Complete Research Protocol (HRP-503)

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Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 6, 21, 22, 24, 25, 26 and 27 do not apply.*
    - *For exempt research: Section 6 may not apply. Section 6.1 will still apply if there is a study intervention.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

Response Example
Intervention Group:
Control Group:

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response: **R**emote vs. **I**n-Person **S**tudy **E**valuation (RISE) Above Smoking

PRINCIPAL INVESTIGATOR:

Name
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Response:

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VERSION NUMBER/DATE:

Include the version number and date of this protocol.

Response: – 2026.04.21

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
13	2026.04.21	Updating accrual number so that UP TO 102 people may be accrued at each site	No
12	2026.02.05	Staffing only	No
11	2025.11.14	• Adding Perceived Stress Scale • Submitting META ads for approval	No
10	2026.10.27	Staffing only	No
9	2026.09.30	Mod and Continuing Review	No
8	2025.09.16	Staffing only	No
7	2025.06.27	• Modifications to Qualitative Interview • Submitting REDCap form where Qualitative Interview progress will be tracked	No

		Updated Smoking and Vaping History and Demographics to include specific questions about the participant's race	No
6	2025.06.03	Staffing only	No
5	2025.05.02	Submitting reminder call scripts	No
		Submitting UPenn-specific ads for META	No
		Adding a survey assessing use of the Quit Kit	No
4	2025-03-26	Adding response choices to capture accuracy of "pronunciation" in addition to "association" on the Short Assessment of Health Literacy	No
		Submitting the randomization plan	No
		The consultant responsible for conducting qualitative interviews is moving from MUSC to Wake Forest in early April, 2005.	Yes
		Submitting a UPenn-specific recruitment flyer	No
3	2025-03-07	Adding referrals for smoking cessation and social services.	No
2	2025-01-15	Splitting Treatment and Assessment Visit payments into $10 for breath sample for CO assessment and $20 for the rest of the visit.	Yes
		Adding $10 travel reimbursement for UPenn in-person participants only	Yes
		Changed time between Treatment & Assessment Visits 2 & 3 to 2 weeks instead of 3 weeks	Yes
		We will collect expired-air carbon monoxide samples from in-person participants.	Yes
		We will ask participants who are ≥21 years old to have a pack of their usual brand of cigarettes with them at their Intake appointment.	No
		Adding recruitment materials from BuildClinical	No
		Adding a medication module to REDCap to collect participant medication information	No
		Updating gender identity response options	No
		Adding a sexual identity question to Smoking, History, and Demographics form at Intake	No
1	2024-12-17	Adding a qualitative interview at the end of participation for ~15% of trial participants	Yes

		Adding a cost analysis component for research participants and research staff	No

FUNDING:

Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.

Response: National Institutes of Health (NIH): National Center for Advancing Translational Sciences (NCATS)

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: NIH - National Center for Advancing Translational Sciences

This protocol covers the UG3 phase (first two years) of our 5-year multi-phase (UG3/UH3) grant application. The UG3 phase includes Aims 1 and 2 (a multi-site randomized controlled trial (RCT) conducted at UB and UPenn) and the initial data collection for Aim 5 (qualitative interviews to inform the UG3 to UH3 transition and cost analyses that will continue in the UH3 phase). The UH3 phase, not included in this protocol, includes single-site RCTs based at the Medical University of South Carolina (MUSC) and the University of Alabama-Birmingham (UAB).

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response: We anticipate all consent and data collection will be electronic, within REDCap, as will correspondence with the IRB. Any paper files will be stored at the location listed below.

Location: Unit on Behavioral Health Research and Treatment (UBHEART)

Diefendorf Hall 3rd Floor locked cabinets within locked offices

Address: South Campus, University at Buffalo

Department: Psychology

1.0 Study Summary

Study Title	Improving Efficiency, Quality, and Equity: Randomized Controlled Evaluations of Remote vs. In-Person Clinical Trial Methods
Study Design	Experimental: 2 Remote vs In-Person Intake Groups x 2 Remote vs In-Person Treatment and Assessment Groups
Primary Objective	Conduct an innovative, rigorous experimental evaluation of remote vs. in-person methods on trial efficiency (accrual) and quality (retention, treatment adherence, bio-specimen completion rates).
Secondary Objective(s)	The quantitative, qualitative, and cost data generated from this project will establish a translational science evidence base which will guide the design of future clinical trials. Additional dissemination efforts (e.g., project website, webinar series, conference presentations, publications, newsletters and press releases, and a national workshop) will target the consortium of more than 60 leading academic health centers in the United States currently receiving Clinical and Translational Science Award (CTSA) Program funding from the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) and the clinical trialist community at large.
Research Intervention(s)/ Investigational Agent(s)	Remote vs. In-Person Intake visit and Remote vs. In-Person Treatment/Assessment Visits – Participants will be randomized to complete either a remote or in-person Intake visit and if eligible for the study, will be re-randomized to either remote or in-person treatment and assessment visits.
IND/IDE #	N/A
Study Population	Adults (18+ years old)
Sample Size	204 (up to 102 at UB and up to 102 at UPenn)
Study Duration for individual participants	Max duration ~ 6 Hours total: • 1 1-hour intake visit • 5 30-60 minute treatment/assessment visits
Study Specific Abbreviations/ Definitions	CFIR/HE - Consolidated Framework for Implementation Research 2.0 integrated with the Health Equity Implementation Framework CLIC - Center for Leading Innovation & Collaboration CO – carbon monoxide CPD – cigarettes per day CSW – Creative Scientist Workshop CTSA – Clinical and Translational Science Award CTSI – Clinical and Translational Science Institute EHR – electronic health record IP – In-Person ITT - intention-to-treat

	MUSC – Medical University of South Carolina NCATS – National Center for Advancing Translational Sciences NRT – Nicotine Replacement Therapy PHQ-9 – Patient Health Questionnaire 9 R – Remote RCT – randomized controlled trial RIC – Recruitment Innovation Center SDOH – social determinants of health T/A – treatment/assessment TIN – Trial Innovation Network UAB – University of Alabama Birmingham UDS – urine drug screen UPenn – University of Pennsylvania

2.0 Objectives*

2.1 Describe the purpose, specific aims, or objectives of this research.

Response:

Aim 1: Evaluate the accrual efficiency of the Remote vs. In-Person Intake Groups.

Aim 2: Examine key metrics of trial quality in Remote vs. In-Person Treatment and Assessment Groups.

Exploratory Aim 5: Examine the impact of remote vs. in-person trial efficiency (Aim 1) and quality (Aim 2) for participant sub-groups that experience health inequities.

2.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response:

Aim 1: We hypothesize that percent attendance at the Intake Visit (a major recruitment bottleneck for in-person trials) will be greater in the Remote Intake Group compared to the In-Person Intake Group.

Aim 2: Given the weak evidence base, we will test the competing hypotheses that Remote Treatment and Assessment will increase or decrease retention rates, and treatment adherence/ utilization, and rates of bio-specimen completion, compared to the In-Person Group.

(Aims 3 and 4 will be in the UH3 Phase of this grant and are not relevant to the current protocol.)

Exploratory Aim 5: Since the impact of remote trials on health equity is unclear, we will explore whether the differences between remote and in-person methods vary as a function of participant race/ethnicity, age, and other characteristics linked to health inequities and under-representation in RCTs. We will also explore

the role of patient-reported social determinants of health (SDOH) and barriers to trial participation to better contextualize and understand racial/ethnic and/or age differences in the effects of remote trial methods.

3.0 Scientific Endpoints*

3.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should ***not*** *be a date.*

Response: Endpoints include differences in visit completion rates between those randomized to Remote vs. In-Person Intake Visit; differences in retention, bio-specimen completion, and treatment adherence / utilization between those randomized to Remote vs. In-Person Treatment/ Assessment Visit.

4.0 Background*

4.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response:

SPECIFIC AIMS

As noted in PAR-22-167, "…intervention development…is currently fraught with inefficiency…". Remote trials (aka "virtual trials" or "decentralized trials"), in which patients are screened, receive treatment, and/or provide outcome data without traveling to a study site, have emerged as a promising approach for addressing systematic barriers to trial participation. The COVID-19 pandemic markedly increased interest in and use of remote trial methods; out of necessity, trialists quickly patched together remote approaches1–4. Unfortunately, these patches were developed post facto and, as such, were often fragmented – institution-specific, even trial specific– with unknown effects on trial quality (rigor) [5,6]. While many predict that remote methods are the "new normal" for clinical trials1,7–18, the evidence supporting such a shift is weak, consisting of anecdotal reports, uncontrolled studies, and expert opinion. The same is true for hypothesized limitations of remote methods[3,6,7,19]. Put simply, there has yet to be a direct, experimental test of in-person versus remote methods on trial efficiency, quality, and health equity. Such tests are critical for developing a stronger translational science evidence base to develop and disseminate robust best practices regarding remote trial methods.

Consistent with NCATS principles, we aim to rigorously evaluate the impact of remote trial methods on "quality and efficiency" (CTSA Goal 4) via 3 first-of-their-kind randomized controlled trials (RCTs). Consistent with the call for "bold…experimental approaches" (PAR-22-167), RCTs are the gold standard for comparing treatments – and, by extension, for testing the impact of remote methods on trial (accrual) efficiency and quality (rigor). To maximize the extent to which the project's results will be "disease agnostic," we employ a purposively heterogeneous approach to disease/condition across 3 different use cases: a larger, multi-site demonstration trial in the UG3 Phase and two smaller, single-site dissemination projects in the UH3 Phase. To isolate the impact of remote vs. in-person trial methods on trial accrual efficiency and quality in each trial, and to ensure project results are applicable to hybrid designs involving combinations of remote and in-person methods, we will employ two-stage randomization. First, to examine accrual efficiency, we will randomize participants to Remote vs. In-Person Intake for full consent and eligibility evaluation. Second, to assess metrics of trial quality, participants eligible at intake will then be re-randomized (within Intake Group) to either Remote or In-Person Treatment and Assessment. All participants will be assessed through 3-month follow-up.

UG3 Phase: We propose a larger (N=200 participants who initiate treatment), multi-site (UB, UPenn CTSAs) RCT. Participants will receive pharmacotherapy for cigarette smoking, a prevalent, highly significant public health problem [20,21]. Specific aims include:

Aim 1: Evaluate the accrual efficiency of the Remote vs. In-Person Intake Groups. We hypothesize that percent attendance at the Intake Visit (a major recruitment bottleneck for in-person trials) will be greater in the Remote Intake Group compared to the In-Person Intake Group.

Aim 2: Examine key metrics of trial quality in Remote vs. In-Person Treatment and Assessment Groups. Given the weak evidence base and conflicting opinions noted above, we will test the competing hypotheses that Remote Treatment and Assessment will increase or decrease retention rates, and treatment adherence/utilization, and rates of bio-specimen completion, compared to the In-Person Group.

UH3 Phase: Two smaller dissemination projects (N=100 who initiate treatment in each trial) will focus on: (a) a mHealth intervention for depression (MUSC CTSA), and (b) an opioid overdose prevention (education and naloxone) intervention (UAB CTSA). Thus, Aims 3-4 parallel UG3 Aims 1-2, with an emphasis on determining the degree to which the findings for remote vs. in-person trial methods generalize across conditions and treatment modalities (i.e., are disease- and treatment-agnostic).

