

- Institutional notifications:

- Notify UPKL Quality/Risk Management and other required institutional bodies for serious noncompliance or safeguarding-related breaches per policy [1,2].

- Aggregated reporting:

- Summaries and trend analyses of deviations and violations, with CAPA status, are included in annual progress reports and closeout submissions to the REC/IRB [1,3].

- Minor deviations:

- Logged, trended, and reviewed periodically. Escalate to REC/IRB if patterns suggest emerging risk or material impact.

Interaction with analysis populations

Consistent with the Statistical Analysis Plan, deviations are categorized as:

- Important deviations affecting analysis populations (e.g., ineligibility, invalid or missing primary outcome data due to noncompliance).
- Other deviations not affecting primary analyses but tracked for sensitivity analyses and transparency.

Predefined rules determine inclusion/exclusion in analysis sets; deviations are summarized in the final report to align with SPIRIT-aligned transparency standards [1].

Protocol amendments

- When amendments are required:

- Scientific, ethical, operational, or data-protection changes that may affect objectives, outcomes, eligibility, consent materials, safeguarding procedures, biospecimen handling, data flows, or risk–benefit assessments.

- Immediate changes necessary to eliminate an apparent hazard may be implemented promptly, with expedited notification and a formal amendment submitted without delay [1–3].

- Preparation:

- Amendment cover memo summarizing rationale, changes, tracked revisions, risk–benefit reassessment, need for re-consent, and impact on ongoing activities and data comparability.

- Updated documents: protocol, consent/assent and parental permission forms, participant information sheets, instruments or guides (including ASHRS materials), SOPs, data management plan, DPIA if data flows or risks change [1,3].

- Submission and approval:

- Submit to the REC/IRB and, where applicable, institutional authorities and the Data Protection Officer for DPIA updates. No implementation before written approval, except to remove immediate hazards [1–3].

- Communication and implementation:

- Version control with unique identifiers and effective dates; update the regulatory binder and electronic repositories.

- Site roll-out plan: staff training on changes; competency checks; system configuration updates (eCRF, audit trails); transition rules specifying from which date/participant the new procedures apply; documentation of any parallel runs required to preserve data integrity.

- Re-consent:

- Obtain re-consent/assent and parental permission when changes materially affect participation, risks, or data use, including genetic/epigenetic components or new data sharing; document and file per requirements [1–3].

- Transparency:

- Maintain an amendment history log; reflect material amendments and their justifications in dissemination outputs consistent with SPIRIT principles for protocol reporting [1].

Roles and responsibilities

- Principal Investigator: final classification of deviations/violations; approves reports; leads RCA/CAPA; signs and submits amendments; ensures implementation and training.
- Site Coordinator: maintains deviation/violation logs and amendment trackers; ensures document/version control; coordinates training and rollout.
- Data Manager: updates eCRF checks and audit trails; validates system changes; preserves data comparability across versions.
- Clinical Safety Lead: ensures alignment with safeguarding procedures; evaluates participant risk implications; advises on re-consent content.
- All study personnel: promptly report deviations; adhere to updated procedures; complete required training before implementing amendments.

Record keeping and inspection readiness

All deviation/violation records, RCA/CAPA documentation, REC/IRB correspondence, amendment versions, training logs, and implementation evidence are maintained with complete audit trails and are available for inspection. Records are retained per institutional policy and applicable regulations [1,2].

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
2. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
3. US Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): OHRP; 2007.

13.4 Insurance/indemnity and funding disclosures

Insurance and indemnity arrangements

This prospective observational study involves minimal procedural risk beyond completion of questionnaires/interviews and venous blood collection. Notwithstanding the low-risk profile, insurance and indemnity arrangements are in place to protect participants against study-related harm, consistent with ethical guidance and Good Clinical Practice principles adapted to non-interventional research [1–3].

- Institutional cover: The University Psychiatric Clinic Ljubljana (UPKL), as the hosting institution and study sponsor, maintains institutional liability insurance that covers the acts and omissions of its employees and authorized research staff when acting within the scope of their duties, training, and the approved protocol/SOPs. This institutional cover applies to study-related injury or harm that is directly attributable to protocol-specified procedures conducted at or under the auspices of UPKL, including venipuncture for biospecimen collection and research interviews/assessments.

- No-fault research insurance: Where required by the REC/IRB or institutional policy, the sponsor will maintain or procure no-fault research insurance to provide compensation for injury that is more likely than not caused by study procedures, independent of negligence determinations, in accordance with CIOMS and Helsinki guidance on provision of treatment and fair compensation for research-related harm [1,3]. Evidence of current cover (insurer, policy number, limits, and period of insurance) will be provided to the REC/IRB prior to study initiation and kept on file for inspection.

- Scope and exclusions: Coverage includes necessary medical treatment costs and reasonable, documented out-of-pocket expenses arising from harm directly caused by study procedures, as assessed by the sponsor's claims process. Coverage does not extend to:
  - Clinical events that are solely a consequence of participants' underlying illness or usual clinical care not mandated by the research protocol.
  - Harm resulting from non-adherence to the approved protocol, willful misconduct, criminal acts, or procedures performed by personnel outside their authorization or competency.
  - Idiosyncratic reactions or events unrelated to study activities, as determined by medical review and the insurer's terms.
  These provisions do not limit any statutory rights participants may have under applicable law.

- Data protection incidents: Obligations to mitigate, notify, and remediate personal data breaches are governed by GDPR and institutional policies; insurance and indemnity do not limit data subjects' rights under GDPR, including the right to lodge a complaint or seek redress [5]. Any cyber/privacy liability coverage is held at the institutional level and managed through UPKL's standard incident and claims processes.

- Investigator and institutional indemnity: Investigators and delegated research staff acting in good faith and in accordance with the approved protocol, applicable laws/regulations, and their professional duties are indemnified by the sponsor/institution for claims arising from the conduct of the study, except in cases of fraud, willful misconduct, gross negligence, or practice outside the scope of authorization [2].

- Claims and participant communication: Information on how to report a study-related injury or concern and how to initiate a claim will be provided in the Participant Information Sheet/consent materials, including contact details for the Principal Investigator and the institutional quality/risk office. Reports will be reviewed promptly, and medically necessary care will be facilitated without delay while coverage determinations are made, consistent with CIOMS and Helsinki guidance [1,3].

Funding sources and role of funders

- Sources of support: The study is supported by institutional resources of UPKL (e.g., personnel time, facilities, data systems). If external funding (e.g., competitive grants or charitable foundation support) is secured prior to or during the study, the sponsor will disclose the source, award identifier, and period of support to the REC/IRB and in all publications and registries, in line with SPIRIT and ICMJE transparency standards [4,6].

- Funders' role: Funders, whether internal or external, will have no role in study design, data collection, data management, statistical analysis, interpretation of findings, manuscript drafting, approval of the final manuscript, or the decision to submit for publication, unless explicitly stated in REC/IRB submissions and acknowledgements. Investigators retain full academic independence, access to all study data, and the right to publish regardless of outcome, consistent with best practice guidance [4,6].

- In-kind support and conflicts of interest: Any in-kind contributions (e.g., instrument licenses, training materials, or assay reagents) and any financial or non-financial relationships with commercial entities or advocacy groups relevant to the study will be declared to the REC/IRB and disclosed in dissemination outputs. All investigators will complete and update conflict-of-interest declarations per institutional and journal requirements [6].

Transparency and regulatory compliance

Insurance/indemnity and funding arrangements will be:

- Documented in the REC/IRB application and maintained in the site regulatory binder.
- Summarized in the Participant Information Sheet/consent documents, including the nature of cover and how to seek compensation for research-related harm, consistent with CIOMS and GCP-aligned expectations [1,2].
- Disclosed in all manuscripts, conference abstracts, and public summaries, in accordance with SPIRIT and ICMJE recommendations on reporting funding and the role of sponsors [4,6].

These measures are intended to uphold participant protections, ensure independence of the research, and meet ethical and regulatory requirements for transparency and accountability [1–6].

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
3. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
4. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
5. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
6. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated 2024.

14 STUDY GOVERNANCE

14.1 Roles and responsibilities

Study oversight structure

The University Psychiatric Clinic Ljubljana (UPKL) is the study sponsor and host institution. Governance follows Good Clinical Practice principles adapted to non-interventional behavioral research and SPIRIT-aligned transparency standards, with GDPR-compliant data protection oversight [1–4].

- Oversight hierarchy (reporting lines):

- Sponsor (UPKL) retains institutional accountability for legal, insurance, and compliance matters.
- Principal Investigator (PI) has overall responsibility for scientific integrity, participant safety, and regulatory/ethics compliance; serves as signatory for REC/IRB and institutional submissions [1–3].
- Co-Investigators/Sub-Investigators report to the PI for domain-specific leadership (clinical, ASHRS development/validation, qualitative components, laboratory/biospecimens).
- Site Coordinator and Research Coordinators report to the PI for operational conduct, regulatory documentation, and participant flow.
- Data Manager and Statistician report to the PI for data quality, database lifecycle, and statistical integrity.
- Clinical Safety Lead reports to the PI with authority to pause procedures when safeguarding or risk

thresholds are met.
- Data Protection Officer (DPO) advises independently on GDPR; operationally interfaces with the PI and Data Manager [4].
- Study Steering Group (SSG) convenes quarterly (or ad hoc) to review progress, safety/compliance metrics, and CAPA; chaired by the PI with invited independent methodological and adolescent mental health advisors.

Key roles and responsibilities

Role	Core responsibilities
Principal Investigator (PI)	Provides overall scientific leadership; ensures protocol fidelity, data integrity, and safeguarding integration; approves delegation of duties; oversees consent/assent processes with minors; serves as REC/IRB and sponsor-facing lead; final authority on protocol deviations/violations classification, RCA/CAPA, and amendments; ensures training and competency; approves data releases and manuscripts [1–3].
Co-Investigators/Sub-Investigators	Lead domain areas (inpatient clinical assessments; school-based control recruitment; ASHRS development/validation; qualitative interviews/analysis; biospecimen oversight); supervise day-to-day procedures; ensure adherence to SOPs; contribute to RCA/CAPA and amendments; mentor staff.
Clinical Safety Lead	Integrates clinical safeguarding with research; ensures timely C-SSRS administration and risk triage; verifies reportable safety events; maintains 24/7 escalation pathways with clinical units and schools; can halt research procedures for safety; co-signs safety submissions as required [1–3].
Site Coordinator	Maintains regulatory binder; manages approvals, version control, training logs, delegation log; coordinates schedules, visit windows, and follow-ups; tracks deviations/violations and amendment roll-outs; organizes SSG meetings and minutes.
Research Coordinators/Assessors	Conduct consent/assent and parental permission per approvals; administer instruments (e.g., C-SSRS, B-NSSI-AT, ISAS, ASHRS modules) and qualitative interviews; ensure privacy and distress protocols; complete eCRFs/source notes; prompt reporting of incidents and deviations.
School Liaison Lead	Coordinates with educational authorities; ensures separation of research from academic evaluation; oversees consent logistics for healthy controls; briefs school staff on safeguarding and confidentiality boundaries.
Data Manager	Designs, validates, and maintains secure eCRF/database with audit trails; implements edit checks; manages coding, pseudonymization, and access control; conducts routine data quality reviews; maintains data dictionaries and versioning; supports data extracts for analysis; logs and investigates data issues; ensures GDPR-aligned technical safeguards [1,4].
Statistician	Finalizes Statistical Analysis Plan; prespecifies analysis populations; conducts and documents analyses (regression, survival, clustering as applicable); leads missing data strategy; runs sensitivity/subgroup analyses; ensures reproducible scripts and code review; contributes to interpretation and reporting [2,3].
Psychometrics/ASHRS Lead	Oversees instrument development, translation/adaptation, item analysis, reliability/validity testing, and calibration; coordinates cognitive testing; maintains version control and change logs; documents TIDieR-relevant details for implementation reporting.
Qualitative Methods Lead	Trains interviewers; ensures COREQ/SRQR-consistent procedures; oversees sampling, data saturation judgments, coding frameworks, credibility checks (e.g., double-coding), and secure handling of transcripts/audio.

Laboratory/Biospecimen Lead	Oversees phlebotomy SOPs, processing, storage, chain-of-custody, and shipments; ensures biobank approvals and MTA/DTA compliance; reconciles specimen inventories with data; reports incidents (e.g., sample mix-ups) and implements CAPA.
Data Protection Officer (DPO)	Advises on GDPR lawful bases, DPIA, data subject rights, processor agreements, and cross-institutional sharing; leads breach risk assessment/notifications; reviews data flows and re-use proposals; independent of study conduct [4].
Quality Assurance/Monitoring Function	Conducts proportionate, risk-based internal monitoring (consent verification, eligibility checks, key outcomes, audit trails); performs targeted source data verification; reviews trends in deviations and implements CAPA; ensures inspection readiness [1–3].
Patient and Public Involvement (PPI) Advisor(s)	Provide adolescent/parent perspectives on feasibility, burden, and communication; review participant-facing materials; advise on dissemination; do not access individual-level data.
Administrative/Finance Officer	Tracks budgets, procurement (licenses, supplies), and contracts; maintains documentation for audits; ensures alignment with funding disclosures.

Delegation, accountability, and decision-making

- Delegation of duties is documented before initiation in a signed delegation log linked to training and competency records; updates are version-controlled. The PI retains ultimate accountability for all delegated tasks [1–3].
- Safety-critical decisions (imminent risk, mandated safeguarding actions, temporary study holds) are taken by the Clinical Safety Lead or PI; any urgent deviations to remove immediate hazards are documented and reported per policy [1–3].
- Scientific decisions affecting outcomes, measures, or analysis plans require PI approval following SSG consultation and REC/IRB approval where applicable.
- Data access follows least-privilege principles: role-based permissions are granted by the Data Manager with PI approval and DPO oversight for special-category data [4].

Communication, meetings, and documentation

- Meeting cadence:

- Daily/weekly operational huddles (PI or delegate, Site Coordinator, coordinators).
- Monthly data quality reviews (PI, Data Manager, Statistician).
- Quarterly SSG meetings reviewing enrollment, retention, safety/safeguarding metrics, deviations/CAPA, and progress on ASHRS validation and analyses; minutes and action logs are archived.

- Incident and deviation reporting uses standardized forms within 48 hours of awareness; CAPA tracking is reviewed monthly.
- All governance, training, monitoring, and meeting records are maintained in the regulatory binder/electronic repository with audit trails and are inspection-ready [1–3].