Exploratory Aim 5: Examine the impact of remote vs. in-person trial efficiency (see Aims 1, 3) and quality (Aims 2, 4) for participant sub-groups that experience health inequities. As the impact of remote trials on health equity is unclear [22,23], we will explore whether the differences between remote and in-person methods vary as a function of participant race/ethnicity, age, and other characteristics

linked to health inequities and under-representation in RCTs. We will also explore the role of patient-reported social determinants of health (SDOH) and barriers to trial participation to better contextualize and understand racial/ethnic and/or age differences in the effects of remote trial methods.

Supplementing all major aims of the proposal, we will conduct: (a) qualitative interviews with a diverse subset of participants to inform the UG3 to UH3 transition and next steps in remote/hybrid trial design, and (b) cost analyses to evaluate the savings hypothesized for remote trial methods.

The proposed translational science forges collaboration across four CTSA hubs to provide important, highly novel, and rigorous experimental data on the impact of remote trial methods on clinical trial efficiency and quality. Our dissemination and sustainability plans will ensure that the knowledge generated is readily accessible. This work will contribute to the development, dissemination, and implementation of best practices in trial design across the CTSA network and beyond.

RESEARCH STRATEGY

1. **Overall impact statement**

Remote trials (aka "virtual trials" or "decentralized trials"), in which patients are screened, receive treatment, and/or provide outcome data without the need to travel to a clinical trial site, have emerged as a promising approach "…to improve clinical research and clinical trial efficiency…" (PAR-22-167). Although work on remote trials has been advancing for over a decade[19], the COVID-19 pandemic markedly increased interest in, and use of, remote methods. Faced with closure of in-person visits – more than 1,100 trials were stopped per month during peak periods of global spread [24,25] – CTSA hub trialists quickly adapted existing processes and/or implemented new processes to allow remote recruitment, eligibility screening, consent, treatment, biospecimen collection, and/or follow-up assessments1. These efforts highlight the modular nature of remote trial methods, which guides our approach (see 3.3). In this context, in which remote methods kept many clinical trials open, there have been numerous suggestions that remote trials will become the "new normal" following the pandemic, either in part or in full1,[7–18]. Some commentaries have been extremely enthusiastic, recommending "…that remote access for clinical trials transitions from serving as a short-term solution to becoming a mainstay necessity in all trials whenever possible" ([10], p. 186). Others have urged "…caution before abandoning or greatly reducing in-person visits …" ([6], p. 1935), noting concerns about remote trial quality [3,6,7,19].

To what extent should remote trial methods become the future of clinical trials? How do we decide? From a translational science perspective, the critical question is: To what extent do remote trial methods (outside the context of a pandemic shutdown) improve the efficiency and quality of clinical research (CTSA Program Goal 4)? At present, evidence for the hypothesized benefits and limitations of remote trial methods is weak, consisting primarily of anecdotal reports, uncontrolled studies, and expert opinion. These sources of evidence are a natural starting point, but they do not provide the rigorous tests and standards of evidence

needed to inform the design of future RCTs in a CTSA 2.0 framework[26]. In other words, it is critically important to directly compare the efficiency and quality of remote and in-person clinical trial methods using experimental designs in order to make informed decisions.

Our first-of-their-kind randomized controlled trials (RCTs) comparing remote vs. in-person methods on trial accrual and trial quality will markedly advance the remote trials translational science evidence base. As described by former NCATS Director Dr. Austin, translational science is the science of science, an emerging field central to the NCATS mission that seeks to understand – and address – inefficiencies in translational research[27]. From this perspective, RCTs are not only the gold standard for comparing the efficacy of candidate treatment approaches; they are a powerful translational science tool for experimentally evaluating the impact of remote vs. in-person methods on trial efficiency and quality, understanding the mechanisms that are responsible for those differences, and testing mechanism-informed approaches to enhance the efficiency and quality of future trials [28–33]. Thus, our proposal is directly responsive to PAR-22-167's call for "bold, new, innovative experimental approaches" that address "… approaches to improve clinical research and clinical trial efficiency (e.g., …clinical trial designs, virtual clinical trials, hybrid and decentralized clinical trials)."

Although there are many metrics of trial efficiency, we focus here on accrual efficiency (Aims 1 and 3), the successful enrollment of participants in a timely manner. Many RCTs fail to achieve their accrual objectives [34–36] and, as a result, are often underpowered to detect true differences in treatment efficacy and/or safety [36], leading to false negative trial results and impeding treatment development. The rationale for remote accrual is straightforward: By eliminating typical barriers to clinical trials participation, remote trials may reduce the recruitment bottleneck and foster greater enrollment. That said, there are barriers that remote trials will not necessarily address, and remote trials may introduce new barriers (e.g., technological barriers, privacy issues, and distractions) or exacerbate existing barriers (e.g., lack of trust/rapport) [6,19]. It bears repeating that these hypothesized strengths and weaknesses of remote trials accrual efficiency (e.g., recent cross-sectional data suggest remote interventions may in some cases widen health disparities [22]) are just that – hypotheses that have not previously been subjected to rigorous evaluation. As detailed below, we will experimentally evaluate the degree to which remote trial methods increase accrual efficiency relative to standard in-person methods.

Even if remote trial methods markedly outperform in-person methods in terms of accrual efficiency, they may do so to the detriment of trial quality (Aims 2 and 4), which we operationalize using metrics common to many if not all clinical trials: 1) retention, 2) treatment adherence/utilization, and 3) biospecimen collection. For a trial to accurately estimate treatment effects, it must be implemented with fidelity. Excessive attrition, missing data because of missed or incomplete visits, and poor treatment adherence are major threats to internal validity. While the quality of remote vs. in-person trials has been the subject of considerable conjecture [1,3,6–19], the proposed experimental evaluations are

significant for markedly advancing our understanding of the quality of data from remote vs. in-person trials.

Our focus on multiple "use cases" enhances the impact and generalizability of our approach across conditions and treatments. No single use case promotes the generalization that we and NCATS seek. Thus, we focus on three different interventions (pharmacotherapy, mobile Health, training/education) for three different major public health problems [20,37–42] (cigarette smoking, depression, opioid overdose), allowing for a robust test of generalizability. In the UG3, we propose a larger, multi-site RCT (RCT1) on pharmacotherapy for smoking cessation. In the UH3, we propose two smaller, single-site demonstration projects (RCT2 and RCT3) designed to facilitate/evaluate condition/treatment-agnostic generalizations. RCT2 focuses on a mobile health (mHealth) intervention for depression, and RCT3 focuses on a training/educational intervention with naloxone distribution to reduce opioid overdose. To further enhance generalizability, we take a purposively heterogeneous approach to sampling design particulars to promote generalizability[43], varying sites, recruitment strategies, and biospecimens (Table 1). To be clear, we are not focused on typical clinical outcomes (e.g., smoking cessation, depression, or opioid use) but rather the impact of remote methods on trial accrual efficiency and quality (see Aims and 6.c). Our collaborative, multi-RCT approach, using pre-specified, harmonized outcomes across the proposed trials, embody the "whole is greater than the sum of its parts" concept (PAR-22-167).

Table 1. A Purposively Heterogeneous Approach to Maximize Generalizability

Study Characteristic	RCT 1	RCT 2	RCT 3
Condition	Smoking	Depression	Opioid Overdose
Intervention	Medication	mHealth	Training
Sites	UB, UPenn	MUSC	UAB
Recruitment Source	Soc Media, Radio	EHR	Clinic/Comm Flyers
Biospecimen	Breath CO	Saliva	Urine

Notes. CO=carbon monoxide; Comm=Community; EHR=electronic health record; mHealth = mobile Health; Soc=Social

We recognize that these three use cases cannot ensure generalizability across all diseases and treatment modalities. However, we believe it is reasonable to start with behavioral/mental health conditions because: (1) they are major contributors to morbidity and mortality in the US [20,37–42]; (2) the treatments employed (pharmacotherapy, mHealth, and training/education) are generalizable across many diseases; (3) they are among the most appropriate for remote trial methods, with many other conditions requiring assessment and/or intervention (e.g., surgery, chemotherapy) that preclude fully remote and many remote/in-person hybrid options; and (4) they allow robust harmonization of study design and outcomes across trials, which strengthens the proposed evaluation of disease- and treatment-agnosticity. Future work will be needed to fully evaluate generalizability. However, given that we currently have no experimental data on the impact of remote trial methods at present, the proposed trio of harmonized

trials provides an outstanding foundation for guiding trial design with rigorous evidence over anecdote.

Our results, regardless of outcome, will inform the design and implementation of future clinical trials throughout the CTSA network and beyond. Regardless of results, data from these RCTs will strengthen the translational science evidence base for choosing remote vs. in-person approaches in a wide range of trials and provide a foundation for further translational science in this area. If the remote group outperforms the in-person group on accrual efficiency (Aims 1 and 3), without compromising trial quality (Aims 2 and 4), trialists would have a strong rationale for choosing remote methods in the future. Conversely, at the extreme, if the remote methods do not significantly enhance accrual efficiency and compromise trial quality, the results would provide an evidence-based counterpoint to the remote trials zeitgeist and provide preliminary data on optimal hybrid designs. Moreover, assessment of qualitative data from participants will inform future research and dissemination, and the proposed cost analysis will inform and guide key stakeholders (e.g., NIH, trialists, participants) on budgetary impact of remote vs. in-person trial methods.

The impact of the proposed work is further strengthened by our exploration of the impact of remote methods on participant diversity (Exploratory Aim 5). As we discuss in our recent JAMA viewpoint [23], remote trials may improve participation more among some groups than others; alternatively, remote trials designs diminish trial participation in other groups. We will leverage this timely and important opportunity to better understand the effects of remote methods on the critical issue of diversity, with a specific focus on racial/ethnic diversity. Minoritized groups face significant health inequities yet remain underrepresented in clinical trials and, for this reason, are a critical focus of the CTSA network (e.g., CTSA Goal 3, NOT-TR-19-015, and a recent JCTS Special Issue 44). Further, our consideration of SDOH, self-reported barriers to clinical trials, and participant preferences for remote vs. in-person visits will deepen our understanding of the effects of remote methods as a function of sample diversity. [22,45] We will take a similar approach in considering other participant factors related to health equity. For example, because remote trial methods rely largely on access to technology, we will explore whether and how remote trial methods fare for engagement of participant sub-groups that are least likely to use the internet and/or do not have broadband access, such as adults over 65 years of age (compared to younger participants) and residents of rural areas (compared to urban areas) (see [23]).

Finally, the overall impact of the proposed work is enhanced by our focus on dissemination of the methods and results of the proposed studies so that our work will benefit and inform future studies throughout the CTSA network and beyond in a sustained fashion (see HSCTI 4.7 – Dissemination Plan and Sustainability Plan). Thus, "…the deliverables and outcomes available at the completion of the project will improve the efficiency and effectiveness of clinical translation…" (PAR-22-167).