Training and competency management

- Role-specific training (consent with minors, suicide risk assessment, trauma-informed interviewing, instrument administration, phlebotomy, data entry, GDPR) is mandatory before task delegation; refreshers occur at least annually or upon amendment.
- Competency is verified via observation or checklist-based assessment; retraining is triggered by monitoring findings or protocol changes [1–3].

Interfaces with external stakeholders

- REC/IRB: The PI is the primary contact; the Site Coordinator manages submission logistics; the Clinical Safety Lead co-signs safety reports as needed.
- Institutional bodies: UPKL Quality/Risk Management (serious noncompliance), Biobank oversight (specimens), IT/security (systems), and Legal/Contracts (data and material transfer agreements).
- Schools/educational authorities: The School Liaison Lead coordinates access, safeguarding briefings, and privacy protections for control participants.

Continuity planning

- Deputy roles are designated for the PI, Clinical Safety Lead, Site Coordinator, Data Manager, and Statistician to ensure uninterrupted operations during absences. Handover notes, current logs, and system access are maintained to support seamless transitions.

Conflicts of interest and independence

- All investigators complete annual conflict-of-interest declarations. The sponsor/funders have no role in design, data collection, analysis, interpretation, or publication decisions unless explicitly disclosed; academic independence and access to data are guaranteed [3].

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
2. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
3. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
4. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.

14.2 Committees: Steering, Data Monitoring

Overview and proportional oversight

Given the study's prospective, non-interventional behavioral design with usual-care management and proportionate procedural risks (questionnaires/interviews and venipuncture), no independent Data Monitoring Committee (DMC/DSMB) is constituted. In line with SPIRIT-aligned governance and GCP/CIOMS principles for minimal-risk observational research, oversight is provided through a Study Steering Group (SSG), an internal Data Quality and Safeguarding Oversight function, and routine REC/IRB reporting, with predefined triggers for ad hoc review and temporary pauses should safety, ethical, or data-integrity concerns arise [1–3].

Study Steering Group (SSG)

- Composition and independence:

- Chair: Principal Investigator.
- Voting members: Co-Investigators/Sub-Investigators (clinical, ASHRS psychometrics, qualitative, biospecimen), Clinical Safety Lead, Statistician, Data Manager, Site Coordinator, School Liaison Lead.
- Independent advisors (non-voting unless specified): an external adolescent mental health specialist and an external biostatistics/psychometrics expert with no study operational roles or financial interests.
- PPI advisor(s) attend for agenda items on burden/feasibility and dissemination; they do not access individual-level data.

- Responsibilities:

- Scientific oversight of aims, outcomes, and fidelity to approved methods.
- Review of recruitment/retention, follow-up completion, missingness, and protocol adherence.
- Appraisal of safeguarding metrics (e.g., C-SSRS-triggered actions, inpatient self-harm events), data protection issues, protocol deviations/violations, and CAPA effectiveness.
- Review of ASHRS development/validation progress, translations/adaptations, and psychometric analyses.
- Endorsement of protocol amendments and operational changes prior to REC/IRB submission; assessment of potential impacts on data comparability.
- Recommendations on pauses/resumptions of specific procedures (e.g., sensitive modules, blood draws) if warranted by safety/ethics/data integrity.
- Oversight of dissemination plans and transparency commitments.

- Meetings and materials:

- Scheduled quarterly, hybrid format; ad hoc within 10 business days upon predefined triggers (serious unanticipated problem, suspected data breach, repeated serious deviations, material safeguarding signal).
- Receives consolidated reports: enrollment/retention; data quality KPIs; safeguarding and incident summaries; deviation/CAPA trends; biospecimen quality metrics; psychometric progress; GDPR compliance updates.

- Decision-making and documentation:

- Quorum: PI plus at least 50% of voting members; independent advisors invited for all quarterly meetings.
- Decisions by simple majority; the PI has tie-breaking authority. Dissenting views are minuted.
- Minutes, decisions, and action logs (responsible person, timeline, success indicators) archived in the regulatory binder; summaries circulated to the study team within 5 business days and, when relevant, shared with institutional leadership and REC/IRB.

Internal Data Quality and Safeguarding Oversight

- Composition:

- Data Manager (lead), Statistician, Site Coordinator, Clinical Safety Lead, and a QA/Monitoring representative; PI or delegate attends monthly.

- Responsibilities:

- Continuous review of data completeness, timeliness, audit trails, and edit-check exceptions for key measures (e.g., C-SSRS, B-NSSI-AT, ISAS, ASHRS modules).
- Verification of consent/assent documentation and eligibility determinations; targeted source data checks proportionate to risk.
- Aggregation and trend analysis of inpatient self-harm/heteroaggression events, safeguarding escalations, protocol deviations/violations, and CAPA implementation.
- Oversight of biospecimen chain-of-custody discrepancies and reconciliation.
- Preparation of monthly dashboards and a quarterly integrated report to the SSG.

- Meeting cadence and triggers:

- Monthly scheduled meetings; ad hoc within 72 hours following serious safeguarding incidents, suspected privacy breaches, or material data-integrity concerns.

- Outputs and escalation:

- Written recommendations to the PI on operational adjustments, retraining, SOP refinements, or temporary holds on specific procedures.
- Immediate escalation to the PI and Clinical Safety Lead for any unanticipated problems involving risk; REC/IRB notifications prepared per reporting timelines, with SSG informed at the next meeting or

via extraordinary session when warranted.

Safety Working Huddles

- Purpose and composition:

- Short, focused reviews convened by the Clinical Safety Lead (with relevant unit clinicians, PI delegate, Site Coordinator) to examine recent risk-triggered events and near-misses and to ensure timely safeguarding actions.

- Frequency:

- Biweekly during peak enrollment or ad hoc within 48–72 hours of a serious incident.

- Scope and outputs:

- Case-agnostic aggregate review, confirmation of required clinical actions, and immediate operational fixes; brief notes feed into monthly oversight and SSG reports.

Information reviewed by oversight bodies

- Enrollment and retention by cohort; reasons for refusal/withdrawal where available.
- Visit/assessment window adherence; instrument completion rates and missing-data patterns for primary/secondary measures.
- Safeguarding indicators: frequency and context of inpatient self-harm and prevented events; C-SSRS risk stratification distributions; timeliness of risk escalations and follow-up actions.
- Deviations/violations and CAPA status; recurrence monitoring and effectiveness checks.
- Data protection/privacy incidents and remediation; access-log anomalies.
- Biospecimen metrics: collection success, processing times, storage nonconformities, and reconciliation.
- Psychometric milestones for ASHRS (item performance, reliability/validity evidence, version control).

Communication pathways and stakeholder interface

- Internal: Decisions and action items disseminated to investigators and coordinators within 5 business days; critical safety/data-protection directives communicated immediately.
- External: The PI ensures timely REC/IRB reporting of unanticipated problems/serious noncompliance and includes oversight summaries in annual progress reports. Institutional quality/risk offices receive required notifications. Schools/educational partners are informed of operational changes affecting logistics or safeguarding boundaries through the School Liaison Lead, without disclosing individual data.

Rationale for not constituting an independent DMC

Given the non-randomized, minimal-risk behavioral design with no investigational intervention and established institutional safeguarding pathways, an independent DMC is not proportionate. Oversight needs are met through the SSG, internal monitoring, and REC/IRB governance, consistent with SPIRIT-aligned proportionality and GCP/CIOMS guidance. Should risk, complexity, or external funding conditions change (e.g., addition of an interventional component), the sponsor and PI will re-evaluate the need for an independent DMC and update the governance plan accordingly [1–3].

References

1. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
3. Council for International Organizations of Medical Sciences (CIOMS). International ethical

guidelines for health-related research involving humans. Geneva: CIOMS; 2016.

14.3 Communication plan and progress reporting

Internal communication structure and tools

- Channels and platforms:

- Institutional email and calendaring for formal notices and scheduling.
- Secure video-conferencing for hybrid meetings; attendance recorded by the Site Coordinator.
- Sponsor-approved electronic data capture (EDC) and query-management functions for data issue tracking; role-based access enforced by the Data Manager.
- Controlled electronic repository for the regulatory binder, minutes, decision logs, training records, and CAPA trackers with audit trails and version control.

- Cadence and participants:

- Daily/weekly operational huddles led by the PI or delegate with the Site Coordinator and coordinators to review screening, enrollment, inpatient assessments, follow-up logistics, and near-term risks.
- Monthly data quality meetings (PI, Data Manager, Statistician, Clinical Safety Lead, Site Coordinator) to review key performance indicators (KPIs), unresolved queries, and trends.
- Quarterly Study Steering Group (SSG) meetings for integrated oversight; ad hoc sessions convened per predefined triggers.

- Communication norms:

- Agendas circulated ≥24 hours in advance; action items assigned with owners and due dates.
- Decisions documented in a decision log; changes to procedures communicated via controlled “study notice” memos linked to relevant SOPs and the protocol.

Routine progress monitoring and reporting

- Monitoring approach:

- Proportionate, risk-based oversight aligned with GCP/CIOMS and SPIRIT principles, emphasizing participant safety, data integrity, and protocol fidelity in a non-interventional design [1–3].
- KPI dashboards refreshed monthly and at quarter-end, highlighting:
  - Screening, eligibility, enrollment, and cohort balance (clinical vs control).
  - Visit adherence and instrument completion for C-SSRS, B-NSSI-AT, ISAS, ASHRS; missingness patterns; timeliness of data entry.
  - Inpatient self-harm/heteroaggression event counts, context, and safeguarding actions; C-SSRS risk distributions and escalation timeliness.
  - Protocol deviations/violations and CAPA status; recurrence monitoring.
  - Consent/assent version compliance; training currency; eCRF/audit-trail anomalies.
  - Biospecimen collection, processing times, storage reconciliation, and nonconformities.

- Report frequency, format, and content:

- Weekly operational summary (email): recruitment status, immediate scheduling risks, outstanding site needs.
- Monthly data quality report (slide deck plus annotated KPI tables): completeness and timeliness metrics, open/overdue queries, edit-check exceptions, proposed corrective actions.
- Quarterly integrated progress report to the SSG (narrative plus dashboards): aggregated conduct metrics, safety/safeguarding summaries, deviations/CAPA trends, GDPR/privacy updates, and ASHRS development/validation milestones.
- Closeout readiness checks in the final two quarters: archiving status, dataset lock plan, and publication timeline.

Stakeholder-specific reporting

- Sponsor/Institution:

- Monthly internal dashboards and quarterly narrative summaries to sponsor leadership focusing on conduct, safety indicators, compliance, and resource/risk forecasts, maintaining investigators' academic independence.

- REC/IRB:

- Annual progress report including enrollment/withdrawals, summary of adverse events/safeguarding actions, deviations/violations with CAPA, amendments, data protection incidents, and any new risk–benefit information, consistent with REC/IRB requirements and CIOMS/OHRP guidance on continuing review and unanticipated problems [2,4,5].
- Immediate or expedited submissions for unanticipated problems/serious noncompliance per timelines below.

- Funders (if applicable):

- Reports per award conditions, typically semi-annual or annual, covering milestones, recruitment, data quality, budget status, and risk register updates, with prior sponsor review for accuracy and confidentiality.

- Partner institutions/educational authorities:

- Operational notices limited to logistics and safeguarding boundaries without individual-level data; periodic aggregate summaries of participation and burden indicators when agreed and ethically approved.

Urgent and off-cycle communications

- Participant safety and safeguarding:

- 24/7 escalation pathway to the Clinical Safety Lead and PI for imminent risk or serious safeguarding concerns arising from C-SSRS or observed events; research procedures may be paused immediately to remove hazards, with subsequent documentation and notifications per policy [1,2].
- Ad hoc Safety Working Huddles within 48–72 hours to confirm clinical actions and operational fixes.

- Data protection and security:

- Suspected personal data breaches reported immediately to the Data Manager and DPO; triage and risk assessment initiated without delay. Notifications to the supervisory authority occur within 72 hours when required under GDPR; affected data subjects are informed when criteria are met [4].

- Serious deviations/violations and unanticipated problems:

- Internal notification to the PI and Site Coordinator within 24 hours of awareness; preliminary classification and containment within 48 hours.
- REC/IRB initial report for events that increase risk, compromise consent, or materially affect data integrity within 7 calendar days; follow-up information within 15 days or per REC/IRB instruction, consistent with CIOMS/OHRP guidance [2,5].

- Governance escalation:

- Ad hoc SSG convened within 10 business days for material safety, ethics, or data-integrity concerns; recommendations minuted and implemented with tracked CAPA.

Documentation, version control, and transparency

- All meetings produce approved minutes within 5 business days, including attendance, decisions, rationales, action items, and due dates; records are archived with audit trails in the regulatory repository.
- Progress reports, dashboards, and submissions are version-controlled; superseded documents are retained for traceability.

- Public transparency:

- Plain-language study updates at major milestones and a lay summary of results will be disseminated via institutional channels after database lock and primary analyses, in line with SPIRIT-aligned dissemination practices and confidentiality obligations [3,4].

- Change management:

- When amendments are approved, a structured rollout communication details the effective date, affected procedures, training requirements, and transition rules; completion of training is tracked before implementation [1–3].

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline E6(R2): Good Clinical Practice. Geneva: ICH; 2016.
2. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
4. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
5. US Office for Human Research Protections (OHRP). Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events. Rockville (MD): OHRP; 2007.

15 TRIAL REGISTRATION, PROTOCOL TRANSPARENCY, AND OPEN SCIENCE

15.1 Trial registration and protocol transparency

Registration requirement, registry selection, and timing

This is a prospective, non-interventional behavioral and psychosocial observational study conducted in Slovenia. While prospective registration is not legally mandated in the EU/Slovenia for non-interventional studies and is not required by ICMJE for purely observational designs, prospective registration is planned to strengthen transparency, deter selective outcome reporting, and align with CIOMS recommendations to publicly register human health research where feasible [1–4].

- Primary registry: ClinicalTrials.gov (Observational Study record), to be registered prospectively before enrolling the first participant.
- Secondary registry: ISRCTN (WHO ICTRP primary registry) to provide redundancy and indexing within the WHO International Clinical Trials Registry Platform (ICTRP) [2].
- If registry identifiers are not available at protocol approval, the record numbers will be added to the protocol footer and all participant-facing materials at first reprint; the protocol master file will be updated accordingly.

Public and scientific titles

- Scientific title: Prespecified in the protocol and reproduced verbatim in both registries.
- Public title: A plain-language version harmonized with the scientific title, emphasizing adolescent self-harm risk assessment and longitudinal follow-up, without disclosing sensitive or potentially stigmatizing terms beyond what is necessary for clarity and ethical transparency [1–3].