2. **Innovation**

To be succinct, there has never been an experimental test of in-person versus remote trial methods. Our proposal fills this critical gap and responds directly to PAR-22-167's call for "bold, new, innovative experimental approaches…" with three first-of-their kind RCTs. Innovation is strengthened by conducting these RCTs in three different conditions, with three different treatment modalities, and across four CTSA hubs, with harmonized primary outcomes across the RCTs. Additional innovations include: a relatively novel 2-stage randomization that addresses critical problems with typical 1-stage randomization and enables the evaluation of select hybrid designs (see 5.2); the use of emerging tools to reduce fraud and enhance remote biospecimen capture (see Prelim Studies 4.1); our exploration of the degree to which remote methods address issues related to participant diversity and health equity in clinical trials (Exploratory Aim 5). Thus, the proposed research uniquely and substantially advances the evidence base regarding remote trial methods.

3. **Collaboration**

The proposed translational science is a collaboration among scholars at five CTSA hubs: the University at Buffalo (UB; Drs. Hawk, Mahoney, & Wilding) Clinical and Translational Science Institute, the Medical University of South Carolina (MUSC; Drs. Dahne, & Carpenter) South Carolina Clinical & Translational Research Institute, the University of Pennsylvania (UPenn; Dr. Schnoll) Institute for Translational Medicine and Therapeutics, the University of Alabama at Birmingham (UAB; Drs. Cropsey, Li, & Nghiem) Center for Clinical and Translational Science and Wake Forest University (WFU; Allen) Wake Forest Clinical and Translational Science Institute. Consistent with PAR-22-167, the proposed work represents both new cross-CTSA collaborations (UB-MUSC and UB-UAB; MUSC-UPenn, UAB-UPenn) and significantly expands the scope of existing UB-UPenn and MUSC-UAB collaborations.

Table 2 summarizes the contributions of each hub to the proposal (see also Milestone plan and HSCTI 2.7 and 3.5). We have extensive expertise in conducting RCTs for the proposed use cases (see 4.2). The UB group's experience transitioning from in-person to remote visits [3,4] (see 4.1) and their translational science efforts in the CTSA network (see Eligibility Statement) led them to conceive of the proposed evaluation of remote trial methods. The UB team recruited the MUSC team for its' widely recognized expertise in remote trials involving multiple use cases and development of tools to facilitate remote trials (see 4.1). Recognizing that a remote trial approach may represent a method for increasing access to clinical trials,

Contribution	UB	Penn	MUSC	UAB
Domain Expertise				
Translational Science	X			
Remote Trials Methods			X	
Implementation Science		X	X	
Qualitative/mixed methods			X	
Cost analysis				X
Smoking/med. (RCT1)	X	X		
Dep./mHealth (RCT2)			X	
Opioids/Education (RCT3)				X
Project Activities				
Project Design	X	X	X	X
Project Management	X		RCT2	RCT3
IRB/Regulatory/SOPs	RCT1	RCT1	RCT2	RCT3
Data Collection	RCT1	RCT1	RCT2	RCT3
Data Management/Analysis	X		X	X
Dissemination	X	X	X	X

especially for under-resourced populations, we recruited UPenn's Dr. Schnoll for his expertise in implementation science (see 4.3). Since late 2020, the UB, MUSC, and UPenn investigators have met bi-weekly to develop and refine this proposal. In consultation with NCATS program staff, we agreed it was important to conduct an additional dissemination project in the UH3 phase. In the Summer of 2022, we recruited UAB's Dr. Cropsey (a long-time collaborator with MUSC46,47) to lead RCT3, which focuses on an education and naloxone intervention to prevent opioid overdose (see 4.2). UB, as the lead site, will oversee harmonization of data across studies/sites and primary data management and analyses.

All hubs were involved in the development of the research plan and harmonized outcomes. In response to reviewer comments, we have further strengthened and expanded collaboration. Across all RCTs, UAB's Dr. Nghiem (a collaborator of Dr. Cropsey's) will lead a micro-cost analysis of remote vs. in-person methods (see 6.3), and WFU's Dr. Allen (a collaborator of Dr. Dahne's), will conduct qualitative interviews and analyses (see 6.3). Consultant Dr. Rachel Shelton (a collaborator of Dr. Schnoll's), from Columbia University/Irving Institute CTSA, brings expertise in health equity and SDOH to strengthen our approach to understanding and enhancing participant diversity (Aim 5). All hubs will be involved in decisions about any UG3-to-UH3 modifications (see Milestone Plan) and in dissemination efforts in the UH3 Phase (see Dissemination Plan).

Our proposal benefits from the input of additional key partners. The need for evidence-based guidance on remote trials is reinforced and informed by the MUSC team's recent Remote Trials Roundtable (see 4.1) and Dr. Schnoll's (UPenn) leadership of a nation-wide group of trialists' on the transition to a remote framework for trials for persons with HIV2. Our consultation with the Trial Innovation Network (TIN Consultation #817) solidified our single IRB plan, which employs SmartIRB (see letters of support), and we will continue to consult the Recruitment Innovation Center (RIC) on use of the MyCap smartphone app for remote assessments. The UB team secured Gregory Wilding, Ph.D., Director of the UB CTSI Biostatistics, Epidemiology, and Research Design (BERD) core, as the project statistician, and has worked with the UB REDCap team to develop and refine the plan for electronic data capture, e-consent, and project management for this multi-trial proposal. As in our ongoing work, we will work closely with the Clinical Research Facilitation, Community Engagement, and Recruitment and Special Populations cores of the UB, MUSC, UPenn, and UAB hubs. Finally, given the alignment of the proposed work with NCATS' focus on translational science in general [27] and CTSA Goal 3 in particular, we look forward to working with NCATS, the Center for Leading Innovation & Collaboration (CLIC), and other CTSA hubs to disseminate project results, implement tools and approaches, and take the next steps in programmatic translational science around remote trials (see HSCTI 4.7 – Dissemination Plan).

4. **Preliminary Studies**

4.1. **Experience with remote trial methods**.

4.1.1. UB hub. The proposed project was conceptualized by Drs. Hawk and Mahoney after they completed a mixed methods, quasi-experimental study of shifting from in-person to remote visits (caused by the COVID-19 pandemic)[3,4]. A small cohort (n=23) followed remotely during the shutdown of in-person visits was compared to a pre-COVID-19 in-person cohort (n=51) to examine the rates of visit completion and biospecimen collection. Qualitative data from the COVID-19 cohort revealed that although 87% were willing to engage in remote visits in the future and many reported benefits (not having to travel [73%], feeling more comfortable in their homes [47%]), participants also experienced challenges with remote visits (less personal interaction and support [40%], less accountability to adhere to treatment [33%], challenges with remote technology [33%]). Quantitatively, participants in the remote cohort completed an average of 84% of visits and returned 93% of mailed saliva specimens, neither of which was significantly lower than the in-person rates in the pre-COVID-19 cohort (90% and 100%, respectively). Though these data suggest that remote visits did not weaken trial quality, there were important limitations: (a) the pandemic stay-at-home order may have made it easier to complete remote visits, (b) "remote" participants had already completed in-person visits, weakening the remote vs. in-person contrast, (c) sample size was modest, limiting statistical power to detect differences, and (d) the nonrandomized, quasi-experimental design leaves the interpretation open to potential confounds. Thus, rigorous research, as proposed here, is needed to assess the impact of remote treatment and assessment on trial quality.

4.1.2. MUSC hub. Drs. Carpenter and Dahne co-direct MUSC's Remote and Virtual Trials Program, a component of the MUSC CTSA. Dr. Carpenter has led clinical trials for over 15 years. Much of his work focuses on product sampling to increase rates of quit attempts and smoking cessation, including 3 trials of nicotine replacement therapy (NRT)[48–50], 1 study of snus[51], 2 studies of e-cigarettes [52,53], 1 study of varenicline [47], and 1 newly funded trial of NRT vs. varenicline. All but 1 of these studies have been remote large-scale trials. Although the outcome data are impressive, the data on trial accrual efficiency are most germane to this proposal. Each of these remote trials met or exceeded the target sample size and did so remarkably quickly, enrolling an average of 743 participants (range=100-1245) at an average rate of 44 patients per month (range=8-81) – a stark contrast to many in-person studies. Thus, Dr. Carpenter's remote trial experience not only demonstrates the feasibility of the proposed study, it also provides excellent preliminary data for our hypothesis that remote enrollment enhances clinical trial accrual efficiency (Aims 1 and 3). Moreover, retention rates were also impressive: 78-90% of all study "visits" were completed (see Aims 2 and 4).

Drs. Carpenter and Dahne have also led the development of methods to improve the efficiency and quality of remote trial methods. Their recent review discusses these tools in depth[7], many of which we include in the proposed study: remote screening, tele-consent, automated assessment, and remote biomarker collection. Here we focus on recent innovations led by Dr. Dahne that will be employed in

the proposed RCTs: Cheatblocker will be employed for all proposed RCTs; iCO™/REDCap integration will be used in RCT1.

"Cheatblocker" detects participants who repeatedly complete study screening to prevent their fraudulent entrance to a trial. The plugin is available to all CTSAs via the REDCap Repository of External Modules. In 23 months since release, cheatblocker has been implemented by 60 institutions, demonstrating our capacity for disseminating disease- and treatment-agnostic innovations to the broader CTSA community.

iCO™/REDCap integration is part of Dr. Dahne's work to improve remote biomarker collection. In an R21, Dr. Dahne developed a system that pairs a smartphone-enabled carbon monoxide (CO) monitor, the iCO™, with REDCap. The system is low-cost (c.f., assay of mailed salivary cotinine) and maintains rigor because it video-records the participant (allowing confirmation of participant identity) and syncs all data in an individual REDCap record. In a recent remote trial (NCT04155073), compliance was similar across demographic groups (e.g., Race/ethnicity: 72% White/non-Hispanic vs. 67% non-White/Hispanic; Rurality: 71% rural vs. 72% nonrural). Dr. Dahne recently received NCATS funding (R41 TR004224) to expand this platform in a disease agnostic fashion to include additional remote patient monitoring devices. The goal of this work is to disseminate these tools across the CTSA network and beyond to improve the quality of remote clinical trials.

4.1.3. UAB hub. Dr. Cropsey's recent, large clinical trial (R01 DA039678) began enrollment 2/8/2017, with the goal of randomizing 500 participants under criminal justice supervision using traditional in-person RCT methods. After enrolling 233 participants (In-Person), compensation was augmented to improve retention (Incentive; N=129). When clinical trials transitioned to remote methods due to COVID-19, Dr. Cropsey consulted Drs. Carpenter and Dahne for best practices. In March of 2020, the trial successfully transitioned to remote methods (except for baseline assessment) while maintaining the higher compensation (Hybrid; N=153) and incorporating biochemical verification via the iCO. Dr. Cropsey recently completed long-term follow-up with all participants (10/13/2022) and examined retention across the three groups to inform our study design herein. While retention among all three groups was similar during the intervention weeks (W1-W4), by Month 3 the Hybrid group (66%) had better retention than the In-Person (60%) or Incentive (57%; p=0.044) groups. By Month 6, the Hybrid group had a retention rate of 68% compared to In-Person (56%) or Incentive (60.5%; p=0.016). Participants demonstrated 90.5% adherence with sending CO measurements via the iCO across all study time points, demonstrating the feasibility of this approach. While promising for remote treatment, these non-experimental data are subject to numerous limitations (see 4.1.1).