Prespecified registry data elements

Registry entries will include, at minimum, the WHO Trial Registration Data Set items and registry-specific fields, harmonized across ClinicalTrials.gov and ISRCTN [2–4]:

- Sponsor and responsible party: University Psychiatric Clinic Ljubljana (UPKL) as Sponsor; Principal Investigator as the registry Responsible Party.
- Study design: Observational, prospective cohort with a healthy comparison group; time perspective: prospective; setting: inpatient psychiatric units (UPKL) and school-based recruitment for controls.

- Enrollment target: Approximately 400 adolescents (about 200 high-risk inpatients and about 200 healthy controls), ages 13–19, all sexes.
- Conditions/key terms: Adolescent self-harm, suicidal behavior, non-suicidal self-injury (NSSI), suicide risk, psychosocial risk/protection.
- Interventions/exposures: Usual clinical care only; no experimental behavioral intervention.
- Outcomes (concise, prespecified):

- Primary: Short- and medium-term self-harm risk (ASHRS scores) and prospectively recorded self-harm incidents during hospitalization and at follow-up.
- Secondary: Suicidality (C-SSRS), NSSI characteristics (B-NSSI-AT, ISAS), psychosocial/clinical domains; exploratory genetic/epigenetic markers.

- Eligibility criteria: Age 13–19; clinical cohort hospitalized for suicide risk or NSSI; healthy controls recruited via systematic school examinations; key exclusions as per protocol.
- Locations and contacts: UPKL Centre for Mental Health (Ljubljana) and collaborating educational sites; country: Slovenia.
- Ethics: Research Ethics Committee/IRB approval details and date.
- Key dates: Anticipated start of enrollment; primary and final completion dates.
- Data monitoring/oversight: Study Steering Group and proportionate internal monitoring (no independent DMC), consistent with non-interventional design.
- Data sharing and dissemination: High-level plan referencing GDPR-compliant sharing of deidentified data or analytic code upon reasonable request and with agreements, and lay summary dissemination.

Responsibilities for registry accuracy and updates

- The Principal Investigator is the Responsible Party for registry submissions; the Site Coordinator maintains the PRS/ISRCTN records under PI oversight.
- Version control and timeliness:

- Prospective registration prior to first consent.
- Substantive changes (e.g., eligibility, outcomes, sample size, timelines, sites) will be updated promptly, and no later than 30 days after approval of a protocol amendment; administrative updates occur as needed and at least annually until study completion [1,3].
- Final status, actual enrollment, and completion dates will be posted at closeout; links to the protocol, Statistical Analysis Plan, and primary results will be added when available.

- Consistency checks: Public/scientific titles, objectives, outcomes, eligibility, and timelines in the registry will match the REC/IRB-approved protocol and any approved amendments.

Protocol, SAP, and analysis transparency

- The REC/IRB-approved protocol and dated amendments will be made publicly accessible via a stable institutional repository; the Statistical Analysis Plan and core analysis code (non-identifying) will be shared upon publication of primary results, subject to GDPR and institutional approvals [3,4].
- Any deviations from prespecified outcomes or analyses will be explicitly labeled and justified in the registry results narrative and in publications, consistent with SPIRIT-aligned reporting practices [3].

Justification if registration is not feasible

If, due to administrative constraints, dual registration cannot be completed before first enrollment, at minimum one ICTRP-recognized registry entry (ClinicalTrials.gov or ISRCTN) will be posted as soon as practicable with a clear statement of retrospective timing, and the full protocol and SAP will be time-stamped in an institutional repository to preserve transparency and interpretability of findings [1–4].

References

1. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Updated 2019.
2. World Health Organization. International Clinical Trials Registry Platform (ICTRP): WHO Trial Registration Data Set (TRDS) 2017. Geneva: WHO; 2017.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
4. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.

15.2 Protocol and analysis plan access

Scope of documents to be shared

- Documents planned for public sharing:

- REC/IRB-approved protocol (current version) and a tracked-change history of all amendments.
- Statistical Analysis Plan (SAP), including statistical codebook, shell tables/figures/listings, and version history.
- Qualitative Analysis Plan (QAP) aligned with COREQ/SRQR, including coding framework development steps and credibility checks.
- Mixed-methods integration memo (if applicable), describing convergence/triangulation procedures and priority rules.
- Instrument development documentation for ASHRS (version history, scoring guidance, validation summary); see restrictions below for item-level sharing.

- Documents that will not be openly posted:

- Third-party copyrighted questionnaires or full item content under license; citations and licensing routes will be provided.
- Operational SOPs that could compromise safeguarding or data security.
- Any document containing personal data, confidential commercial information, or security-sensitive details, consistent with GDPR and institutional policy.

Timing and version control

- Protocol:

- Initial protocol posted in the institutional repository at prospective registration.
- Approved amendments posted within 30 calendar days of REC/IRB approval, with a version chronology and concise impact notes, consistent with SPIRIT-aligned transparency [1].

- SAP:

- Time-stamped “SAP-final” posted before database lock for the primary analysis.
- Any post-lock clarifications disclosed as an addendum with rationale and date; deviations from prespecification will be labeled in publications [1,2].

- QAP and mixed-methods plan:

- QAP posted before qualitative coding commences; the mixed-methods integration memo posted before formal integration analyses, with subsequent minor refinements documented [3–5].

- Registry cross-links:

- ClinicalTrials.gov/ISRCTN records will be updated with links to the current protocol/SAP within 30 days of posting or amendment [1,2].

Location and identifiers

- Repository: University Psychiatric Clinic Ljubljana (UPKL) institutional repository with persistent identifiers (DOI/handle) and metadata aligned to FAIR principles for research objects (documents and code, not participant data) [6].

- Discoverability: Links to repository records will be included in study registry entries and publications.

Analysis code and reproducibility materials

- Statistical code:

- Clean, non-identifying analysis scripts (e.g., R/Stata/SAS) for primary and key secondary analyses will be archived alongside the SAP at first results publication, with README files, software versions, and random seed specifications to support reproducibility [1].

- Qualitative materials:

- Codebooks, coding frameworks, and exemplar de-identified excerpts (risk-assessed for re-identification) will be shared with QAP after results publication where ethically permissible under GDPR and REC/IRB approvals [3–5].

- Mixed-methods:

- Integration matrices and decision logs will be posted with the mixed-methods memo at results dissemination.

Access restrictions and safeguards

- Rationale:

- The dataset comprises special-category personal data from minors, including sensitive mental health, trauma, sexuality/gender identity, and genomic/epigenomic information; open posting of individual-level data or full transcripts is incompatible with GDPR, local ethics approvals, and CIOMS guidance on proportional risk mitigation [2,3].

- Open vs controlled access:

- Open access: Protocol, amendments, SAP, QAP, integration memo, ASHRS validation summary, and analysis code (non-identifying).

- Controlled access: De-identified, analysis-ready datasets, qualitative transcripts, and genomic/epigenomic data may be shared under a managed access model subject to:

  - REC/IRB and DPO confirmation that the proposed reuse is compatible with original consent and GDPR lawful bases [2,3].

  - Approved data access request with a scientifically sound proposal, analysis plan, and risk–benefit assessment.

  - Data Use Agreement (DUA)/Material or Data Transfer Agreement specifying purpose limitation, prohibition of re-identification, no onward sharing, secure environment, and destruction/return timelines.

  - Additional approvals for biospecimens/genetic data per biobank governance and applicable laws.

- Redactions:

- Documents will be screened and, if needed, redacted to remove direct/indirect identifiers, security-sensitive content, or proprietary material.

Intellectual property and instrument licensing

- ASHRS:

- To prevent version drift and protect psychometric integrity, finalized ASHRS items and scoring instructions will be released after validation under a non-commercial research license with citation requirements; change logs and validation summaries will be open. Translation/adaptation requests will follow a managed permission process to maintain measurement equivalence [1].

- Third-party measures:

- Licensed instruments (e.g., where applicable) will not be redistributed; users should obtain permissions from rights holders.

Request process and decision timelines

- Contact point: Study email and repository request form managed by the PI with Data Manager and DPO oversight.
- Review and response:

- Acknowledgment within 10 business days; decision within 30–60 business days depending on complexity (e.g., need for REC/IRB/DPO review or biobank approval).

- Prioritization:

- Requests aligned with public health value, adolescent mental health, and reproducibility/verification will be prioritized, subject to privacy safeguards.

Archiving and longevity

- Availability:

- Public documents (protocol, SAP, QAP, integration memo, code) will remain available for at least 10 years post-publication or per institutional policy, with format migration as needed.

- Version history:

- Repository records will maintain immutable time-stamped versions; superseded files retained with clear provenance.

Citations and transparency in reporting

- Publications and registry results will cite the repository identifiers of the protocol, SAP, and relevant analysis plans; any departures from prespecified methods will be explicitly disclosed and justified in line with SPIRIT and STROBE/COREQ/SRQR reporting standards for mixed-methods behavioral research [1,3–5].

References

1. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
2. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
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4. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–57.
5. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for Reporting Qualitative Research: a synthesis of recommendations. Acad Med. 2014;89(9):1245–51.
6. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018.

15.3 Open science, reproducibility, and materials availability

Principles and standards

The study adopts open science practices to maximize transparency and reproducibility while protecting participants' privacy and respecting instrument licensing. Materials and code will be shared under FAIR principles with clear provenance, persistent identifiers, and version control, and reporting will align with SPIRIT guidance applied proportionately to this observational behavioral design, TIDieR (for procedural fidelity), STROBE (for observational reporting), and COREQ/SRQR (for qualitative components) [1–6]. Data sharing will comply with GDPR and CIOMS guidance for special-category data from minors, using a managed access model for individual-level data and sensitive documents [7,8].

Materials to be shared, access levels, and timing

- Participant-facing materials (open access; at prospective registration and upon amendment):
  - Plain-language information sheets and consent/assent forms for adolescents and parents/guardians (contact details redacted).
  - Recruitment scripts and outreach leaflets for inpatient and school settings.
  - Follow-up reminder scripts and communication templates.
- Case report forms and eCRF specifications (open access; at first data capture release):
  - Instrument-by-instrument CRFs, including administration rules, skip logic, and windowing notes for baseline, inpatient monitoring, 6- and 18-month follow-ups.
  - Event logging forms for self-harm and heteroaggressive incidents captured during hospitalization.
- Data dictionary and codebooks (open access for metadata; controlled for fully annotated versions with derived variables; at analysis lock):
  - Variable-level dictionary with labels, response options, scoring ranges, timing, and missingness codes.
  - Derivation specifications for composite scores and time-to-event endpoints.
  - Harmonization map between clinical and control cohorts for shared variables.
- Questionnaires and instruments (mixed access; at instrument-specific milestones):
  - ASHRS: final item set, scoring guide, and user manual released after validation under a non-commercial research license; version history and validation summary openly posted; translation/adaptation via managed permissions to protect measurement equivalence and prevent version drift [1].
  - Third-party measures (e.g., C-SSRS, B-NSSI-AT, ISAS, DASA-YV): not redistributed; citations, licensing routes, and administration details provided. Site-specific administration checklists and scoring quality-assurance notes will be shared openly where they do not reproduce proprietary content.
- Qualitative materials (open for guides and frameworks; controlled for data excerpts; at qualitative analysis start/close):
  - Semi-structured interview/focus group guides and prompts; reflexivity statement template; credibility/trustworthiness checklist aligned with COREQ/SRQR [4,5].
  - Codebooks and theme development memos (open); exemplar de-identified excerpts (controlled) following re-identification risk assessment and REC/IRB approvals [5,8].
- Procedural fidelity and training materials (open summaries; controlled detailed SOPs; posted with protocol/SAP and updates):
  - TIDieR-aligned procedural descriptions for assessments: provider qualifications, training dose, mode (in-person), schedule (baseline; inpatient event monitoring; 6 and 18 months), tailoring rules (e.g., language/cultural adaptations), permissible modifications, and adherence checks [2].
  - Administration checklists and competency sign-off forms for C-SSRS, ASHRS, and event logging (open).
  - Risk-escalation workflow diagrams and decision trees (redacted/open summary); full safeguarding SOPs and security-sensitive documents under controlled access due to safety/privacy considerations [7,8].
- Biospecimen and laboratory documentation (open summaries; controlled SOPs; at biospecimen first release):
  - High-level collection, processing timelines, storage conditions, and QC metrics (open).
  - Detailed SOPs, chain-of-custody templates, and QC worksheets (controlled) to avoid security risks and facility disclosures.
- Pilot/feasibility and cognitive testing reports (open; upon completion):
  - ASHRS cognitive interviewing summary, item performance summaries, and change logs.
- Deviations and CAPA templates (open; upon first posting):
  - Blank deviation log, CAPA template, and monitoring checklists.

Reproducible analysis assets

- Statistical analysis plan and code (open; SAP posted before lock; code at first results publication):
  - Clean, non-identifying scripts for primary and key secondary analyses with software versions, random seeds, and session info; modular functions for score derivation; mock TFL shells; and end-to-end README to recreate figures/tables [1].

- Sensitivity/supplementary analysis scripts and simulation notebooks (open) where they do not embed protected data.

- Qualitative analysis assets (open/controlled; at qualitative publication):

- Analytic memos, codebooks, intercoder procedures, and credibility checks (open); de-identified excerpts and audit trail elements (controlled) [4,5,8].

- Mixed-methods integration (open; at integrative results):

- Integration matrices, convergence/discordance logs, and decision rules.

Data and transcript sharing, de-identification, and access controls

- Open access: Metadata (protocol, SAP, QAP), code, CRFs, data dictionary, and non-identifying reproducibility materials as above.
- Managed access (application + DUA/MTA; REC/IRB/DPO compatibility review):

- De-identified, analysis-ready quantitative datasets; de-identified qualitative transcripts/excerpts; and linked genomic/epigenomic datasets. Releases will apply proportionate risk controls (e.g., removal/generalization of rare attributes, date shifting, suppression of small cells, separation of keys, and secure enclaves for higher-risk data) consistent with GDPR and CIOMS [7,8].

- Not shared:

- Any direct identifiers or linkage keys; full audio files; raw genomic data without additional approvals; and documents with security-sensitive operational details.

Replicability of behavioral assessment procedures (TIDieR-aligned summary)

- What and why:

- Behavioral assessment battery targeting self-harm risk and correlates, including ASHRS, C-SSRS, B-NSSI-AT, ISAS, psychosocial scales, and prospective inpatient event logging to refine risk stratification [2].

- Who provides:

- Trained clinicians/psychologists and research staff with documented competency; periodic refreshers and calibration sessions.