4.2. **Experience conducting large-scale RCTs on the proposed use cases**.

4.2.1. RCT 1: Pharmacotherapy for cigarette smoking. Over the past 20 years, Drs. Hawk and Mahoney (UB) and Schnoll (UPenn) have led or co-led many

smoking cessation RCTs involving medication (nicotine replacement therapy [NRT], varenicline, bupropion)[54–61], and they collaborated on a large, pharmacogenomic multi-site RCT (U01 DA020830)[62]. The UB team conducted a programmatic, theory-based series of RCTs testing a treatment modification designed to enhance the ability of these medications to reduce smoking reinforcement (R21 CA111763; Pfizer GRAND; R01 CA206193)[59–61]. Many of Dr. Schnoll's trials focus on under-resourced sub-groups of smokers, including those with HIV63, cancer[54], and serious mental illness [64,65]. He has also led NCI-supported groups to review and document study design alterations, including moving to remote trial designs as a consequence of COVID-192. His current grants examine implementation strategies to enhance utilization of evidence-based treatments (P50 CA244690; K24 DA045244; R01 HG012670) [66].

4.2.2. RCT 2: mHealth treatment for depression. Dr. Dahne has expertise in the development, evaluation, and dissemination of mHealth interventions and is PI of five active NIH grants in this area (R01 CA268023; R01 CA258669; R41 DA053856; R42 MH108219; K23 DA045766). One line of work focuses on expanding the reach of evidence-based depression treatment by developing a self-guided mobile app adaptation of Behavioral Activation (BA) treatment for depression[67]. The resulting mHealth intervention, called "Moodivate", is feasible, acceptable, and efficacious [68,69]. Regarding feasibility and acceptability, whereas most publicly available mHealth interventions have poor engagement[70], nearly 70% of Moodivate participants continued to use the app 4 weeks after initial download. Compared to a Treatment as Usual (TAU) control, Moodivate participants had significantly greater decreases in depression which were sustained across the trial period[110]. At study end, 53% of Moodivate participants (vs. 25% of TAU) had less than minimal symptoms of depression. Dr. Dahne is currently evaluating Moodivate via a large-scale clinical effectiveness trial across 20 MUSC primary care and family medicine clinics (planned N=635). Trial enrollment has been ongoing for 24 months and the current n=609 (25 participants enrolled per month). This ongoing trial utilizes the same study recruitment procedures that will be deployed within the MUSC demonstration project, highlighting feasibility of study recruitment.

4.2.3. RCT 3: Training interventions for prevention of opioid overdose. Dr. Cropsey's UAB team has conducted two opioid overdose prevention and naloxone distribution trials; one used traditional in person training/distribution methods with phone follow-ups and one was fully remote (F31 DA052158; Dr. Carpenter from MUSC was a collaborator). The in-person trial recruited from high-risk venues such as the ED and treatment facilities, resulting in 438 participants recruited over 36 months, in contrast with the remote trial that recruited via online platforms in three states and recruited 111 participants over 11 weeks. Overall, remote methods resulted in similar rates of opioid overdose knowledge after training and high treatment satisfaction. Specifically, the remote trial (vs. traditional recruitment) resulted in similar increases in opioid overdose knowledge (remote: M=6.8/9 pre- and M=8.2/9 post-training; $p<0.001$ vs in person: M=7.4/9 pre- and M=8.3/9 post-training; $p<0.001$), more reversals (e.g., 16% vs. 11%), faster recruitment (M=8.9/week vs. M=2.8/week), and higher

retention (3 month follow-up: 94% vs 50.3%). However, these two separate trials were not a randomized test of remote vs. in person methods such as proposed herein.

4.3. Experience with disease- and intervention-agnostic translational science in the CTSA network and beyond.

Most trialists do not take a disease- and treatment-agnostic translational science [27] perspective. We do.

4.3.1. UB hub. Dr. Hawk takes a distinctly translational science approach as Director of the UB CTSI's biennial Creative Scientist Workshops (CSWs), facilitated events designed to foster cross-CTSA innovation and collaboration in addressing the major barriers faced by the network. He also led a supplement (UL1 TR001412-03S1) to conduct the first-ever RCTs to evaluate the impact of a promising method for stimulating and nurturing new cross-CTSA collaborations[71]. The provocatively-titled 2021 CSW, Remote Trials: Future or Fiasco?, featuring a keynote by the Director of the National Institute of Minority Health and Health Disparities and attended by representatives of 32 CTSA hubs, focused on the same important but largely unanswered questions that drive the current proposal (see Eligibility Statement for additional information).

4.3.2. MUSC hub. The REDCap plug-ins developed by Dr. Dahne (e.g., cheatblocker; see 4.1.2) are versatile tools that can enhance trials for a range of conditions, and the MUSC Remote and Virtual Trials Program, which Drs. Carpenter and Dahne co-direct, is explicitly disease- and treatment-agnostic, as is Dr. Allen's qualitative work on a population-wide genomic screening program [72–75]. Moreover, Dr. Dahne was recently named the inaugural Director of Translational Science for MUSC's CTSA, which will allow her to lead efforts to advance translational science both within MUSC's CTSA and across the CTSA network.

4.3.3. UPenn Hub. Dr. Schnoll is a national leader in implementation science, and his work covers a range of diseases and treatment modalities. For example, he serves as PI on an NCI-funded P50 (CA244690) that supports 5 clinical trials focused on testing the use of implementation strategies informed by behavioral economics to improve utilization of evidence-based interventions (i.e., tobacco treatment, serious illness conversations, patient reported outcomes, MRI for breast cancer early detection for women with dense breasts, and breast and ovarian cancer genetic testing). He is also PI of an NHGRI grant (R01 HG012670) testing implementation strategies to improve the use of genetic testing to guide treatment in neurology and cardiology. Dr. Schnoll is a mentor for NCI's Training Institute for Dissemination and Implementation Research in Cancer (TIDIRC) and Washington University's Institute for Implementation Science Scholars.

4.2 Include complete citations or references.

Response:

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5.0 Study Design*

5.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: Interventional - This study will employ a randomized, parallel-group design. After an initial verbal consent and Phone Screen for basic eligibility, participants will be randomized (within-site) to complete either a Remote or In-Person (IP) Intake Visit. Except for mode of delivery (remote vs. in-person), the Intake is identical for the two groups. Participants who are eligible at the Intake will be re-randomized (within site and Intake Group) to complete either Remote or In-Person Treatment and Assessment Visits. Except for mode of delivery (remote vs. in-person), treatment/assessment is identical for the two groups.

Thus, the design is a 2 Remote vs. In-Person Intake Group x 2 Remote vs. In-Person Treatment/Assessment Group factorial design. (See Study Schema below)

Study Schema

Randomization #1: R vs IP Intake

Randomization #2: R vs IP Intake Treatment/Assessment

Trial Module	**Screening**		**Treatment and/or Assessment**				
Activity	**Quick Screen**	**Intake Visit**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Week			0	1	3	9	13
Group		R	R	R	R	R	R
			IP	IP	IP	IP	IP
		IP	R	R	R	R	R
			IP	IP	IP	IP	IP

Notes: IP = In-Person; R = Remote

6.0 Study Intervention/Investigational Agent

6.1 Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.

Response: Although all study participants will receive dual NRT (patches and lozenges) to help them quit smoking, the intervention being evaluated in this study is random assignment to remote vs. in-person Intake and random assignment to remote vs. in-person treatment and assessment.

6.2 Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those

drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response: All participants will receive an 8-week supply of NRT patches and lozenges during their participation. NRT will be stored in a locked cabinet inside a locked room on a restricted-access floor in Diefendorf Hall on the UB South Campus. The project coordinator and senior staff will be responsible for overseeing the distribution of NRT to in-person participants and the assembly of "Care Packs" that will be sent to remote participants. Logs will be used to maintain inventory and ensure that products are used only by research participants.

6.3 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response:

N/A (nicotine replacement therapy is being used consistent with over-the-counter labeling)

7.0 Local Number of Subjects

7.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: The UB site will enroll 100 participants into the study. The University of Pennsylvania will also enroll 100 participants into the study. Total enrollment = 200 participants.

Update 2026.04.21: Updating accrual number so that UP TO 102 people at each site may participate. We are nearing the end of recruitment and need to accrue our last participants into the study in early May. Increasing the accrual goal will mean that we don't have to withhold treatment for 1-2 people at each site who were recruited before the study ended. Note that we may not need to go up to 102 at one or both sites but we want that option in case it's needed.

7.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response: We estimate that at each site ~330 participants will be screened by phone for basic eligibility and that ~165 will be eligible on the phone screen. We anticipate that ~124/165 will attend the intake visit, and that ~20% will be screening failures at intake or drop out prior to completing the study.

7.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: Each CTSA hub has extensive experience conducting clinical trials (see Preliminary Studies in Section 4.0 above). Community participants will be recruited via social media web sites (e.g., Facebook), print media (e.g., at primary care offices, community organizations), radio and/or TV advertisements. We will employ targeted advertising to over-recruit participants from racial/ethnic minority backgrounds. We will accrue ~11.1 participants per month (~5.5/site/month x 2 sites) who initiate treatment from Year 1, Month 7 through Year 2, Month 12. The feasibility of meeting our accrual goals is supported by our recent and ongoing in-person trials with smokers (see Preliminary Studies in Section 4.0 above). For example, in 2020, the Buffalo hub enrolled 100 community participants in a much more demanding study (10 visits/participant, including 2 lengthy lab visits under acute abstinence from smoking, as well as 9 weeks of daily ecological momentary assessment; (R01 CA206193), despite enrollment for all non-COVID trials at our university being closed for 2.5 months due to the COVID-19 pandemic.

8.0 Inclusion and Exclusion Criteria*

*8.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

Inclusion criteria:

- Age18+ years
- 5+ CPD for 6+ months

• At least moderate motivation to quit smoking (Motivation to Stop Scale - 4-item version (corresponds to 6+ on the Motivation to Stop Smoking Scale)
• Stable residential address (where mail can be received; can also have PO Box) within 1.5 hours of study site (per self-report)
• Able to read, speak, and verbally comprehend English
• Valid e-mail address that is checked regularly or regular access to text messages (to access follow-up assessments)
• Own an iOS or Android smartphone
• Willing to be randomized to attend remote or in-person visits
• Agree to refrain from use of other tobacco products and use of non-study cessation treatments while participating in the trial

*8.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

Exclusion criteria:

• Use of tobacco/nicotine products other than cigarettes (except blunts, spliffs, cigars, little cigars, cigarillos) for average of 5+ days per week over the past 3 months
• Allergy/intolerance to NRT patch or lozenge
• Pregnant, breastfeeding, or planning to become pregnant in next 4 months
• Use of varenicline, NRT (e.g., patch, gum, lozenge), or bupropion in past 7 days for purpose of quitting smoking
• Consumption of >28 alcohol-containing drinks per week

• Suicide attempt with at least some wish to die in past 3 months
• Mental illness (such as schizophrenia, bipolar disorder, or major depression) that led to hospitalization in the past 30 days
• Unable/unwilling to provide informed consent or follow directions, inappropriately responsive, based on staff observations
• High risk involvement with illicit or nonmedical prescription drugs (NIDA-modified ASSIST=27+
• Only for participants who are 21 years old and older: refusal to provide a pack of cigarettes for documentation at the Intake visit

8.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response: We will <u>not</u> include any of the special populations noted below.

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

8.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: We will *not* include non-English speaking individuals because the study requires independent completion of extensive self-report questionnaires, most of which have not been validated in languages other than English.

9.0 Vulnerable Populations*

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

9.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

☒ **N/A**: This research does not involve pregnant women.

9.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

9.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

9.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

9.5 For research that involves ***cognitively impaired adults****, safeguards include:*
NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

9.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. ***Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response: N/A This study does not target vulnerable populations.

10.0 Eligibility Screening*

10.1 Describe ***screening procedures*** *for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response: After obtaining verbal consent, potential subjects will be screened by telephone for most eligibility criteria (see section 8). Participants eligible based on the phone screen will be invited to attend an intake visit. At the intake visit, participants will receive an overview of the study and, if interested, provide informed consent. Interested participants will complete additional screening procedures (see section 8), as we will assess baseline characteristics (see section 12.3).

We will provide smoking cessation referrals for people who are not eligible for the RISE Above Smoking study and who still want to quit smoking. We will also provide a social services referral for people who endorse having difficulties on the Accountable Health Communities Core Health-Related Social Needs Screening Tool.

- Smoking Cessation Programs Philadelphia_03.07.25
- Smoking Cessation Resources for NY State 03.07.25
- Social Services Resource 03.07.25

All eligibility criteria are described in the Section 8. Data will be collected with the following attachments:

- RISE Phone Screen – 2024-10-23.docx (1/21/25 – gender identity response options updated)
- Eligibility Screening Questions from Intake.docx
- NIDAQS1_VASPVapingAndSmokingRev.pdf

☐ **N/A:** There is no screening as part of this protocol.

11.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

11.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response: Community participants will be recruited through study advertisements and research registries. We will employ some/all of the following approaches.

Flyers
Flyers with basic study information, including contact information, may be placed (with permission) in local businesses and public bulletin boards, and provided to participants in other ongoing research studies.

In-House Data Bases
We maintain lists of participants in previous/ongoing studies who have indicated their interest in learning about new research projects.

Meta (Facebook and Instagram)
We will advertise on Facebook and Instagram via Meta's standard interface.

Meta Business Suite is used by institutions and businesses to expand the reach of advertisements to Facebook and Instagram users. These advertisements are created and run through a Facebook/Instagram business account that allows for ads to be placed in relevant users' feeds. Meta provides up-to-date data on advertisement performance (e.g., site visits, time spent viewing an advertisement, etc.), which will allow our research team to gain more insight about how to adjust our advertising to maximize the number of leads we receive.

Meta is affordable and user-friendly. This platform allows the advertiser to control the stream of ad exposure to potential research participants by allocating certain amounts of money that will determine the number of ads displayed for Facebook and Instagram users . Meta will charge us based on the number of impressions an ad receives. Because of this, Meta may be much more affordable than other recruitment companies used in this study (i.e. Build Clinical).

Meta provides it's privacy policy included at this link: https://mbasic.facebook.com/privacy/policy/printable/#1, which all users agree to upon the creation of their Facebook or Instagram account.

Ads will be developed through Meta Business Suite and ads will be posted on Facebook and Instagram. The ads will display stock/royalty-free

images downloaded from Pixabay (https://pixabay.com/photos/) and other websites that provide stock photography.

Each ad that will appear on Facebook and Instagram will have three components: 1) primary text, included as a caption on the advertisement, 2) an image, and 3) a link to a RedCap survey where can will fill out a brief questionnaire with their contact information and a few questions to assess their initial eligibility (Link to https://redcap.link/VASP). The RedCap recruitment survey that we will use will also have a CAPTCHA set up that the participant will have to complete before proceeding with the survey. The collection of personal information provided by an interested participant will be stored within a secure RedCap database, rather than being collected and stored by Meta.
Update 05/02/2025: UPenn will start advertising using Meta as soon as their ads are approved.
Update 11/14/2025: Headlines, images, and text for META ads at UB were approved on 12/2/2024 with our initial submission; we are now requesting approval for full ads

BuildClinical

The UB site will contract the services of BuildClinical to help us meet our recruitment goals. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. This resource has worked with IRBs in the US to ensure adherence to all appropriate guidelines and procedures. BuildClinical utilizes study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc. and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software encrypts all inputted information and keeps participant information private and HIPAA compliant. Their backend servers are stored in the US at some of the most secure data centers in the world.

BuildClinical provides a full privacy policy that is available to everyone who clicks through an ad to their landing page. The policy is available here: https://www.buildclinical.com/policy. The RISE study project coordinator will be provided with a secure login to access information entered on the BuildClinical website by participants interested in the RISE study. Participants will be contacted to provide more information and to assess initial eligibility through a phone screen. Their information will be kept in the secure RISE REDCap database.
Attachments include:

- Ads (_BCFS001380-UB-Hawk-Smoking-Feed.pdf)
- BCFS001380-UB-Hawk-Smoking [Landing Page].pdf
- BCFS001380-UB-Hawk-Smoking-Ad Copy.pdf
- BCFS001380-UB-Hawk-Smoking-ScreeningForm.pdf
- BCFS001380-UB-Hawk-Smoking-Video1.pdf
- BCFS001380-UB-Hawk-Smoking-Video2.pdf

Buffalo Research Registry

The Clinical and Translational Science Institute's (CTSI) Community Engagement Team (CET) hosts the Buffalo Research Registry (BRR), a resource that connects researchers looking to recruit participants and community members looking to get involved with research. To participate in the registry, volunteers complete a voluntary intake form. Volunteers have agreed to be contacted about potential research opportunities based on their self-reported information. Key personnel from the CTSI will serve as the conduit between our research team and the registry volunteers, will verify our IRB study approval, review inclusion and exclusion criteria and will sort the registry data accordingly. In terms of recruiting for our study, CTSI personnel will pull volunteer reports using the inclusion and exclusion criteria, will centrally invite volunteers to participate in the study and provide a warm hand off to our team. There are three ways we are sharing our study, including:

Electronically- Using the volunteer report from REDCap, key personnel from the CTSI will send initial e-mail invites to introduce our study to registry volunteers.

Post Mail- Key personnel from the CTSI will provide our team with contact information (i.e. first name, last name, post mail address) to prepare a mailing. This information will be shared in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail. We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed.

We also plan on conducting follow-up by phone/email after initial contact. This contact information will be provided in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail. We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed.

We will have no access to the health information provided in the registry.

ResearchMatch

ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch Network to use ResearchMatch for the purposes of conducting recruitment feasibility analysis or participant recruitment. The Vanderbilt IRB provides oversight for ResearchMatch as a recruitment tool and this has been documented within the ResearchMatch IRB Letter of Understanding (available upon request). However, individual requests to use ResearchMatch as a recruitment tool are required to be approved by the participating institution's IRB. Potential volunteers will be contacted using the IRB-approved content. Volunteers will then have the option of replying yes or no through a set of quick links available in the notification. If a volunteer chooses to

respond in the affirmative they will authorize ResearchMatch to release their contact information to the UB site who will be responsible for managing that information according to institutional guidelines.

11.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: We will only recruit via public advertisements to which interested participants self-identify and databases of prior participants who have given permission to be recontacted for future studies. In addition, we will only contact participants and collect study data by methods to which they have requested/consented. To enhance privacy and confidentiality during the phone screen, all phone screens will be conducted from secure offices in the Unit on Behavioral Health Research and Treatment (third floor of Diefendorf Hall).

11.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response:

NOTE: BuildClinical advertisements and strategies are still under development. We will submit them to the IRB via a modification to get approval before using them for study recruitment.

12.0 Procedures Involved*

*12.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response:

Prior to the start of the trial, the protocol will be registered on the clinicaltrials.gov registry.

Brief Phone Screen and Randomization #1 to Remote vs. In-Person Intake (~30 minutes). After a brief overview of the project and reminders that they can refuse to answer any questions and that they can stop the screen at any time, we will obtain verbal consent to initial screening. For those who agree, we will collect

contact information (e.g., phone, email, address) and demographics and screen for basic eligibility (including proximity to study site, tobacco and alcohol consumption, self-reported suicidality, other major unstable psychiatric conditions, and pregnancy). For supplemental analysis, we will also assess select SDOH and preferences for remote/in-person visits. Screen-eligible participants will be informed that the next 'visit' (Intake) will include full informed consent and additional eligibility screening. We will explain the rationale for random assignment to remote vs. in-person Intake (Randomization #1) and that, following the Intake visit, assignment to remote vs. in-person T/A (Randomization #2) will occur. After reminding participants of their right to withdraw at any time, we will obtain verbal consent (as with previous randomizations involving minimal risk[81,82]) to complete Randomization #1, after which we will schedule the resulting remote or in-person Intake visit.

(Randomization #1) to Remote vs. In-Person Intake Group and associated primary Aim 1 analyses will be stratified by site and race/ethnicity (as in our prior work, e.g., R01CA206193; this is important given our exploratory analyses involving the impact of remote trial methods for underrepresented groups, as described in Exploratory Aim 5).

Intake Visit (~1 hour). In-Person intakes will be completed at each clinical site (UB, UPenn). Remote intakes will be completed by Zoom (HIPAA compliant) by the research team that conducted the phone screen (UB or UPenn). Participants will complete e-consent and study assessments in REDCap (on their own device for remote Intakes). Other components of the visit will be identical for Remote and In-Person Intakes. Participants will receive a detailed overview of the study and, if interested, complete informed consent. Eligibility assessments include illicit/non-medical drug use and willingness to refrain from use of other tobacco/nicotine products and non-study cessation treatments while participating in the trial. We will collect detailed sociodemographics; baseline smoking characteristics and recent use of tobacco, marijuana, and alcohol; alcohol dependence; depression; additional SDOH; proficiency with mobile devices and computers; and baseline side effects.

To complement the self-reported smoking behavior, we will ask **only** those participants who are at least 21 years old to bring a pack of their usual brand of cigarettes to the intake meeting, letting them know that we will take a picture of the pack at the visit and that if they forget to bring a pack (it need not be full), then we will need to reschedule the intake. Participants who are at least 21 years old who refuse to show the pack of cigarettes at intake will be ineligible.

For in-person visits, we will also collect expired-air CO. Because it is cost-prohibitive to send CO monitors to all remote intake participants, and we want eligibility criteria to be comparable across remote and in-person groups, CO at in-person intakes will be recorded but not used to exclude participants.

For participants confirmed eligible at the Intake, we will complete Randomization #2 to remote vs. in-person T/A and inform the participant of the method of their

T/A visits. We will work with participants to choose a tentative target quit date (T/A Visit 2 – see Study Schema Figure in Section 5, above), around which we will schedule other T/A visits.

The second stage randomization (Randomization #2) to Remote vs. In-Person Treatment and Assessment visits) and associated Aim 2 analyses will be stratified by site as well as the Intake Group (Randomization #1).