- Modes and where:

- In-person assessments in inpatient units (clinical cohort) and educational settings (controls); follow-ups at the clinic or designated locations with privacy safeguards.

- When and how much:

- Baseline within hospitalization intake window; continuous inpatient incident monitoring; follow-ups at 6 and 18 months for the clinical cohort; single baseline for controls.

- Tailoring and modifications:

- Language and cultural adjustments per adaptation plan; accommodations for participant burden/safety (e.g., pausing or rescheduling sensitive modules) documented in fidelity logs.

- Adherence and fidelity:

- Administration checklists, time-stamping, missed-item tracking, and periodic inter-rater checks for risk-rating instruments; predefined triggers for remedial training. Fidelity summaries will be publicly posted in aggregate.

Versioning, identifiers, and discoverability

- All public materials will be deposited in the institutional repository with persistent identifiers, version histories, and metadata to enable discovery and citation, following FAIR recommendations [3].
- Registry entries will cross-link to current protocol and reproducibility objects; publications will cite repository identifiers for the protocol, SAP, analysis code, and key materials [1,6].

Restrictions, ethics, and licensing

- Privacy, safety, and consent limits:

- Given minors' special-category data, open posting of individual-level data and full transcripts is precluded; reuse requires purpose limitation, no re-identification, and secure environments, per GDPR and CIOMS [7,8].

- Intellectual property:

- ASHRS final content and scoring guidance will be released under a non-commercial research license with citation requirements and controlled translation workflow to protect psychometric integrity; third-party instruments will not be redistributed.

Request process and timelines

- Requests are submitted via the study contact/repository form. Acknowledgment within 10 business days; decision within 30–60 business days depending on need for REC/IRB/DPO or biobank approvals. Prioritization will favor proposals with strong public health value and reproducibility aims, subject to privacy safeguards.

References

1. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
2. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
3. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016;3:160018.
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6. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4(10):e296.
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8. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
9. Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, et al. Promoting an open research culture. Science. 2015;348(6242):1422–5.

16 DATA SHARING, DISSEMINATION, AND PARTICIPANT COMMUNICATION

16.1 Data access, sharing, and reuse plan

Overview and guiding principles

This plan specifies what will be shared, when, how access will be governed, and under which legal/ethical conditions, applying FAIR principles to maximize transparency and reuse while protecting minors' special-category data and genomic information in accordance with GDPR and CIOMS guidance [1,2,3]. Because the dataset contains highly sensitive mental health, trauma, sexuality/gender identity, and genetic/epigenetic data from adolescents, individual-level data will not be openly posted; controlled access will be used to support responsible reuse [1,2].

Data types, scope, and levels of access

- Quantitative datasets: de-identified, analysis-ready files including demographic, clinical, psychosocial scales (e.g., C-SSRS, B-NSSI-AT, ISAS), ASHRS scores, inpatient incident logs, and follow-up outcomes.
- Qualitative data: de-identified transcripts/excerpts and coding outputs, where consent and re-identification risk assessment permit.
- Genomic/epigenomic data: de-identified variant-level and methylation data, plus high-level laboratory QC metadata; raw genomic files and biospecimens are subject to additional governance.
- Metadata and documentation: data dictionary (variable-level metadata), derivation specifications, codebooks, and harmonization maps; shared openly where they do not embed protected content.
- Analysis assets: clean, non-identifying statistical code and analysis notebooks for primary and key secondary outcomes.

Open access will be limited to non-identifying materials (protocols, analysis plans, code, high-level metadata). Individual-level data and qualitative materials will be available only via managed access.

Timing of data availability and embargo

- Primary quantitative dataset: within 12 months of publication of primary results or 24 months after primary completion (whichever is earlier), subject to approvals below.
- Qualitative materials: after main qualitative results are published and once re-identification risk review and consent compatibility are confirmed.
- Genomic/epigenomic datasets: after relevant primary analyses are published and upon approval by the biobank/genomics governance committee.

Interim sharing for reproducibility checks of accepted manuscripts may be prioritized under expedited review where privacy risk is low and approvals are in place.

De-identification/anonymisation and risk controls

Given the realistic risk of re-identification in small subgroups and with genomic data, all releases will apply proportionate safeguards consistent with GDPR and recognized anonymisation guidance [1,4,5]:

- Removal of direct identifiers; separation and secure storage of linkage keys.
- Generalization or suppression of rare attributes; aggregation of small cells.
- Date shifting and/or use of age bands; locale masking where necessary.
- Differential handling of free text; redaction of indirect identifiers.
- For qualitative data, redaction/pseudonymisation of names, places, services, and other unique narratives; exclusion of excerpts where risk remains non-trivial.
- For genomic/epigenomic data, controlled-access release only; no open posting due to enduring identifiability.

All datasets will undergo a documented disclosure risk assessment before release; residual risk and applicable controls will be stated in the Data Use Agreement (DUA).

Access routes, platforms, and security

- Open repository: institutional repository records for protocols, analysis plans, code, and high-level metadata with persistent identifiers and versioning to support FAIR discovery [3].
- Controlled-access delivery:

- Standard route: secure data enclave hosted in Slovenia with role-based access, multi-factor authentication, restricted export, and audit logging. Where an enclave is not feasible for the requester, encrypted transfer of project-specific data extracts may be permitted under enhanced contractual and technical controls.
- Genomic/epigenomic data: access via biobank-governed controlled systems; cross-linkage with

phenotypes only within the secure environment.

Cross-border data transfers outside the EU/EEA will proceed only where GDPR adequacy or appropriate safeguards (e.g., Standard Contractual Clauses) are in place and approved by the institutional Data Protection Officer (DPO) [1].

Eligibility, conditions, and approvals for access

Access may be granted for scientifically sound, ethically compatible proposals that:

- Align with the original consent and purpose limitation (adolescent self-harm, mental health, and related psychosocial or methodological questions); proposals outside scope require additional REC/IRB review and, where necessary, re-consent or waiver [2].
- Demonstrate a clear analysis plan, feasibility, and expertise to handle sensitive data responsibly.
- Commit to privacy-preserving practices and publication of results with appropriate acknowledgments.

Required approvals and agreements:

- Scientific and ethical compatibility check by the Study Data Access Committee (DAC) and confirmation by the DPO of GDPR compliance and transfer mechanisms.
- REC/IRB compatibility confirmation; additional biobank/genomics committee approval for genetic/epigenetic data.
- Executed DUA (and, where relevant, Material Transfer Agreement) specifying:

- Purpose limitation and prohibition of re-identification or linkage with external identifiers.
- No onward sharing; sub-processor controls for cloud/IT services.
- Security controls, incident reporting, and audit rights.
- Publication, acknowledgment, and citation requirements.
- Data destruction or certified return at project end or on request.

Request procedure and timelines

- Submission: applicants provide a data request form, scientific proposal and analysis plan, team CVs, institutional approvals (as applicable), and a list of requested datasets/variables.
- Triage and review: acknowledgment within 10 business days; DAC decision within 30–60 business days depending on complexity and whether REC/IRB/DPO or biobank approvals are needed.
- Appeals: applicants may submit a reasoned appeal for reconsideration to the Sponsor within 30 days of decision; a senior review panel independent of the study team will issue a final determination.

Priority will be given to proposals with high public health value, replication/verification aims, and method development that improves adolescent risk assessment, subject to privacy constraints.

Duration of availability and versioning

- Controlled-access data will be available for at least 10 years after primary results publication or per institutional retention policy, with format migration and checksum monitoring to maintain usability and integrity.
- Versioned releases will be labeled with a semantic version number, change log, and date; superseded versions will be preserved for auditability with clear provenance.

Restrictions and non-shareable elements

- Not shared: direct identifiers or linkage keys; full audio files; highly sensitive free text that cannot be adequately de-identified; raw genomic files without explicit biobank approval; security-sensitive SOPs.
- Third-party copyrighted instruments (e.g., full item content for licensed scales) will not be redistributed; citations and licensing routes will be provided.
- Any sharing inconsistent with participant consent, REC/IRB stipulations, or GDPR will be declined.

Reuse expectations, citation, and reporting

- Users must cite the dataset and documentation identifiers, acknowledge the Sponsor and funders, and register secondary analyses where applicable to enhance transparency.
- Derived datasets and code produced under the DUA should be returned for archiving in the controlled repository where feasible, enabling iterative improvement of the research resource.
- Material changes to prespecified analyses should be disclosed in publications, adhering to STROBE/COREQ/SRQR as appropriate for study design and to good practice for secondary data analyses [2,3].

Licensing

- Open materials (protocols, analysis plans, non-identifying code, and metadata) will be released under a permissive license (e.g., CC BY 4.0 for documents; MIT or equivalent for code) unless funder or institutional policy requires otherwise.
- De-identified datasets will be licensed via DUA terms tailored to the approved purpose; no commercial use or re-identification is permitted without explicit, prior approval and updated ethical review.

Participant and public communication

A lay summary of the data-sharing approach, including privacy protections, will be made available to participants and on the institutional website. Any substantial changes to this plan that affect participants' interests will be submitted for REC/IRB review and communicated transparently.

References

1. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
2. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
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4. European Data Protection Board. Guidelines 05/2020 on consent under Regulation 2016/679 (replacing WP29 259). Brussels: EDPB; 2020.
5. Article 29 Data Protection Working Party. Opinion 05/2014 on Anonymisation Techniques (WP216). Brussels: European Commission; 2014.

16.2 Publication and authorship policy

Dissemination plan

Study findings will be disseminated through peer-reviewed publications, conference presentations, and stakeholder-facing products, prioritizing scientific rigor, participant privacy, and non-stigmatizing language. Primary manuscripts will cover: (a) cohort design and baseline characteristics; (b) primary

and secondary outcomes on self-harm risk trajectories; (c) ASHRS development, validation, and scoring; and (d) exploratory genomic/epigenomic correlates, each with non-overlapping aims and cross-referencing to prevent redundant publication. Target journals include adolescent psychiatry, suicidology, clinical psychology, public health, and psychometrics outlets. Abstracts, posters, and oral presentations will be submitted to relevant national and international meetings in child and adolescent mental health, suicidology, and behavioral science.

To enhance translation, brief practitioner summaries and infographics will be prepared in Slovene and English for clinicians, school health professionals, and social care providers. Policy briefs will be offered to relevant ministries and professional bodies when findings have clear practice or system implications. Media communication will be coordinated through institutional communications, using aggregate results and avoiding identifiable subgroup descriptions.

Preprints may be posted to reputable servers prior to journal submission to accelerate access while clearly indicating non–peer-reviewed status and subsequent versioning, consistent with ICMJE guidance and journal policies [1].

Authorship criteria, roles, and order

Authorship will follow ICMJE Recommendations: authors must meet all four criteria—substantial contributions to conception/design or data acquisition/analysis/interpretation; drafting or critical revision; final approval; and accountability for all aspects of the work [1]. Role attribution in publications will use the CRediT taxonomy (e.g., conceptualization, methodology, investigation, data curation, formal analysis, supervision, project administration, writing—original draft, writing—review and editing) to increase transparency [2].

Authorship order will reflect the magnitude and nature of contributions as agreed prospectively in a living authorship plan approved by the Steering Group, with updates documented at key milestones (end of data collection, analysis lock, manuscript drafting). Students and early-career researchers who lead prespecified analyses and manuscript drafting will be considered for first authorship, consistent with ICMJE criteria. Group authorship may be used where collective contributions predominate; named contributors and their roles will be listed.

Each manuscript will designate a guarantor (typically the PI or senior author) who accepts overall responsibility for the integrity of the work from inception to publication [1]. All authors will disclose conflicts of interest and funding, and affirm data access and responsibility statements as required by target journals [1].

Acknowledgment of non-author contributions

Individuals who contribute to the study but do not meet authorship criteria will be acknowledged with permission, including but not limited to: participant advisory contributors; recruitment and data collection staff; data managers; translators/adaptors; administrative personnel; and members of oversight bodies (e.g., Steering Group, Data Access Committee). Institutional partners (e.g., participating schools and clinical units) and funders will be acknowledged according to their policies. Medical writing or editorial assistance (if used) will be disclosed with source of funding and degree of involvement, per good publication practice and ICMJE recommendations [1].

Reporting standards and transparency

Manuscripts will adhere to EQUATOR-aligned reporting guidelines appropriate to design and methods: STROBE for observational quantitative analyses, COREQ or SRQR for qualitative components, and instrument-development/validation reporting guidance for psychometric work (including comprehensive description of measurement properties, scoring, and validation samples) [3–5]. Protocol and statistical/qualitative analysis plans, and non-identifying analysis code will be cited with persistent identifiers, and deviations from prespecified analyses will be transparently labeled and justified. Where applicable, registry entries will be updated to link primary results and protocols.

Participant, community, and stakeholder communication

Participants and stakeholders will receive aggregate, plain-language summaries in Slovene (and English on request) after primary results are published. Summaries will include accessible infographics, key implications for clinical care and school-based support, and information on where to find full reports. Delivery channels may include secure email/SMS links (for those who consented to recontact), clinic noticeboards, institutional websites, and partner schools, ensuring no disclosure of individual participation. No individual clinical or genomic/epigenomic results will be returned through publications; any clinically actionable findings identified in routine care will continue to be managed within standard clinical pathways, not via research outputs. Community and practitioner briefings will be scheduled to coincide with major publications, aligning with ethical guidance to share findings with participants and communities in culturally and linguistically appropriate formats while protecting confidentiality [6,7].

Publication governance, timelines, and dispute resolution

- Manuscript proposals: Investigators will submit a short concept (rationale, research questions, dataset, methods, author list/roles) to the Steering Group. Concepts are logged to prevent topic overlap and to ensure timely progression.
- Timelines: Drafting of the primary outcome and ASHRS validation manuscripts will commence within 3 months of database lock for the respective analyses. Secondary and exploratory manuscripts will follow a staged plan.
- Data citation and reuse: Publications arising from secondary analyses under data-use agreements must cite the dataset and protocol identifiers and acknowledge the Sponsor and funders; results should adhere to approved purposes and privacy constraints.
- Disputes: Authorship or contribution disputes will be addressed initially within the study team; unresolved issues will follow COPE guidance and institutional research integrity procedures, with an impartial adjudication panel if needed [8].

Ethical, legal, and language considerations

All dissemination will avoid stigmatizing language and will use people-first, recovery-oriented terms appropriate to adolescent mental health. Reporting will use aggregate data with cell-size suppression for small subgroups to mitigate re-identification risks, consistent with GDPR principles and journal privacy expectations [7,9]. Third-party instruments under license will not be reproduced beyond fair-use excerpts; permissions and attributions will be observed.

Public involvement and recognition

Public and patient involvement (PPI) contributors who informed study priorities, materials, or interpretation will be offered co-authorship when they meet ICMJE criteria; otherwise, they will be acknowledged by name or group (with permission) and their roles described, and PPI reporting will follow GRIPP2 short-form items in relevant manuscripts [10].

References

1. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Updated 2019.
2. Brand A, Allen L, Altman M, Hlava M, Scott J. Beyond authorship: Attribution, contribution, collaboration, and credit. Learn Publ. 2015;28(2):151–5.
3. EQUATOR Network. Enhancing the QUAlity and Transparency Of health Research: Reporting guidelines. BMJ. 2008;337:a2973.
4. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4(10):e296.
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6. Council for International Organizations of Medical Sciences (CIOMS). International ethical

guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
7. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
8. Committee on Publication Ethics (COPE). How to handle authorship disputes: a guide for new researchers. Version 1. 2014.
9. Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG. Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers. BMJ. 2010;340:c181.
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16.3 Participant and community communication of results

Objectives and principles

This plan specifies how aggregate study findings will be communicated in accessible formats to participants, caregivers, public/patient partners, communities, and participating sites, while protecting confidentiality and minimizing risk of harm. Communications will prioritize clarity, cultural and linguistic appropriateness, non-stigmatizing language, and proportionality to the sensitivity of adolescent self-harm data, consistent with CIOMS ethical guidance, SPIRIT-aligned transparency, and GDPR [1–3].

Audiences and eligibility for recontact

- Primary audiences: adolescent participants and, where appropriate, their parents/guardians; patient/public partners; participating clinical units; partner schools; and community stakeholders (e.g., youth mental health services and professional bodies).
- Recontact basis: only individuals who consented to receive updates will be contacted directly; contact preferences (email/SMS/post) collected at consent can be changed or revoked at any time without affecting care or participation [2,3].
- Privacy: direct communications will not disclose participation status in public channels or to third parties; identifiers are not included in any public-facing materials [2].

Timing and sequencing

- Interim updates: brief annual study progress notes (aggregate recruitment and high-level milestones) to opted-in participants and sites.
- Primary results: lay summaries released within 12 weeks of first primary manuscript publication and after REC/IRB confirmation that content is consistent with consent and approvals.
- Secondary results: shorter summaries bundled semiannually to avoid message fatigue, or aligned to major publications if they have clear practice relevance.
- End-of-study wrap-up: comprehensive lay report within 6 months of the final major publication, including links to open materials and how to request controlled-access data/code.

Formats and channels

- Participant lay summary (2–4 pages): plain-language overview, key findings, what the results mean for adolescent well-being, and where to find help; infographic highlights; FAQs; pointers to full reports. Delivered via:

  - Secure link sent by email/SMS to consented contacts.
  - Printed copies available at UPKL clinics and partner schools (without imagery that could be triggering).
  - Institutional website page with downloadable PDFs; no tracking of individual access.

- Micro-summaries: one-page infographic and a 60–90 second animated explainer for adolescents.
- Practitioner brief: 2-page practice note for clinicians and school health staff focusing on implications and cautions.
- Community briefings: scheduled webinars or in-person sessions with Q&A for participating wards and schools; recordings posted on the institutional website after review.
- Media statements: coordinated through institutional communications; aggregate data only; no small-cell reporting that could enable re-identification [2].

Language, accessibility, and inclusivity

- Language: Slovene as default; English versions on request. Additional translations may be prepared if substantial non–Slovene-speaking subgroups are engaged.
- Readability: adolescent-appropriate (target CEFR B1–B2); glossary for clinical terms.
- Accessibility: screen-reader–compatible PDFs, high-contrast design, dyslexia-friendly fonts, large-print versions, and alt text for graphics.
- Safety-by-design: content warnings for sensitive topics; neutral, non-graphic wording; inclusion of crisis resources (national helplines and UPKL contact pathways) on the first page of participant-facing materials.
- Stigma reduction: people-first, recovery-oriented language; explicit statements that self-harm risk is multifactorial and that help is available.

Content boundaries and confidentiality safeguards

- Aggregate only: no individual results (clinical, psychosocial, genetic/epigenetic) will be returned via research communications. Any clinically actionable findings identified in routine care will continue to be managed through standard clinical pathways, not via research outputs [1,2].
- Small-cell suppression: subgroup data will be aggregated to avoid identifiability; minimum cell-size rules applied across all public materials [2].
- Genomic/epigenomic caution: community materials will avoid overstating genetic determinism and will present such findings, if any, cautiously with clear uncertainty statements.

Roles, responsibilities, and review

- Lead: Principal Investigator (PI) oversees content accuracy and alignment with approvals.
- Preparation: Communications Officer drafts materials with input from the Youth and Caregiver Advisory Panel and clinical leads to ensure appropriateness for adolescents and caregivers.
- Scientific review: Steering Group validates fidelity to published findings and guards against overinterpretation.
- Ethics and privacy check: REC/IRB and Data Protection Officer (DPO) review participant-facing summaries for compatibility with consent, GDPR, and safeguarding requirements prior to release [2,3].
- Distribution: Site Coordinators manage clinic- and school-based dissemination; the Data Manager maintains the contact list and opt-in/opt-out records.

Site and community engagement

- Participating wards and schools will receive site-tailored packets (posters, one-page summaries, slide decks) for internal briefings that avoid any participant-identifying details.

- Stakeholder roundtables with clinicians, educators, and youth services will be convened at the time of major publications to discuss implications and feasible practice changes.
- Policy-facing briefs may be shared with relevant ministries and professional societies when findings have system-level relevance, ensuring non-identifiable, aggregate presentation.

Feedback and two-way communication

- Feedback channels: a dedicated study email and optional anonymous webform for questions or concerns about summaries.
- Responsiveness: acknowledgment within 10 business days and substantive responses within 30 business days; clinically urgent queries redirected to care pathways rather than addressed via research communications.
- Evaluation: brief, optional surveys embedded in digital summaries to gauge clarity, usefulness, and perceived sensitivity; findings inform iterative improvement.

Record-keeping and version control

- Each lay output will carry a version number, date, and a link to the corresponding peer-reviewed publication and repository record.
- Superseded summaries will be archived on the institutional website with clear labeling to preserve transparency.

Contingencies and updates

- Material changes to communication plans that affect participants' interests (e.g., new safety information) will be submitted for REC/IRB review and communicated promptly using the same channels, in line with ethical guidance on ongoing transparency to participants and communities [1–3].

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council (General Data Protection Regulation). Official Journal of the European Union. 2016;L119:1–88.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.

17 FINANCE AND RESOURCES

17.1 Funding source(s) and budgeting

Funding sources and role of funders

The study is supported by intramural resources from the University Psychiatric Clinic Ljubljana (UPKL; personnel time, clinical space, and core IT support). Applications to national competitive schemes (e.g., Slovenian public research and health innovation calls) and philanthropic sources are in progress to underwrite genotyping/epigenetic assays, extended data management, and open-access dissemination. Any additional award secured before or during the study will be disclosed in the trial registry and publications, with formal documentation of the funder's role.

Funders have no authority over the study design, conduct, data collection, data management, analysis, interpretation, writing, or the decision to submit results for publication. The Principal Investigator (PI) and Steering Group retain full academic independence, consistent with SPIRIT recommendations and good publication practice on transparency of funding and roles [1,2]. Any conditions attached to new funding will be reviewed to ensure they do not compromise scientific independence or participant protections; if necessary, protocol amendments will be submitted for REC/IRB approval prior to implementation.

Budget summary and major cost categories

The budget is structured to align with the longitudinal, multi-method observational design, inpatient recruitment, development/validation of the Adolescent Self-Harm Risk Scale (ASHRS), and genomic/epigenomic components. Estimated costs are organized as follows (amounts to be finalized upon award):

Category	Scope (examples)
Personnel	Research assistants (screening, consent, assessments), data manager, biostatistician/psychometrician, qualitative analyst, laboratory technician/phlebotomy support, part-time PI/co-investigator effort, PPI coordination
Participant-related costs	Travel reimbursement for 6- and 18-month follow-ups, small tokens of appreciation where permitted, translation/reading aids for accessibility, crisis resource materials
Data collection and measures	Printing/e-consent and CRFs, tablets for secure ePRO capture, training and fidelity monitoring for standardized instruments (e.g., C-SSRS), licensing/permissions if required for third-party tools, secure REDCap/server maintenance
Clinical and inpatient monitoring	Time for ward-based event logging and DASA-YV monitoring, integration with hospital incident systems, secure storage of source documents
Biological sampling and analyses	Consumables for venipuncture and DNA extraction, genotyping/targeted sequencing, DNA methylation arrays, QC and bioinformatics pipelines, biobanking storage fees
Data management and security	De-identification workflows, controlled-access enclave or equivalent secure environment, backup and disaster recovery, audit logging, software licenses for analytics
Analysis	Statistical/psychometric software (e.g., R/RStudio server, Mplus or equivalent), qualitative analysis tools, HPC/cloud time where required
Governance and compliance	REC/IRB fees (if applicable), Data Protection Officer review, insurance/indemnity (if not covered centrally), committee meetings (Steering, DAC)
Training and PPI	Staff training in suicide risk assessment, safeguarding, and GDPR; PPI honoraria and meeting costs, youth-appropriate co-design workshops
Dissemination	Open-access publication fees where required by policy, conference registration and presentation materials, policy/practice briefs, bilingual lay summaries and microsummaries
Contingency (5–10%)	Unforeseen costs (e.g., additional follow-up contacts, inflationary increases, replacement equipment)

Participant payments will be modest, proportionate, and approved by the REC/IRB to avoid undue influence. Third-party instrument licensing will be budgeted only where legally required; freely available instruments will be used with appropriate permissions and training.

Financial management, oversight, and reporting

- Sponsorship and budget holding: UPKL acts as Sponsor and budget holder. The PI is accountable for scientific deliverables and day-to-day budget execution; the institutional Finance Office provides financial administration, payroll, and procurement support.

- Approvals and procurement: Expenditures follow UPKL policies and applicable Slovenian/EU public procurement rules. Competitive quotes will be obtained for laboratory and IT services above institutional thresholds, with conflict-of-interest checks documented.
- Monitoring and variance control: A grant-specific cost center will be used. The PI and Project Administrator review burn rates monthly against the work plan; variances greater than 10% at category level trigger a corrective action plan and, where needed, re-budgeting with funder notification.
- Audits and records: Source financial records (invoices, payroll certifications, effort reports, contracts) are retained per institutional and funder retention schedules and made available for internal audit, external audit, or inspection. Any audit findings will be addressed with time-bound corrective actions.
- Role of governance bodies: The Steering Group reviews budget status quarterly to ensure resources align with milestones and risk controls. The Data Access Committee's operations are budgeted and reported separately to preserve independence.
- Financial reporting: Narrative and financial reports will be submitted to funders per award terms, including statement of expenditures by category, justification of variances, and forecast to completion. Publications will disclose funding and the funders' role in accordance with SPIRIT and ICMJE guidance [1,2].
- Compliance and integrity: Financial management adheres to the ALLEA European Code of Conduct for Research Integrity, emphasizing accountability, transparency, and appropriate recognition of contributions [3], and to ethical sponsor responsibilities for ensuring adequate resources and independence of research teams [4].

Any material change to funding, budget allocations, or sponsor role will be documented through protocol amendments as appropriate and communicated to the REC/IRB and trial registry to maintain transparency.

References

1. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200–7.
2. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Updated 2019.
3. ALLEA. The European Code of Conduct for Research Integrity. Revised Edition. Berlin: ALLEA; 2017.
4. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.

17.2 Participant reimbursements/compensation

Principles and safeguards

Participant payments in this study are designed to reimburse out-of-pocket expenses and provide modest recognition of time and effort without creating undue influence, coercion, or inequity, consistent with CIOMS, the Declaration of Helsinki, EU/UK guidance for research with minors, and SPIRIT recommendations on transparent reporting of participant compensation [1–5]. For adolescents, special care is taken to avoid incentives that could sway participation decisions; reimbursement and compensation are proportionate to burden, not contingent on specific responses, biospecimen provision, or completion of all activities, and are approved by the REC/IRB before implementation [1,2,4,6].

What will be provided

- Reimbursement of expenses:

- High-risk inpatients: generally no travel costs for baseline/inpatient activities; travel reimbursement applies for 6- and 18-month follow-up visits (public transport fares or mileage at institutional rates) and necessary caregiver travel where applicable.

- Healthy controls: reimbursement for travel to the assessment site if incurred.
- Other direct costs (e.g., parking, documented communication costs for scheduling) may be reimbursed when reasonable and pre-approved.

- Modest compensation for time and inconvenience:

- A small, REC/IRB-approved token of appreciation per completed assessment contact to recognize time and burden (e.g., low-value voucher). Inpatient clinical care receives no payment; tokens relate only to research assessments.
- Compensation is prorated: participants receive the token for each attended research contact (baseline/enrolment; follow-ups at 6 and 18 months for the inpatient cohort; single assessment for healthy controls), regardless of whether all instruments are fully completed, to reduce pressure to continue [1,4].

- No performance or outcome-based payments:

- No differential payments by answers, clinical status, or self-harm events; no bonuses for biospecimen provision; no lotteries or high-value incentives [1,2,6].

Determination of amounts

- Amounts are set using a burden-based rubric considering estimated contact duration, cognitive/emotional effort, sensitivity of topics, travel time, and local norms, benchmarked against minimal hourly rates for youth-friendly activities and typical transport costs, and aligned with institutional policies [1,3].
- Final figures, caps (per visit and per participant), and eligible expense categories will be specified in the REC/IRB application and participant information sheets; any changes will require prior REC/IRB approval and communication to participants.
- For minors, compensation levels are intentionally low to minimize inducement; reimbursement covers actual, reasonable costs, with receipts where feasible [1,3,6].

Methods and timing of payment

- Reimbursements:

- Preferably paid to the parent/guardian (for participants under the age threshold set by REC/IRB) via electronic bank transfer upon submission of receipts or mileage forms; cash handling by clinical staff is avoided.
- Where electronic transfer is impractical, reimbursement may be provided via prepaid voucher or institutional mechanism consistent with accounting controls.

- Tokens of appreciation:

- Provided as low-value retail or multi-store vouchers or equivalent electronic codes immediately after each research contact, or via electronic transfer where appropriate and permitted.