Treatment / Assessment (T/A) Visits (30-60 min). Except for method of delivery, treatment is identical for the Remote and In-Person T/A Groups, consisting of 5 visits (see schedule of visits in Section 5, above) and, beginning at T/A Visit 2, a total of 8 weeks of dual NRT (long-acting patch plus short-acting lozenge).

Participants will be provided with "Care Packs" following the Intake Visit, and upon completion of T/A Visits 1 and 3. For in-person participants, Care Packs will be provided at the end of the visit. For Remote participants, we will mail Care Packs. This approach has worked well in recent trials (R01 CA206193; R01 CA243914; R21 CA241842). Care Pack 1 will include a personal CO monitor (remote participants only), standardized self-help materials, and a U.S. Bank card for remuneration. Care Packs 2 and 3 will consist of study medication for treatment Weeks 1-4 and 5-8, respectively.

At T/A Visit 1, participants will provide an expired-air CO sample (to assess recent smoking). Remote participants will receive a personal iCOquit™ Smokerlyzer© CO monitor in their first Care Pack along with instructions regarding downloading the iCOquit app and accessing a pre-populated account that can be accessed by them and study staff. At T/A Visit 1, staff will walk the participant through the procedure for providing a breath sample and verify the reading in the app account. In addition to CO, participants will complete study measures (detailed below), receive instructions on use of NRT, and be encouraged to review standardized self-help materials. Subsequent clinic visits are similar in process and content. Medication adherence is encouraged throughout treatment, and we will assess (via self-report) the amount of medication (patches and lozenges) used since the previous visit (for calculating adherence)[83] at T/A Visits 3 and 4. Participants will be remunerated following each completed visit ($30/visit for 6 visits [Intake and T/A Visits 1-5]; to avoid potential confounds, remuneration is identical for the Remote and In-Person conditions.) All remuneration is made by convenient, remotely reloadable Visa card.

Research staff provide participants with visit reminders via their preferred method of communication (phone, text message, email), and in-person participants will be provided with parking passes for study visits. These procedures have worked very well in our previous/ongoing work

If selected to do a qualitative interview about their study experiences (see Section 12.2 below), participants will be contacted after the end of their participation in the clinical trial.

Study medication. Participants will receive a total of 8 weeks of dual NRT (participants who smoke 11+ cigarettes per day will receive 21 mg patches to use for 8 weeks; participants who smoke 10 or fewer cigarettes per day will receive 14 mg patches; all participants will receive 2 mg lozenges, starting on the target quit date, T/A Visit 2); dual NRT is superior to single NRT products[84]. We will monitor adverse events, which are expected to be uncommon/mild, at each visit.

Operational definitions of adverse events (AEs) and serious adverse events (SAEs), as well as reporting mechanisms of AEs/SAEs to are described in the attached RISE AE/SAE Manual (see Attachments).

12.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response:

Aim 1: Accrual Efficiency. As is typical of RCTs, the primary metrics of accrual efficiency will be based on visit milestones. As detailed above, we hypothesize that the percentage of screen-eligible participants who attend the Intake Visit, a major accrual bottleneck for in-person trials, will be greater among those randomized to Remote compared to In-Person intake. Though dropout from Intake to T/A Visit 1 is typically modest, we will also calculate accrual efficiency from Intake-to-T/A Visit 1 and overall accrual efficiency (n achieving T/A Visit 1 / n for Randomization #1) for the Remote and In-Person Intake Groups.

Aim 2: Trial Quality. The internal validity of a clinical trial is seriously threatened by poor retention (especially differential attrition), extensive missing data, and/or poor treatment adherence/utilization, which is why we focus on these 3 domains of trial quality.

Retention. Using visit milestone data, we will calculate retention (n of T/A Visits 2-5 completed) for each participant, supplemented by visit-specific data to provide a detailed examination of the retention time course.

Biospecimen completion/return rates. In remote trials, a person may complete a 'visit' but fail to provide a biospecimen (e.g., the biospecimen materials are not in the same location as the participant) or may collect the biospecimen but not return it to trial staff. Therefore, for each participant, we will assess the number of biospecimens (expired-air CO readings) completed/returned (for T/A Visits 1-5).

Treatment adherence. Participants are instructed to use NRT for 8 weeks, beginning on the date of T/A Visit 2 visit; thus, medication adherence will be assessed at T/A Visits 3 and 4. As is typical[85], we will assess patch and lozenge use since the previous visit and convert the data to percent adherence.

The table below shows our primary outcomes for each study aim by study visit:

Trial Module	Screen	Treatment and/or Assessment				
Visit	**Intake**	**V1**	**V2**	**V 3**	**V4**	**V5**
Aim / Outcome						
Aims 1, 3, 5: Trial Accrual						
Intake Visit Attendance	X					
Aims 2, 4, 5: Trial Quality						
Retention (# visits complete)		N/A	X	X	X	X
Treatment Adherence/Utilization		N/A	N/A	X	X	N/A
Biospecimen completion/return rate		X	X	X	X	X

Notes. N/A = not applicable. Retention focuses on participants who attend V1 and treatment adherence/utilization will be assessed in 4-week intervals only at V3 and V4. V=Visit.

Exploratory Aim 5: Equity Moderators. Race and ethnicity, age, and other sociodemographic characteristics (e.g., gender, biological sex, relationship status, current address) will be assessed per the NIH-supported PhenXToolkit[86]. To better understand processes that contribute to differences between remote and in-person trial methods, including variability in these effects as a function of health inequities (Exploratory Aim 5), we will assess at screening/intake: (a) multiple brief indices of SDOH, including medical mistrust[87] and discrimination in health care[86], health literacy[86], insurance status[86], internet access[86], a composite measure of socioeconomic status that incorporates education, income, and occupation[88,89], and housing instability, food insecurity, and transportation problems[90]; as well as measures of willingness to use telehealth and access/comfort/proficiency with telehealth technology (as in[92,93]), and preferences for remote vs. in-person visits. We will also assess treatment outcome expectancies[94] (see also[48,95)] and self-efficacy[96] at T/A Visits 1, 2, and 3.

Additional measures. To characterize the sample and to consider, where appropriate, as covariates or exploratory moderators, we will assess nicotine dependence and smoking history[86]. Supplemental clinical measures include recent smoking and use of other tobacco/nicotine products, alcohol, and marijuana (self-report, using a timeline followback [TLFB] approach), expired-air CO, craving and withdrawal[86], and adverse events at all T/A visits; these clinical measures are not relevant to our specific aims but are included to support ecological validity – clinical trials always assess clinical outcomes. In addition, in keeping with typical procedures in smoking cessation trials, we will collect prescription medication information from each participant.

Qualitative interviews. To better understand participants' experiences in remote vs. in-person trial components, quantitative data will be supplemented with qualitative key informant interviews with ~15% of trial participants. The SOP for this research component (RISE Standard Operating Procedures for Qualitative Interviews.docx) is attached (see Section 12.3). Updated version submitted on 06/27/2025. This component will occur after the conclusion of each participant's study involvement (typically within 30 days of the scheduled date for the final visit, T/A Visit 5). Participants will be selected to enhance representative data from diverse perspectives (e.g., different study arms, diverse participant sociodemographic characteristics, completers vs. refusals/dropouts). Interviews will be conducted by Dr. Allen (WFU) and her staff using the

Consolidated Framework for Implementation Research 2.0 integrated with the Health Equity Implementation Framework (CFIR/HE)[97,98], which focuses on multilevel implementation determinants through a health equity lens (e.g. explicit consideration of factors like discrimination, stigma). The interview guide (attached in Section 12.3; updated version submitted on 06/27/2025) will assess participant's experience, satisfaction, and recommendations to identify multilevel facilitators and barriers to trial participation[97,98] and recommendations for enhancing future participant experience, including alternative hybrid designs. Interviews will be conducted via videoconference and audio-recorded. A REDCap form was created to track contact attempts, completion, and payment for qualitative interviews (attached).

Cost-effectiveness. We will use standard micro-costing techniques[99] to estimate the costs of implementation for remote vs. in-person trial methods. Using the societal perspective, we will account for both healthcare and non-healthcare costs incurred for researchers and participants[100]. Expenditures will be classified in one of four categories: 1) staffing/personnel, including fringe benefits; 2) other recurring costs, including supplies, medication, and services; 3) capital expenditures, including furniture and computers; and 4) overhead costs. To collect research cost data, we will implement a time and motion study[101,102] every quarter to capture staff time spent on pre-defined tasks involving remote and in-person trial components/participants (see RISE0Staff Time and Motion 2024.12.10.docx in section 12.3), and we will interview key staff to augment the assessment of resource use. Brief patient surveys (see RISE-PPT Cost survey 2024.12.10.docx in section 12.3) will gather information on time, work/productivity loss, transportation costs, childcare and/or eldercare, and any other forgone resources needed for their participation.

Update 05/02/2025: We are adding a survey for the participants to complete to assess their use of the Quit Kit.

Update 11/14/2025: Many participants in the (RISE) trial report experiencing significant stress that impacts their smoking cessation success, ability to attend sessions, and overall mental health. As major aims of the RISE study include the evaluation of accrual efficiency (i.e., intake attendance) and trial quality (i.e., retention rates and treatment adherence), it is important to determine the extent to which stress is affecting participants' ability to attend sessions and adhere to the treatment protocol. Further, it is important to understand the impact of perceived stress on the variance between remote and in-person attendance, with the latter requiring expenditure of additional time and financial resources for participants. To this end, we would like to add the 10-item Perceived Stress Scale self-report questionnaire to survey sets at five visits: Intake, as well as at Treatment and Assessment visits 1-4.

12.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response:

Characterizing the sample:

1. Fagerstrom Test of Cigarette Dependence (FTCD)
2. Smoking and Health History and Demographics (1/21/25 – added a sexual identity question)
3. Alcohol dependence/problems (AUDIT)
4. Depression (PHQ-8; without suicidal ideation question)

Social Determinants of Health:

5. Trust in Medical Researchers – Hall et al (2006; short form; https://www.phenxtoolkit.org/protocols/view/871102)
6. Discrimination in Health Care – Peek et al (2011; https://www.phenxtoolkit.org/protocols/view/280901)
7. Short Assessment of Health Literacy (SAHL - https://www.phenxtoolkit.org/protocols/view/270401)

7a. Health Literacy answer changes 2025.03.26

8. Internet access
9. Computer Proficiency Questionnaire (Boot et al, 2013)
10. Mobile Device Proficiency Questionnaire (Roque & Boot, 2015)
11. Treatment adherence – Med Accountability
12. Expired-air carbon monoxide (breathCO_VASP.pdf)
13. Timeline Follow-back (TLFB) for past 7-day use of tobacco/nicotine products, cannabis, and alcohol - TLFBSetup_VASPrevised.pdf
14. Craving (QSU-Brief)
15. Withdrawal (MNWS)
16. Side effect checklist (SEC)
17. Treatment outcome expectancies and abstinence self-efficacy
18. RISE Qualitative Interview Guide 2024-12-17
19. RISE Standard Operating Procedures for Qualitative Interviews 2024-12-17
20. RISE-PPT Cost survey 2024.12.10
21. RISE-Staff Time and Motion 2024.12.10
22. Medications_RISEDev.pdf
23. Quit Kit Assessment 2025.05.02

24. Qualitative Interview Form added to REDCap

Update 6/27/2025: To better characterize the sample, a question will be added to the Smoking and Vaping History and Demographics questionnaire that is completed at the orientation visit asking participants about their race. The additional questions were created using the PhenX Toolkit protocol which was developed using the All of Us Research Program survey. Please refer to SmokingHistoryAndDemographics_Updated 2025.06.27.