- Processing timelines and documentation:

- Standard processing target is within 30 calendar days of receipt of complete documentation for reimbursements; same-day provision for vouchers at visits where feasible.
- Study staff record the nature, amount, date, and justification for each payment in a secure log separate from research data, with no linkage to responses, to preserve confidentiality and comply with audit requirements [5].

Limits, conditions, and eligibility

- Participation status:

- Payments are available only to enrolled participants (and, where applicable, their caregiver for travel costs) who attend the research contact; withdrawal at any time does not forfeit amounts already earned for prior contacts [1,4].

- Caps and exclusions:

- Per-visit and total study caps are defined to prevent disproportionate sums; luxury or non-essential expenses are not reimbursed. Food/drink are not routinely covered unless required for reasonable accommodation.

- Conflict and role separation:
  - Clinical care teams do not condition care on participation or handle payments, maintaining separation between treatment and research to reduce perceived pressure [2,4].
- Legal and tax compliance:
  - All payments follow institutional accounting policies and applicable Slovenian/EU financial and tax regulations. If required by law, aggregate annual reporting of payments will be performed by the institution, not by participants.

Fairness, consistency, and transparency

- Standardization:
  - A site-wide payment schedule specifies the same reimbursement rules and token values for all participants within a cohort and visit type to ensure equity across sexes, ages, diagnoses, and recruitment sources.
- Communication:
  - The payment schedule, eligible expenses, documentation requirements, and processing timelines are described in the consent/assent and caregiver information materials in clear, age-appropriate language; participants may ask questions at any time without affecting participation.
- Monitoring:
  - The Steering Group periodically reviews payment logs for consistency and unintended patterns; any concerns about undue influence prompt protocol review and, if needed, REC/IRB consultation and amendment [1,5].

Special considerations for a vulnerable population

- Sensitivity and burden:
  - Given the high-risk adolescent psychiatric context and sensitive topics (self-harm, trauma), tokens are intentionally modest; staff remind participants that declining any question will not affect payments or care, mitigating pressure during distressing content [1,2,4].
- Caregiver involvement:
  - For participants under the REC/IRB-defined age for direct receipt of funds, reimbursements flow to caregivers; adolescents may receive the modest token (e.g., voucher) directly when appropriate and permitted by REC/IRB, with caregiver awareness [3,6].
- Contingencies:
  - Remote follow-ups (if approved) maintain the same reimbursement/compensation structure, with electronic voucher delivery and reimbursement for reasonable communication or data costs where applicable and pre-agreed.

References

1. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for health-related research involving humans. Geneva: CIOMS; 2016.
2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
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6. European Medicines Agency (EMA). Ethical considerations for clinical trials on medicinal products conducted with minors. Rev. 1. London: EMA; 2017.

18 APPENDICES AND SUPPLEMENTARY MATERIALS

18.1 Appendices and supplementary materials

Appendix inventory and access control

The following appendices provide operational materials, templates, and tools referenced throughout the protocol. Materials containing personally identifiable information, site identifiers, or proprietary instrument content are controlled-access and will be shared only under approved data/materials access agreements and with REC/IRB and rights-holder permissions, consistent with SPIRIT-aligned transparency, GDPR, and CIOMS guidance [1–3].

ID	Title	Brief contents	Applies to
A1	Schedule of Activities (SoA)	Tabular schedule of enrolment, inpatient monitoring, 6- and 18-month follow-ups; instrument timing and source data mapping.	All cohorts
A2	Informed consent and assent packet	Participant information sheets (adolescents, caregivers), consent/assent templates, recontact preferences, data-sharing options; readability at CEFR B1–B2; Slovene and English versions.	All cohorts
A3	Recruitment materials	Clinic and school scripts, flyers, invitation letters, opt-in/opt-out forms, clinician referral checklist; non-stigmatizing, safety-screened language.	All cohorts
A4	Participant-facing safety resources	Crisis contacts, help-seeking guidance, confidentiality boundaries, distress management options during/after assessments.	All cohorts
A5	Case report forms (CRFs) and eCRF screenshots	Baseline, inpatient monitoring, and follow-up CRFs; item-level source-to-variable mapping; skip logic specifications.	All cohorts
A6	Data dictionary and codebook	Variable names, labels, permissible values, derivations, scoring algorithms, missing data codes, time-stamps, provenance fields.	All cohorts
A7	Instrument packet: suicidality and self-harm	Administration guides and scoring worksheets for C-SSRS; B-NSSI-AT administration notes; ISAS (functions/frequency) scoring summary; instrument permission letters (if applicable).	All cohorts
A8	Adolescent Self-Harm Risk Scale (ASHRS) materials	Item pool, cognitive debriefing summaries, pilot forms, final candidate forms, scoring specifications, item selection decision log, user guide.	High-risk cohort
A9	Psychometric analysis plan (PsychoSAP)	Prespecified steps for ASHRS and legacy measures: data screening, EFA/CFA, IRT, reliability, validity, measurement invariance, responsiveness; calibration and cut-point development.	All cohorts
A10	Statistical analysis plan (SAP)	Primary and secondary analyses, model specifications (regression, survival), covariate handling, subgroup/sensitivity analyses, multiplicity approach, interim data handling, mock tables/figures.	All cohorts
A11	Qualitative materials	Semi-structured interview/focus group guides for participant and PPI inputs; sampling matrix; moderation prompts; debrief form; COREQ/SRQR-aligned coding framework and codebook template.	As applicable per protocol
A12	Translation and cultural adaptation dossier	Forward–back translation records, reconciliation minutes, cognitive interviewing reports, harmonization notes, developer permissions; adaptation decisions for Slovene context.	All translated instruments
A13	Training curriculum and competency checklists	Training slides and manuals for standardized administration (e.g., C-SSRS), trauma-informed interviewing, safeguarding, REDCap/ePRO use, biospecimen SOPs, GDPR; competency checklists and certification logs.	Study staff

A14	Fidelity and quality assurance tools	Assessment session checklists, spot-audit forms, inter-rater reliability procedures and forms, instrument adherence logs, corrective action templates.	Study staff
A15	Inpatient monitoring logs	Daily/shift logs for self-harm and heteroaggressive incidents; DASA-YV scoring sheets per shift; incident prevention and response fields; linkage to clinical incident systems.	High-risk cohort
A16	Safeguarding and distress SOPs	Stepwise procedures for acute risk detection, escalation pathways, mandatory reporting, participant withdrawal for safety, post-assessment follow-up; documentation templates.	All cohorts
A17	Adverse event/incident reporting forms	Report templates, definitions, grading rules, timelines, responsibilities, and escalation paths aligned with institutional policies.	All cohorts
A18	Biospecimen collection and handling SOPs	Venipuncture procedures, labeling, chain-of-custody, processing, storage, shipment, QC; linkages to data IDs; withdrawal/destruction procedure.	All cohorts (biological sampling)
A19	Data protection and privacy pack	GDPR-compliant DPIA summary, role-based access controls, pseudonymization keys handling, breach response checklist, audit trail specifications, retention/archiving matrices.	Data management
A20	Data sharing and access documents	De-identified dataset specification, synthetic data notes (if applicable), analysis environment description, data use agreement templates, requester checklist, DAC workflow.	External requesters
A21	Governance charters and logs	Steering Group and Data Access Committee charters; membership rosters; meeting agendas/minutes templates; conflict-of-interest disclosure forms.	Governance
A22	Version control and document management	Master file index, nomenclature conventions, version history log, amendment crosswalk linking protocol and appendices.	Study team
A23	Dissemination materials	Templates for lay summaries, practitioner briefs, micro-summaries, slide decks; small-cell suppression rules; approval workflow checklist.	All audiences
A24	Source-to-regulatory mapping	Crosswalk of protocol/SPIRIT items, STROBE elements, and COREQ/SRQR items to study documents; audit readiness checklist.	Oversight

Notes on use and alignment

- Instruments and administration: Use of C-SSRS, B-NSSI-AT, ISAS, and ASHRS follows standardized manuals and training materials (A7–A8, A13–A14), with scoring and interpretation aligned to the Measures and Statistical/Psychometric Analysis sections. Psychometric evaluations are prespecified in A9 in line with COSMIN recommendations [4].
- Translation and adaptation: All non–Slovene-origin instruments follow documented forward–back translation with cognitive debriefing and developer permission where required (A12), consistent with ISPOR good practice [5].
- Qualitative materials: Interview/focus group guides (A11) mirror constructs assessed quantitatively to support triangulation and are reported using COREQ/SRQR principles [6,7].
- Data governance: Data capture, privacy, audit, and sharing materials (A5–A6, A19–A20) operationalize GDPR and ethical guidance on confidentiality and proportionality [2,3].
- Safety and safeguarding: SOPs, incident forms, and inpatient logs (A15–A17) implement the risk management framework described in the protocol, ensuring timely escalation and documentation consistent with institutional policies and ethical guidance [3].
- Transparency and reporting: The SoA (A1), SAP (A10), PsychoSAP (A9), and governance documents (A21) support SPIRIT-aligned prespecification and STROBE-consistent reporting for observational elements [1,8].

Availability and request process

- Internal access: The Investigator Site File contains the current versions of all appendices. Site staff access via the secure document repository with role-based permissions; superseded versions are archived per A22.
- External access: Upon publication of primary results, de-identified analysis code, SAP, PsychoSAP, and instrument user guides (excluding copyrighted content) will be posted in the institutional repository. Controlled materials (e.g., item-level copyrighted instruments, identifiable templates) are available on reasonable request subject to approvals and data use agreements (A20).
- Versioning: Each appendix includes a version number, date, and change summary; amendments are synchronized with protocol updates and REC/IRB approvals, where applicable.

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19 PROTOCOL SUMMARY

Overview

Prospective, longitudinal, multi-method observational study in Slovenia to characterize self-harm among high-risk adolescents and improve short- and long-term risk identification. The study combines clinical/psychosocial assessments, inpatient incident monitoring, and genomic/epigenomic analyses, with healthy adolescents as controls. A rapid risk screen (Adolescent Self-Harm Risk Scale, ASHRS) will be developed and validated for use during and after psychiatric hospitalization.

Design and setting

- Design: Observational cohort with a healthy control group; no experimental intervention.
- Setting: Centre for Mental Health, University Psychiatric Clinic Ljubljana (UPKL), including the Intensive Child and Adolescent Psychiatry Unit and Unit for Adolescent Psychiatry; healthy controls recruited via systematic school/educational examinations.

- Follow-up: High-risk inpatients assessed at baseline/admission, monitored during hospitalization, and reassessed at 6 and 18 months; healthy controls assessed once at enrollment.

Population

- High-risk cohort: ~200 adolescents (age 13–19) hospitalized for suicidal behavior or non-suicidal self-injury (NSSI), identified using C-SSRS (suicidality) or B-NSSI-AT (NSSI).
- Healthy control cohort: ~200 adolescents (age 13–19) from schools/colleges attending routine examinations; single assessment.
- Key exclusions (clinical cohort): acute psychosis, intellectual disability, severe physical/CNS illness, acute poisoning, or other conditions precluding valid consent/assessment.

Objectives

- Primary: Identify clinical, demographic, psychosocial, genetic, and epigenetic factors associated with occurrence and persistence of self-harm; develop and validate ASHRS to assess short- and medium-term risk.
- Secondary: Describe NSSI characteristics and functions; evaluate heteroaggression risk during hospitalization; examine trajectories of psychosocial constructs (e.g., self-regulation, trauma symptoms, attachment).
- Exploratory: Identify subgroups/profiles of risk and protection; investigate DNA methylation and genetic variants in relation to self-harm outcomes.

Outcomes and measures

- Self-harm and suicidality: C-SSRS; prospectively recorded inpatient self-harm and prevented/aborted events; survival/time-to-event outcomes post-discharge.
- NSSI features: B-NSSI-AT; ISAS (frequency, functions).
- Short-/medium-term risk: ASHRS (development, scoring, responsiveness).
- Psychosocial domains: self-regulation, emotional functioning, personality/traits (including borderline features), attachment/relationships, trauma, coping, family/peer/social support, substance use.
- Heteroaggression risk: DASA-YV during inpatient care.
- Genomic/epigenomic: Blood-derived genetic variants and DNA methylation.

Procedures

- Baseline (inpatient): Consent/assent; core clinical/psychosocial battery; blood draw; ASHRS candidate items; risk management as per clinical care.
- Inpatient monitoring: Shift-based logging of self-harm and heteroaggressive incidents; DASA-YV.
- Follow-ups (6 and 18 months, high-risk cohort): Reassessment of self-harm, suicidality, psychosocial factors, ASHRS; blood draw as specified.
- Healthy controls: Baseline-only assessment mirroring non-clinical measures; single venous sample where applicable.

Sample size and feasibility

- Target enrollment: ~400 total (approximately 200 high-risk inpatients; approximately 200 healthy controls), aligned with feasibility at UPKL and sufficient for multivariable modeling, time-to-event analyses, and psychometric development/calibration of ASHRS.

Data management and analysis

- Data capture: Secure REDCap/electronic CRFs; Slovenian-language instruments; data stored on servers physically located in Slovenia with restricted access and audit trails; GDPR-compliant pseudonymization and governance.
- Analyses: Descriptive statistics; regression and survival models for self-harm outcomes; longitudinal/repeated-measures models for trajectories; subgroup and sensitivity analyses; cluster/latent profile exploration where justified.
- Psychometrics: Prespecified ASHRS development/validation including dimensionality (EFA/CFA), item response theory, reliability, validity, measurement invariance, and responsiveness; derivation of scoring and cut-points.

Ethics, safety, and participant protections

- Approvals: Conduct under REC/IRB authorization; protocol amendments submitted as required.
- Consent/assent: Age-appropriate materials; parental consent required for participants under 15; voluntary participation with right to withdraw without impact on care.
- Safeguarding: Standardized suicide-risk assessment, escalation pathways, and distress protocols; separation of clinical care from research processes.
- Privacy: Highly sensitive psychiatric, psychosocial, and genetic data handled under strict confidentiality; controlled access; defined retention/archiving; data sharing only in de-identified form per approvals.

Governance, funding, and dissemination

- Sponsor: University Psychiatric Clinic Ljubljana (UPKL).
- Oversight: Principal Investigator and Steering Group; independent Data Access Committee for external data requests.
- Funding: Intramural support with pending external applications; funders have no role in design, conduct, analysis, or reporting.
- Dissemination: Peer-reviewed publications, open-access where feasible; lay summaries for participants and stakeholders; controlled sharing of de-identified data and analysis code per data access procedures.

Timeline

- Enrollment and baseline/inpatient monitoring: Continuous within recruitment window at UPKL units.
- Follow-up windows: 6 and 18 months post-index hospitalization for the high-risk cohort.
- Overall study duration: Sufficient to complete 18-month follow-ups, finalize ASHRS validation, and conduct planned analyses and dissemination.

19.1 Study design and setting

Design

Prospective, longitudinal, multi-method observational cohort with a healthy control group. No experimental intervention; all participants receive usual care. High-risk adolescents are enrolled during psychiatric hospitalization and followed for 18 months; healthy controls complete a single assessment at enrollment.

Setting and geography

- Primary clinical site: Centre for Mental Health, University Psychiatric Clinic Ljubljana (UPKL), Slovenia, specifically the Intensive Child and Adolescent Psychiatry Unit and the Unit for Adolescent Psychiatry.
- Community setting: Educational institutions across Slovenia (primary, secondary, college) for recruitment and single-visit assessment of healthy controls.
- Data environment: Slovenian-language assessments; data systems hosted on secure servers physically located in the Republic of Slovenia with GDPR-compliant governance.

Population and cohorts

- High-risk inpatient cohort: Approximately 200 adolescents aged 13–19 years admitted for suicidal behavior (C-SSRS) or non-suicidal self-injury (B-NSSI-AT).
- Healthy control cohort: Approximately 200 adolescents aged 13–19 years recruited at routine systematic examinations in schools/colleges.
- Key exclusions for the clinical cohort include acute psychosis, intellectual disability, severe physical/CNS illness, and acute poisoning.

Participant flow

- Screening and enrollment (inpatient units and schools): Eligibility confirmation, informed consent/assent, and baseline assessments.
- Inpatient period (clinical cohort): Prospective monitoring of self-harm and heteroaggression events throughout hospitalization.
- Follow-up (clinical cohort): Reassessments at 6 and 18 months post-index hospitalization.
- Completion: Healthy controls conclude participation after baseline; clinical cohort concludes after 18-month follow-up or upon withdrawal.

Main study activities

- Baseline (clinical cohort): Sociodemographics; detailed assessment of self-harm/suicidality (C-SSRS, B-NSSI-AT, ISAS); psychosocial battery (self-regulation, emotional functioning, personality traits including borderline features, attachment/relationships, trauma, coping, family/peer/social support, substance use); ASHRS candidate items; venous blood draw for genomic/epigenomic analyses.
- Inpatient monitoring (clinical cohort): Shift-based logging of self-harm (including prevented/aborted events) and heteroaggression; DASA-YV scoring; linkage to routine clinical incident systems.
- Follow-ups at 6 and 18 months (clinical cohort): Reassessment of self-harm/suicidality, psychosocial constructs, ASHRS; collection of time-to-event outcomes; venous blood sampling per protocol.
- Healthy control assessment: Single-visit battery mirroring non-clinical domains of the clinical cohort; optional venous blood draw as specified.

Timing

- Enrollment: Continuous during the recruitment window at UPKL and participating educational settings.
- Assessment windows: Baseline during hospitalization (clinical cohort) or at school-based visit (controls); follow-ups at 6 ± allowable window and 18 ± allowable window months post-index hospitalization (clinical cohort).

19.2 Objectives and outcomes

Summary of objectives and corresponding outcomes

Objective tier	Objective (concise)	Outcome domains	Key measures/metrics	Timing/source
Primary	Identify factors associated with occurrence and persistence of self-harm in high-risk adolescents	Self-harm and suicidality (occurrence, timing, recurrence, severity)	C-SSRS categories and event history; prospectively logged inpatient self-harm (including prevented/aborted events); post-discharge time-to-event and recurrence counts	Inpatient logs throughout hospitalization; reassessments at 6 and 18 months; interim event capture via contact/records where applicable
Primary	Develop and validate a rapid risk screen (ASHRS) for short- and medium-term self-harm risk	Short-/medium-term risk; predictive and psychometric performance	ASHRS scores; discrimination (e.g., AUC/ROC), calibration indices, sensitivity/specificity, likelihood ratios; reliability; construct/convergent validity; responsiveness to change	Baseline; inpatient rechecks as specified; 6- and 18-month follow-ups; linked to observed events and legacy scales
Secondary	Characterize NSSI features and functions	NSSI form, frequency, methods, context, functions, habituation, impact, desire to stop	B-NSSI-AT; ISAS (frequency, functions)	Baseline; 6 and 18 months (clinical cohort); baseline only (controls)
Secondary	Describe trajectories of psychosocial constructs and their associations with self-harm outcomes	Self-regulation, emotional functioning, personality/traits (incl. borderline features), attachment/relationships, trauma symptoms, coping, family/peer/social support, substance use	Standardized psychosocial questionnaires per protocol; derived composite/scale scores; change over time	Baseline; 6 and 18 months (clinical cohort); baseline only (controls)
Secondary	Evaluate heteroaggression risk during hospitalization	Inpatient heteroaggression risk	DASA-YV shift scores; incident occurrence	Each clinical shift during hospitalization; linkage to incident logs
Exploratory	Identify risk/protection	Multidimensional profiles integrating clinical,	Unsupervised/latent profile or cluster	Baseline and follow-ups

	profiles and subgroups	psychosocial, and behavioral data	variables; derived classes	(clinical cohort); baseline (controls)
Exploratory	Investigate genomic and epigenomic correlates of self-harm risk and persistence	Genetic variants; DNA methylation patterns	Blood-derived genotyping/targeted or array-based methylation indices; derived polygenic/methylation scores as specified	Baseline; follow-up sampling per protocol; linked to self-harm outcomes and psychosocial measures

Measurement approaches and anchors

- Event-based outcomes:

- Inpatient self-harm and prevented/aborted events: prospective shift-level logs linked to clinical incident systems.
- Post-discharge occurrence and timing: C-SSRS interview, structured event history, and, where available, corroborating records; primary time-to-first-event and recurrence counts within 18 months.

- Scale-based outcomes:

- Suicidality: C-SSRS severity and intensity classifications.
- NSSI: B-NSSI-AT (features/context); ISAS (frequency and functions).
- Short-/medium-term risk: ASHRS total and subscale scores; predictive metrics against observed events.
- Psychosocial domains: Pre-specified validated instruments with total/subscale scores; change scores for trajectory analyses.
- Heteroaggression: DASA-YV shift scores and related incidents.

- Biospecimen-derived outcomes:

- Genetic and epigenetic indicators: assay-specific variant/methylation measures and derived risk indices; exploratory associations with behavioral outcomes.

Endpoint hierarchy and analytic alignment

- Primary endpoints:

- Time to first post-discharge self-harm event within 18 months (clinical cohort).
- Inpatient self-harm incidence rate during index hospitalization.
- ASHRS predictive performance for short-term (e.g., inpatient/early post-discharge) and medium-term events (6–18 months), alongside reliability and validity indices.

- Key secondary endpoints:

- NSSI frequency and function profiles; changes from baseline to 6 and 18 months.
- Longitudinal change in psychosocial constructs and their associations with self-harm outcomes.
- DASA-YV–indexed heteroaggression risk and incidents during hospitalization.

- Exploratory endpoints:

- Data-driven risk/protection profiles and their relationship to outcomes.
- Associations between genetic/epigenetic indicators and self-harm occurrence, persistence, and psychosocial trajectories.

19.3 Population and sample size

Target population

- Adolescents aged 13–19 years in Slovenia.
- High-risk inpatient cohort: approximately 200 adolescents hospitalized at the Centre for Mental Health, University Psychiatric Clinic Ljubljana (UPKL) for suicidal behavior or non-suicidal self-injury (NSSI), identified on admission using the Columbia Suicide Severity Rating Scale (C-SSRS) or the Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT).
- Healthy control cohort: approximately 200 adolescents recruited during routine systematic examinations in schools/colleges, without current hospitalization, assessed once at enrollment.

Key eligibility concepts

- Inclusion (high-risk cohort): age 13–19; inpatient admission to the Intensive Child and Adolescent Psychiatry Unit or Unit for Adolescent Psychiatry at UPKL; current suicidal behavior per C-SSRS or NSSI per B-NSSI-AT; capacity/assent with parental consent where required.
- Exclusion (high-risk cohort): acute psychosis, intellectual disability, severe physical or central nervous system illness, acute poisoning, or other conditions precluding informed consent/assent or valid assessment.
- Inclusion (healthy controls): age 13–19; attending routine systematic school/college examinations; capacity/assent with parental consent where required.
- Language: participation supported with Slovene-language materials and instruments.

Recruitment approach

- High-risk inpatients: continuous screening at UPKL units; clinician referral and research staff approach post-stabilization; informed consent/assent obtained prior to baseline assessment.
- Healthy controls: collaboration with educational settings to identify eligible students during systematic examinations; standardized study information and opt-in processes; baseline-only assessment at enrollment.
- Materials: age-appropriate, non-stigmatizing recruitment and consent materials; processes aligned with safeguarding and privacy requirements.

Sample size

- Planned enrollment: approximately 400 participants total (about 200 high-risk inpatients and about 200 healthy controls).
- Rationale: the target accommodates feasibility at UPKL while supporting:

- Psychometric development and validation of the Adolescent Self-Harm Risk Scale (ASHRS), for which samples of ≥200 are commonly adequate for dimensionality assessment and modern test theory modeling when item quality is monitored and model fit is evaluated [9,10].
- Multivariable associations and time-to-event modeling in the clinical cohort, with attention to events-per-variable considerations for stable estimation and to avoid overfitting in parsimonious models [11].
- Estimation of discrimination indices (e.g., AUC) for ASHRS with acceptable precision; the planned sample supports ROC-based evaluation subject to observed event counts and class balance in the high-risk cohort [12].

- Follow-up yield: the target anticipates routine attrition in adolescent longitudinal cohorts; retention strategies (below) aim to preserve sufficient numbers for prespecified analyses.

Retention and follow-up approach

- High-risk cohort follow-up at 6 and 18 months post-index hospitalization using multimodal contact (phone, SMS, email, secure ePRO), flexible scheduling (in-person or remote), and brief, well-sequenced assessments to minimize burden.
- Maintenance of multiple contact points (participant, caregiver, preferred clinician/school contact where permitted), periodic check-ins between waves, and culturally appropriate reminders increase retention in adolescent cohorts [13,14].
- Participant reimbursements/compensation per institutional policy; missed-visit recontact and windowed rescheduling; safety-first procedures for distress or risk disclosure during follow-ups.
- Healthy controls complete a single assessment at enrollment and do not undergo longitudinal follow-up.

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19.4 Procedures, measures, and analysis

Summary of procedures

- High-risk inpatient cohort:

- Baseline (within index hospitalization): consent/assent; sociodemographics; C-SSRS; B-NSSI-AT; ISAS; psychosocial battery (self-regulation, emotional functioning, personality/traits including borderline features, attachment/relationships, trauma symptoms, coping, family/peer/social support, substance use); ASHRS candidate items; venous blood draw.
- Inpatient monitoring: shift-level logging of self-harm (including prevented/aborted events) and heteroaggression; DASA-YV scored each shift; linkage to clinical incident systems.
- Follow-ups (6 and 18 months post-discharge): reassessment of self-harm/suicidality, NSSI features, psychosocial measures, and ASHRS; ascertainment of intercurrent events and time-to-event endpoints; venous blood draw per protocol.

- Healthy control cohort:

- Single assessment at enrollment mirroring non-clinical domains (C-SSRS as applicable for current ideation/behavior, B-NSSI-AT, ISAS, psychosocial battery); optional venous blood draw.

Measures and instruments

- Self-harm and suicidality:

- C-SSRS (ideation, behavior, severity/intensity classifications) [5].
- Prospectively recorded inpatient self-harm (including prevented/aborted events), with standardized definitions and timestamps.
- Post-discharge events via structured event history at follow-ups, anchored to C-SSRS and corroborating records when available.

- NSSI characteristics:
  - B-NSSI-AT (form, frequency, context, habituation, impact, desire to stop).
  - ISAS (frequency and functions) [6].
- Short-/medium-term risk:
  - ASHRS (candidate/final forms): dimensionality, reliability, validity, and predictive performance evaluated against observed events.
- Psychosocial domains:
  - Pre-specified validated scales covering self-regulation, emotional functioning, personality/traits (including borderline features), attachment/relationships, trauma symptoms, coping, family/peer/social support, substance use; total and subscale scores derived per manuals.
- Heteroaggression risk:
  - DASA-YV scored each nursing shift; incident occurrence captured in parallel logs.
- Genomic/epigenomic:
  - Blood-derived genotyping and DNA methylation assays; derived indices (e.g., polygenic/methylation scores) for exploratory analyses.

All non–Slovene-origin tools use translated/adapted versions per best practice; administration follows standardized manuals and staff training. Measurement selection, scoring, and validation are aligned with SPIRIT-aligned prespecification, STROBE reporting for observational elements, and COSMIN guidance for instrument evaluation [1,2,4].

Data sources and capture

- Electronic case report forms in REDCap with role-based access, audit trails, and source-to-variable mapping; ePRO for remote follow-ups.
- Clinical incident systems and inpatient shift logs for event-level data; linkage keys maintained under strict pseudonymization.
- Biospecimen chain-of-custody recorded from collection through processing and storage.
- Data residency and processing on secure servers located in Slovenia with GDPR-compliant governance, minimization, and access controls [3].

Analysis plan

- General principles:
  - Prespecified primary/secondary/exploratory analyses, model assumptions checking, parsimony, and transparent reporting consistent with SPIRIT-aligned planning and STROBE for cohort reporting [1,2].
  - Where multiple comparisons arise in secondary/exploratory analyses, control false discovery rate as appropriate [11].
- Descriptive analyses:
  - Baseline characteristics summarized by cohort; inspection of distributions, outliers, and data completeness.
  - Inpatient event rates (self-harm, prevented/aborted, heteroaggression) summarized per 100 patient-days.
- Primary inferential analyses:
  - Time to first post-discharge self-harm event analyzed using Kaplan–Meier and Cox models; proportional hazards evaluated; covariate selection guided by clinical relevance and events-per-variable considerations [8].
  - Inpatient self-harm incidence modeled using Poisson/negative binomial regression with exposure offsets and, if needed, mixed-effects to account for within-patient clustering across shifts.
- Secondary analyses:
  - NSSI frequency/functions and psychosocial trajectories analyzed with linear or generalized linear mixed-effects models; random intercepts/slopes as indicated; time-by-covariate interactions to assess differential change.
  - Heteroaggression risk: association between DASA-YV shift scores and incident occurrence assessed with time-updated logistic or survival models (e.g., discrete-time hazards).
- ASHRS development and validation:

- Dimension assessment via EFA/CFA; item calibration using appropriate IRT models; reliability (internal consistency/test–retest), construct and convergent validity (with C-SSRS, B-NSSI-AT, ISAS, psychosocial correlates), and responsiveness.
- Predictive performance for short-term (inpatient/early post-discharge) and medium-term (6–18 months) events assessed using discrimination (AUC/ROC), calibration plots/indices, and decision-analytic metrics; internal validation via bootstrapping or cross-validation; transparent reporting per TRIPOD [3,4,7].