12.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: No source records will be used.

*12.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: No individual subject results will be shared with participants or others.

*12.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: We will maintain a list of participants who would like to be notified of study results and provide them with copies of the primary publication(s) that result from this study.

13.0 Study Timelines*

13.1 Describe the anticipated duration needed to enroll all study subjects.

Response: 18 months (see timeline in Section 13.3)

13.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response:
One Phone screen and randomization to remote vs in-person intake (~30 minutes)
One Intake visit (~1 hour)
Five Treatment / Assessment visits (30-60 minutes each)

Typical duration would be ~4 months, with ≤1 month between phone screen and intake and V1-V5 spanning ~3 months, as shown in the Study Schema figure in Section 5.

Participants who are selected to do a qualitative interview will be contacted within 30 days of completion of the main part of the study.

13.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response:

The figure below illustrates our projected timeline for major project activities across all months of the proposed 5-year project. Note that this protocol only covers activities RCT1 in the UG3 Phase.

PROJECT ACTIVITY	UG3 PHASE																								UH3 PHASE																							
	Year 1												Year 2												Year 3												Year 4											
	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
	1	2	3	4	5	6	7	8	9	0	1	2	1	2	3	4	5	6	7	8	9	0	1	2	1	2	3	4	5	6	7	8	9	0	1	2	1	2	3	4	5	6	7	8	9	0	1	2
Investigator & Staff Mtgs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mtgs with NCATS/TIN/RIC	X		X		X		X						X		X		X		X						X		X		X						X		X		X		X					
Dissem - Project Website		X	X	X	X	X	X			X				X			X			X			X			X			X			X			X			X			X			X		
Dissem - Webinars				X						X					X					X			X				X						X				X				X				X		
RCT1: IRB	X	X	X	X	X																																											
RCT1: Finalize SOPs	X	X	X	X	X																																											
RCT1: REDCap database	X	X	X	X	X	X	X	X	X																																							
RCT1: Hire/Train Staff		X	X	X	X	X																																									
RCT1: Dissem - CT.GOV				X																								X																			
RCT1: Recruitment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																								
RCT1: Data Collection																																																
Quantitative data on trial efficiency and quality				FE	X	X	FC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	LE	X	X	LC																						
Qualtitative interviews						X	X	X		X	X	X	X	X	X	X	X	X	X	X					X																								
Cost data				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																						
RCT1: QA, Data Reduction					X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	P	X	X	X	X	X	X	X																						
RCT1: Data Analysis																									X	X	X	X																				
RCT1: Dissem - Paper and Conference Submissions													X																X		X		X															
UG3 to UH3 Transition: Feasibility Assessment																	X	X	X	X	X																										
RCT2&3: IRB																				X	X	X	X																								
RCT2&3: Finalize SOPs																				X	X	X	X																								
RCT2&3: REDCap databases																				X	X	X	X			X																				
RCT2&3: Hire/Train Staff																						X	X		X																						
RCT2&3: Dissem - CT.GOV																									X																				X		
RCT2&3: Recruitment																									X	X	X	X	X	X	X	X	X	X	X	X	X	X									
RCT2&3: Data Collection																																																
Quantitative data on trial efficiency and quality																									FE	X	X	FC	X	X	X	X	X	X	X	X	X	X	X	LE	X	X	LC					
Qualtitative interviews																											X	X	X	X	X	X	X	X	X	X	X	X	X								
Cost data																									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
RCT2&3: QA, Data Reduction																										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
RCTall: Data Analysis																																									X	X	X	X	X	X	X	X	
RCTall: Dissem - Paper and Conference Submissions																																															X	
Dissem - Data sharing repository																												X																	X			
Dissem - CSW Planning																																																

Notes. CSW = Buffalo CTSI biennial Creative Scientist Workshop; CT.GOV = Registration on ClinicalTrials.gov; Dissem = Dissemination activity; FC = first participant complete; FE = first participant enrolled; LC = last participant complete; LE = last participant enrolled; Mtg = Meeting; QA = Quality assurance; P= site visit to the University of Pennsylvania site for RCT1; RCT = Randomized controlled trial; RCT1 = multi-site demonstration project; RCT2&3 = single-site RCT dissemination projects; RCTall = combination of all three RCT datasets.

As shown in the table, the 2-year UG3 Phase is focused on completion of a multi-site RCT demonstration project (RCT1 pharmacotherapy for smoking cessation) which will expand the translational science evidence base around the topic of clinic trial design. Specifically, RCT1 will assess the impact of remote vs. in-person methods on the key quantitative metrics of trial efficiency (accrual) and quality (retention, treatment adherence, and biospecimen collection); qualitative data from participants and cost data will also be collected. Key preparations for the UH3 phase will also be completed in Year 2, including the feasibility assessment.

We will accrue ~11.1 participants per month (~5.5/site/month x 2 sites) who initiate treatment from Year 1, Month 7 through Year 2, Month 12.

14.0 Setting

14.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response:

Space for participant recruitment, screening, and faculty/staff offices and meeting rooms is available in the Unit on Behavioral Health Research and Treatment (UBHEART); ~8000 sq. ft., located in Diefendorf Hall). As Co-Director of UBHEART, Dr. Hawk can ensure that the project will have access to all necessary resources. UBHEART is a secure facility, with key access to the elevator and swipe/key/intercom systems for stairwell entrance. In addition, rooms within UBHEART, particularly those containing study records, are locked in individual cabinets within individual rooms.

Dr. Hawk has tailored the UBHEART to facilitate large-scale clinical trials. A waiting room and kitchen with refreshments provide a welcome environment for participants, and a large seminar room provides ample space for study overview sessions and team meetings.

Examination and treatment rooms. Intake visits are easily accommodated in the five interview rooms in the UBHEART, all of which have one-way windows for unobtrusive observations. A medical exam room allows for a range of health-related assessments.

Pharmacy. The research pharmacy has an on-site room for storage of medications, reconciliation and randomization procedures, and relevant documentation.

Clinical assessments include 4 hand-held expired-air carbon monoxide monitors.

14.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response: The UB site research activities in this study are not conducted outside of UB or its affiliates.

☐ **N/A:** This study is not conducted outside of UB or its affiliates.

15.0 Community-Based Participatory Research

15.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☒ **N/A:** This study does not utilize CBPR.

15.2 Describe the composition and involvement of a community advisory board.

Response:

☒ **N/A:** This study does not have a community advisory board.

16.0 Resources and Qualifications

*16.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response:

Dr. Larry Hawk, Ph.D., Principal Investigator

My training, research experience, and history of collaboration make me an excellent fit as MPI on this project. My doctoral training in clinical health psychology provided me with an excellent background in theory, methods, and interventions for a range of health behaviors, and this expertise was enhanced by my post-doctoral fellowship at the University of Pittsburgh Cancer Institute. My ability to lead the proposed translational science randomized controlled trials of the impact of remote trial methods on clinical trial efficiency and quality (is

enhanced by: (a) my clinical research expertise in multiple health conditions (tobacco use, ADHD, and anxiety) and intervention modalities (pharmacotherapy, behavioral treatment), (b) my leadership of cross-CTSA, disease- and treatment-agnostic workshops (as Director of the biennial Buffalo CTSI Creative Scientist Workshops, which in 2021 focused on Remote Trials: Future or Fiasco?), and (c) my experience conducting innovative and rigorous randomized controlled trials to evaluate a promising approach to enhancing cross-CTSA collaboration (UL1 TR001412-03S1). Regarding cigarette smoking (the multi-site UG3 demonstration project), I have conducted (as PI, Site PI, and Co-I) many randomized clinical trials (RCTs) involving pharmacotherapy and behavioral counseling (e.g., R01 CA206193, U01 DA020830, R21 CA111763; see, Contribution 5). I have also collaborated with colleagues from a range of disciplines to conduct extensive mechanism-oriented experimental work on the neurophysiological, behavioral, cognitive, and subjective effects of withdrawal, drugs of abuse, and multiple medications. Thus, I am extremely well-suited to lead our team in the proposed RCTs evaluating the impact of remote methods on clinical trial efficiency and quality. I have worked productively with MPI Mahoney on several prior RCTs, including our recent trial involving remote visits (Mahoney et al., 2021) and a multi-site RCT with UPenn's Dr. Schnoll (e.g., Lerman et al., 2015). I am excited to substantially expand the scientific scope of that existing collaboration and form a new cross-CTSA collaborations with MUSC's Drs. Carpenter, Dahne, and Allen and UAB's Dr. Cropsey and Nghiem. Dr. Dahne and I recently co-wrote a JAMA Viewpoint (Dahne & Hawk, 2023) on the potential benefits and pitfalls of remote trials for enhancing health equity.

Dr. Martin Mahoney, M.D., Ph.D., Co-Investigator

I am a senior investigator, physician and cancer epidemiologist. My research has included several clinical trials related to the promotion of smoking cessation and/or harm reduction using novel approaches. As PI or co-investigator, I have played key roles in the design, successful implementation, analyses and interpretation of multiple clinical trials which have relied upon a variety of smoking cessation pharmacotherapies/interventions including: nicotine replacement therapy, nicotine free cigarettes, St. John's Wort, bupropion, a nicotine conjugate vaccine, a nicotine liquid delivery system and varenicline, noncombustible nicotine containing products/devices, as well as of high frequency repetitive transcranial magnetic stimulation (rTMS).

Most recently I have worked with Dr. Hawk to apply an extinction model of smoking cessation, initially pioneered by Rose and colleagues, to examine the impact of extending the use of evidence-based varenicline pharmacotherapy prior to the designated quit date to allow for greater natural exposures to various triggers and cues across multiple contexts.

Other active collaborations continue with Drs. Maciej Goniewicz and Richard O'Connor, along with researchers at the University of Rochester Medical Center, as part the Western NY Center for Research on Flavored Tobacco Products (CRoFT). These ongoing activities seek to extend research on the impact of

flavors on use patterns among tobacco users with a focus on toxicity, health effects, behavior and marketing influences. This collaborative research involves the design and implementation of randomized clinical trials (RCT) where current users of ENDS will be switching to an alternative flavor (e.g., 'tobacco', "cooling' fruit/sweet flavors) and the impact on respiratory and oral health.

In addition, I am working with Dr. Christine Sheffer, on a clinical trial focused on determining an optimal dosing strategy for 20Hz repetitive transcranial magnetic stimulation (rTMS) to yield the best long-term abstinence outcomes for smoking cessation with the fewest undesirable effects.