- Exploratory analyses:

- Latent class/profile or clustering to identify risk/protection subgroups, with external validation against outcomes.
- Genomic/epigenomic associations with outcomes and psychosocial trajectories using regression or penalized models; sensitivity analyses for batch effects and population stratification (if applicable).

- Subgroups and sensitivities:

- Prespecified strata (e.g., sex, age bands) examined via interaction terms.
- Sensitivity to alternative outcome definitions (e.g., excluding aborted events), alternative time scales, and missing data handling choices.

Model diagnostics, influential observation checks, and robustness assessments are documented. Effect sizes with 95% CIs are reported; p-values are interpreted cautiously, emphasizing estimation and uncertainty. Predictive models are developed with attention to overfitting (e.g., shrinkage/penalization) and EPV constraints [8].

Missing data

- Prevention/minimization:

- Design strategies include brief, sequenced assessments; flexible visit modes; reminder systems; and multiple contact points to reduce attrition.

- Handling and assumptions:

- Patterns and mechanisms explored (MCAR/MAR/MNAR) using descriptive diagnostics and auxiliary variables.
- Primary approach under MAR: multiple imputation by chained equations for covariates and scale scores, incorporating cohort, baseline severity, and outcome-relevant auxiliaries; congenial analysis models applied across imputed datasets with Rubin's rules for pooling [9,10].
- For time-to-event outcomes with partially observed covariates, imputation models include event indicators and Nelson–Aalen estimates to preserve associations; for longitudinal mixed models, imputation accommodates multilevel structure where feasible [10].
- Sensitivity analyses for departures from MAR (e.g., pattern-mixture or delta-adjustment) and, where attrition may be informative, inverse probability weighting or joint modeling considered.

- Item-level scoring:

- Standardized missing-data rules per instrument manuals (e.g., prorating within bounds) are applied before scale construction; deviations are prespecified and justified.

- Reporting:

- Extent, reasons, and handling of missingness reported per STROBE; imputation specifications and diagnostics documented.

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19.5 Ethics, safety, governance, and transparency

Consent and assent

- Ethical conduct adheres to the Declaration of Helsinki and CIOMS guidance for research with children and adolescents, respecting developing autonomy, voluntariness, and the right to withdraw without consequence to care [1,2].
- Age-appropriate, plain-language materials are provided; written parental consent is obtained where legally required (under 15 years in Slovenia), alongside adolescent assent or consent as applicable. Processes emphasize comprehension, confidentiality limits, and the distinction between research and clinical care [1–3].
- Capacity is assessed by trained staff; consent is an ongoing process. Re-consent occurs at major amendments or when participants reach the age threshold for independent consent [1–3].
- No financial incentives are tied to risk; reimbursements cover reasonable expenses only, in line with local policy and proportionality principles [2].

Safeguarding, risk, and distress management

- Given the high-risk inpatient population, standardized suicide- and self-harm–risk procedures are embedded: immediate risk appraisal, documented safety planning, clinical escalation to the treating team, and emergency pathways when threshold criteria are met, consistent with contemporary guidance for self-harm management [5].
- Distress protocols include pause/stop options during assessments, on-call clinical support, and rapid referral for acute symptoms (e.g., severe mood, trauma-related distress, substance risks).
- Mandatory reporting and duty-of-care obligations (e.g., imminent risk, abuse concerns) are explained during consent and followed precisely; research staff training covers de-escalation, safeguarding, and adolescent-sensitive communication [2,5].
- Participation burden is minimized by sequencing, brief instruments where feasible, flexible modes (in-person/remote), and opportunities to reschedule without penalty [2].

Privacy, confidentiality, and data protection

- Highly sensitive psychiatric, psychosocial, and genetic/epigenetic data are processed under GDPR principles of lawfulness, purpose limitation, data minimization, storage limitation,

integrity/confidentiality, and accountability; the legal basis for special-category data is scientific research in the public interest with appropriate safeguards [4].
- Identifiers are stored separately from research data using coded keys; access is role-based, least-privilege, and logged. Servers are physically located in Slovenia, with encryption in transit and at rest, audit trails, and documented breach-response procedures aligned to GDPR timelines and notification duties [4].
- Participant-facing materials describe data uses, retention/archiving periods, rights (access, rectification, restriction, objection where applicable), and limits to deletion where derogations for research apply, alongside contact information for the data controller and Data Protection Officer [4].
- Biospecimens follow documented chain-of-custody; genetic/epigenetic data are handled as special-category data with additional access controls and governance review prior to any sharing [4].

Governance and oversight

- The sponsor (UPKL) ensures protocol compliance, resources, and insurance/indemnity; approvals from a competent Research Ethics Committee/IRB are obtained before initiation, with continuing review, safety reporting, and prior approval of amendments [1,2].
- Study oversight includes a Principal Investigator–led team and a Steering Group; data governance is supported by a Data Access Committee for external requests, applying scientific merit, ethical approvals, and privacy-risk assessment.
- Quality management emphasizes proportionate monitoring, documentation, and staff training; responsibilities and communication lines are predefined to ensure timely issue escalation and resolution [1,2].

Registration and protocol transparency

- The study is registered in a publicly accessible registry prior to enrollment; registry fields include objectives, design, outcomes, sample, and data-sharing intent to meet SPIRIT-aligned transparency expectations [6].
- Public protocol and statistical analysis plan access is provided (version-controlled), and substantive amendments are time-stamped and cross-referenced in the registry. Prospective registration supports ICMJE-aligned transparency norms for human studies [7].

Data sharing and access

- De-identified datasets, metadata, variable dictionaries, and analysis code will be shared upon reasonable request following publication, governed by a Data Use Agreement, REC/IRB approvals as required, and an assessment of re-identification risk—especially for small subgroups and genomic/epigenomic data.
- Sharing follows FAIR principles where feasible: findable (persistent identifiers/metadata), accessible (governed access), interoperable (standard formats/terminologies), and reusable (clear licenses/provenance), balanced against privacy and consent boundaries [8].
- Individual-level genetic/epigenetic data may be deposited in controlled-access repositories when permitted by consent and approvals; only aggregate summaries are released publicly by default [4,8].

Dissemination and participant/community communication

- Results will be disseminated in peer-reviewed outlets and scientific meetings with adherence to STROBE for observational reporting and transparent disclosure of protocol deviations and limitations; negative and null findings will be reported [6].
- Lay summaries in Slovene are provided to participants, caregivers (where appropriate), and community partners (schools, youth organizations), co-designed with youth advisors to optimize clarity and reduce stigma.
- Clinically actionable safety information identified during participation is communicated to the treating team under consented arrangements. No individual research test results (e.g., exploratory genetic findings) are returned unless explicitly approved by the REC/IRB and validated for clinical use [1,2,4].

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20 SYNOPSIS

Overview

- Prospective, longitudinal, multi-method observational cohort conducted in Slovenia with a healthy control group; no experimental intervention. High-risk adolescents are enrolled during psychiatric hospitalization at the University Psychiatric Clinic Ljubljana (UPKL) and followed for 18 months; healthy controls complete a single baseline visit.
- Primary behavioral focus is adolescent self-harm (suicidal behavior and non-suicidal self-injury, NSSI), with comprehensive assessment of psychosocial correlates and development/validation of the Adolescent Self-Harm Risk Scale (ASHRS) to support short- and medium-term risk identification.

Design, setting, and duration

- Design: Prospective cohort with repeated measures (clinical cohort) and a baseline-only healthy control group; integrated psychometric, clinical, and exploratory genomic/epigenomic components; reporting aligned with SPIRIT principles and STROBE for observational studies [1,2].
- Setting: Centre for Mental Health, UPKL (Intensive Child and Adolescent Psychiatry Unit; Unit for Adolescent Psychiatry); community educational settings across Slovenia for control recruitment.
- Timeline: Baseline during index hospitalization; inpatient prospective monitoring; follow-ups at 6 and 18 months post-discharge for the clinical cohort; healthy controls assessed once at enrollment.

Population, sampling, and eligibility

- Target population: Adolescents aged 13–19 years in Slovenia.
- Planned sample: Approximately 200 high-risk inpatients and approximately 200 healthy controls (total ≈400), selected to support psychometric development (dimensionality and item calibration), time-to-event modeling with parsimony, and estimation of discrimination indices with acceptable precision [3–6].
- Key inclusion (clinical cohort): Age 13–19; admission for suicidal behavior (C-SSRS) or NSSI (B-NSSI-AT); capacity/assent with parental consent when required.
- Key exclusion (clinical cohort): Acute psychosis, intellectual disability, severe physical/CNS illness, acute poisoning, or conditions precluding valid consent/assessment.
- Healthy controls: Age 13–19; recruited during routine school/college examinations; capacity/assent with parental consent when required; baseline-only participation.

Hypothesis and objectives

- Hypothesis: Short- and medium-term self-harm events will be associated with higher ASHRS scores and with specific clinical and psychosocial risk factors; protective factors will be inversely associated.
- Primary objectives: Identify factors associated with occurrence and persistence of self-harm in high-risk adolescents; develop and validate the ASHRS for short- and medium-term risk prediction.
- Secondary objectives: Characterize NSSI features/functions and psychosocial trajectories; quantify inpatient heteroaggression risk.
- Exploratory objectives: Identify multidimensional risk/protection profiles; examine genomic/epigenomic correlates of risk and persistence.

Outcomes and measures

- Event-based outcomes: Inpatient self-harm (including prevented/aborted events) and heteroaggression; post-discharge time-to-first self-harm and recurrence within 18 months.
- Scale-based outcomes: C-SSRS suicidality classifications; B-NSSI-AT and ISAS for NSSI; ASHRS scores and psychometrics; validated psychosocial scales (self-regulation, emotional functioning, personality/traits including borderline features, attachment/relationships, trauma, coping, social/family support, substance use).
- Biospecimen-derived indices: Genetic variants and DNA methylation measures for exploratory analyses.
- Heteroaggression risk: DASA-YV scored each shift during hospitalization.

Key procedures

- Clinical cohort baseline: Consent/assent; sociodemographics; C-SSRS; B-NSSI-AT; ISAS; psychosocial battery; ASHRS candidate items; venous blood draw.
- Inpatient period: Shift-level logging of self-harm and heteroaggression; DASA-YV each shift; linkage to incident reporting.
- Follow-ups (6 and 18 months): Reassessment of self-harm/suicidality, NSSI, psychosocial domains, ASHRS; ascertainment of intercurrent events; venous blood sampling per protocol.
- Healthy controls: Single baseline visit mirroring non-clinical domains; C-SSRS as applicable; optional venous blood draw.

- Instruments: Validated tools with Slovene translations/adaptations per COSMIN-aligned procedures; standardized administration and scoring [2,7–9].

Analysis approach

- Descriptive: Baseline profiles by cohort; inpatient event rates per 100 patient-days.
- Primary inferential: Kaplan–Meier and Cox models for time to first post-discharge self-harm; incidence modeling of inpatient self-harm using Poisson/negative binomial (with exposure offsets and random effects as needed); EPV-aware model parsimony [5].
- ASHRS development/validation: EFA/CFA; IRT-based item calibration; reliability, construct/convergent validity; predictive performance via ROC/AUC, calibration, and decision metrics; internal validation with bootstrapping or cross-validation; reporting per TRIPOD and best practices in scale development [3,4,6,8,9].
- Secondary: Longitudinal mixed-effects models for NSSI and psychosocial trajectories; heteroaggression modeled with time-updated approaches.
- Exploratory: Latent class/profile analyses; genomic/epigenomic associations with penalized or adjusted models.
- Missing data: Prevention via design/retention strategies; multiple imputation under MAR with sensitivity analyses for departures (pattern-mixture/delta); instrument-specific scoring rules applied before scale construction [10,11].

Data management and privacy

- Data capture: REDCap eCRFs and ePRO with role-based access, audit trails, and source mapping.
- Pseudonymization: Identifiers stored separately; secure linkage keys; encryption at rest/in transit.
- Data residency and governance: Servers located in Slovenia with GDPR-compliant processing of special-category data, including genetic/epigenetic information; breach-response and participant rights procedures in place [12].

Participant safety and safeguarding

- Embedded risk protocols for suicide/self-harm consistent with contemporary guidance: immediate appraisal, safety planning, clinical escalation, and emergency pathways as needed; distress procedures allow pause/stop and rapid referral [13].
- Duty-of-care and mandatory reporting observed; trained staff in de-escalation and adolescent-sensitive communication; participation burden minimized via concise, flexible assessments.

Ethics, consent, and regulatory compliance

- Conduct aligned with the Declaration of Helsinki, CIOMS guidance for research with children/adolescents, and national regulations; REC/IRB approval obtained before initiation, with continuing review and amendment control [14,15].
- Consent/assent: Age-appropriate materials; parental consent where legally required (under 15 years), with adolescent assent/consent; ongoing consent including re-consent at age threshold transitions.
- Insurance/indemnity and institutional sponsorship in place per local policy.

Transparency, dissemination, and data sharing

- Prospective public registration capturing design, outcomes, analysis intent, and data-sharing statements; protocol and analysis plan made accessible and version-controlled; reporting adheres to STROBE and TRIPOD where applicable [1,4,16].
- Dissemination: Peer-reviewed publications (including null findings), scientific meetings, and Slovene lay summaries for participants/caregivers and community partners.
- Data sharing: De-identified datasets, metadata, and code shared on reasonable request under governance (Data Use Agreements, REC/IRB approvals, privacy risk assessment), aligned with FAIR principles and constraints for genomic/epigenomic data [12,17].

Risk–benefit assessment

- Anticipated risks relate to psychological distress during sensitive assessments and privacy concerns given special-category data. Risks are mitigated through safeguarding, trained staff, minimal-burden procedures, strong data protection, and clear consent processes.
- Anticipated benefits include improved understanding of self-harm risk and persistence in high-risk adolescents, validated short- and medium-term risk screening (ASHRS), and evidence to inform clinical management pathways. The risk–benefit balance is favorable given robust protections and the public health importance of adolescent self-harm.

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