Gregory Wilding, Ph.D., Co-Investigator

I am a Tenured Full Professor in the Department of Biostatistics at the State University of New York at Buffalo (UB), housed within the School of Public Health and Health Professions, and have been a member of the faculty in the Department since its inception in 2002. In addition, I am Director of the Biostatistics, Epidemiology, and Research Design Core of the UB Clinical and Translational Research Center where I oversee many of the statistical efforts associated with interdisciplinary projects and develop educational initiatives around advanced research methods. I also hold courtesy appointments within the UB Jacobs School of Medicine and Biomedical Sciences and UB School of Nursing, an Associate Faculty within the UB Institute for Computational and Data Sciences, and am Research Associate within the Buffalo Center for Social Research. Beyond my work at UB, I serve as Professor of Biostatistics and Oncology at the Roswell Park Comprehensive Cancer Center's (RPCCC) Department of Biostatistics and Bioinformatics and as a Research Associate within the Department of Veterans Affairs. Over my 20-year career, I have developed extensive expertise in the design and analysis of clinical and non-clinical studies, based on both experimental and observational designs, and have participated in many aspects of numerous interdisciplinary research projects within and outside of UB resulting in over 250 published manuscripts. Many of these research projects have been grant funded and I have been a statistical coinvestigator on over 45 current or past grants. I have also served on several scientific committees, data safety and monitoring boards, and internal review boards. In order to address barriers to clinical and translational science, I have made substantial contributions to the statistical methodological literature in the areas of clinical trial design, order-restricted inference, and exact inference approaches. I have been responsible for the statistical training of and have personally trained and mentored numerous graduate students, postgraduate researchers and faculty. Given my expertise and administrative roles, I am well positioned to provide the support needed to the researchers in this project.

Dr. Robert Schnoll, Co-Investigator

I lead a lab devoted to research on treatments for nicotine dependence. I have developed and studied behavioral interventions for nicotine dependence, conducted numerous clinical trials of medications for nicotine dependence, and specialize in evaluating novel ways to improve nicotine treatment effectiveness and use, particularly in clinical populations such as cancer patients, smokers with HIV, pregnant smokers, and smokers with serious mental illness. I have conducted large, multi-site clinical trials and trials that evaluated methods for training clinicians to treat nicotine dependence. My current work focuses on the use of novel implementation strategies, including personalized treatments based on a genetically-informed biomarker of nicotine metabolism, to address the gap between the availability and use of evidence-based treatments for nicotine dependence. I devote substantial time to assisting with the training and mentoring of graduate students, post-docs, junior faculty, and researchers in developing countries. I have co-directed career development core facilities for NIH-funded and other extramurally-funded centers and served on advisory committees for NIH and as a member and chairperson on >80 NIH study sections. I have also served as an External Scientific Advisor to NCI cancer centers, the American Cancer Society, and NCI. Currently, I build research collaborations across Penn as Associate Director for Population Science at our Abramson Cancer Center and as Director of the Center for Interdisciplinary Research on Nicotine Addiction and serve as a mentor to dozens of students, fellows and post docs as a K24 mentoring grant recipient and as a scholar/mentor for NCI's Training Institute for Dissemination and Implementation Research in Cancer (TIDIRC) and Washington University's Institute for Implementation Science Scholars. I also co-chair the Implementation Science Working Group for NCI's Cancer Center Cessation Initiative (C3I), where I help build collaborations and facilitate research on the use of implementation science to address tobacco use. For this study, I will be site PI for Penn, overseeing the implementation and completion of the trial and coordination with the Penn CTSA. I will also partner with Drs. Hawk, Mahoney, Dahne, and Carpenter on cross-site activities. I have successfully worked with Drs. Hawk and Mahoney on a past multi-site smoking cessation clinical trial.

CeCe Duerr, M.S., Project Manager

Ms. Duerr has served as Project Coordinator/Manager on multiple clinical trials and laboratory studies involving human subjects and has also worked closely with MPIs Hawk and Mahoney and other study personnel to manage lab resources across concurrent studies.

Eugene Maguin, Ph.D., Staff Scientist

Dr. Maguin has expertise in engineering, programming, and data analysis. He has worked with our team on a variety of projects for the past 4 years.

NOTE that details for additional staff will be provided once the project has begun and we begin hiring.

Describe other resources available to conduct the research.

16.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response:

Larry Hawk, Ph.D., Principal Investigator (2.1 academic months and 0.9 summer months in YR01; 1.2 academic months and 1.2 summer months in YR02-03; 1.5 academic months and 0.9 summer month in YR04; 3 academic months and 0.3 summer month in YR05). Dr. Hawk will be responsible for the scientific, technical, and administrative direction of the proposed research and supervise most aspects of the project. Dr. Hawk will work with other study personnel to develop/finalize IRB, SOPs, staff training, data collection issues, data reduction for the task-based assessments, data management, and data analyses. Dr. Hawk will manage the proposed dissemination activities, including the project website, conference presentations and publications, the webinar series, data archiving, and planning for the Creative Scientist Workshop. Dr. Hawk will work closely with the Statistician and Staff Scientist Maguin to prepare the dataset for archival and will lead discussions with the archival site. Dr. Hawk will meet at least weekly with Project Manager Duerr, meet at least bi-weekly with project staff, and meet at least monthly with Co-Investigators. Effort is greater in YR01, due to the demands of project start-up, and in YR05, due to increased dissemination responsibilities.

Gregory Wilding, Ph.D., Co-Investigator, (0.45 calendar months in YR01-YR02; 0.9 calendar months in YR03; 1.0 calendar months in YR04; 1.8 calendar months in YR05). As the project statistician, Dr. Wilding will oversee the randomization and stratification procedures for the project, work with PI Hawk and Staff Scientist Maguin to coordinate development and management of integrated databases, and lead data analyses. Wilding will work with all study investigators to interpret and disseminate results. Effort parallels the data analysis responsibilities, which peak in YR04-YR05.

Constance Duerr, M.S., Project Manager (9 calendar months in YR01-02; 6 calendar months in YR03-05). Ms. Duerr will assist with IRB submissions, and she will manage human resource issues and staff training and scheduling, purchasing and participant remuneration at the UB site. Ms. Duerr will work closely with study Investigators on participant recruitment and advertising. Ms. Duerr will facilitate coordination and input from all study personnel and schedule and co-lead (with PI Hawk)

team meetings. Ms. Duerr will interface with our Clinical and Translational Science Institute (a CTSA hub) around university-wide tracking of research activities. With assistance from investigators and coordinators at the MUSC and UPenn sites, Ms. Duerr will oversee staff training and reliability/fidelity checks on study procedures and supervise quality control activities and conduct periodic site visits. Ms. Duerr will lead cross-site Coordinator meetings (monthly) and co-lead bi-weekly staff meetings. As needed, Ms. Duerr will assist project staff with screening, scheduling, and visit procedures.

Eugene Maguin, Ph.D., Staff Scientist (3.6 calendar months in YR01-YR02, 6.0 calendar months in YR03-YR05). Dr. Maguin will assist the Statistician with the randomization module and work with the UB Research Information Systems team develop standardized reports for monitoring multiple aspects of study progress, including accrual and randomization, counterbalancing, and stratification within and across groups and sites. Dr. Maguin will develop routines and syntax for integrating individual data streams from REDCap and any other data collection portals into integrated databases for study analysis. He will assist study investigators in data reduction and assist the Statistician in data analysis. Dr. Maguin will also assist MPI Hawk in the archiving of project data, as he has recently done for another project. Lastly, Dr. Maguin will serve as an independent auditor of financial records, a requirement of the University at Buffalo. Effort increases across years as data management becomes increasingly complex across 3 studies, and project data are prepared for archiving.

Senior Research Support Specialists (TBN). Funds are requested to hire two Senior Research Support Specialists (9.0 calendar months each in YR01-YR02; 3 calendar months each in YR03-05). The research specialists will be trained on all study procedures and protocols. In YR01-YR02, the research specialists will conduct screening calls, schedule participants, and conduct intake and follow-up visits for Study 1. For remote visits, the research specialists will prepare all visit kits, process returned kits, and follow-up with participants as needed. The research specialists will assist the Project Manager with quality control (QC) processes, including the monitoring of milestones and data completion and reduction from both Study 1 sites. Two part-time RAs are requested to ensure uninterrupted operations during time-off. Effort is lower in YR03-05, when the research specialists will assist with quality control and data reduction for RCTs 2 and 3 but will not be engaged in data collection for RCT 1.

16.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: Study staff will be available by phone during normal business hours, and they will have prompt access to Co-PIs Hawk (a clinical psychologist) and Mahoney (a physician) for clinical issues that arise in the course of smoking cessation, as in our prior trials. As in our prior work, we will provide participants with contact information and reminder cards and, when appropriate, referrals for resources external to the focus of the project.

16.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: All staff will be provided with copies of the relevant sections of the grant proposal, the IRB protocol, and the participant consent form. Study protocols are available to study staff from a UB Box folder. Training of study staff will include direct observation of mock procedures followed by supervision in real participant interactions.

17.0 Other Approvals

17.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: To protect privacy, participants must either have previously agreed to be contacted about future studies or actively contact us in response to an advertisement or referral to be considered for the study. All study screenings and procedures will be conducted in secure, private rooms. Participants will be informed of their right to withhold any information they wish to keep private, with the knowledge that refusal to provide samples or answer questions may make the person ineligible for further participation in the study. Finally, staff electronic/verbal communications about participants will refer to the participant's unique

study ID number rather than name or other identifying information that might threaten participant privacy.

18.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response: Consent provided by the research participant.

19.0 Data Management and Analysis*

19.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response:
Data Analysis

Preliminary considerations. Prior to locking the database, all data editing will be completed and decisions regarding the evaluability of participant data for inclusion in statistical analyses will be made. The rationale for excluding any data from statistical analyses will be prospectively defined, and classification of all or part of a participant's data as non-evaluable will be documented before the database is locked and the statistical analysis is begun.

Stratification and randomization. For RCT1 (a multi-site study), the first stage randomization (Randomization #1) to Remote vs. In-Person Intake Group and associated primary Aim 1 analyses will be stratified by site and race/ethnicity (as in our prior work, e.g., R01CA206193; this is important given our exploratory analyses involving the impact of remote trial methods for underrepresented groups, as described in Exploratory Aim 5, below). The second stage randomization (Randomization #2) to Remote vs. In-Person Treatment and Assessment) and associated Aim 2 analyses will be stratified by site as well as the Intake Group (Randomization #1). For RCT2 and RCT3, each of which is a single-site dissemination project, second stage randomization will be stratified by Intake Group (Randomization #1).

Both randomization procedures will assign participants to groups in a 1:1 fashion using a stratified permuted block randomization scheme. The randomization lists to be used in this study will be generated by the study biostatistician utilizing statistical software and then implemented using REDCap. A signed randomization plan is uploaded to Click.

Missing data. In our analyses of accrual efficiency (Aims 1 and 3) and retention (part of Aims 2 and 4), loss of data is of considerable interest. Beyond these outcomes, the amount and nature of missing data will be characterized, and no method of imputation will be used for missing data.

A summary of missing data will be provided according to the number of participants, the time points where the data are missing, and clinical site (Aim 1) or RCT (Aim 4). For each clinical site/RCT, the number and percent of participants with no missing data will be presented in tabular form. We acknowledge the possibility of informative missingness, that is, the probability of a particular observation being missing may be related to the health of a participant, and therefore analyses will be interpreted with caution.

Descriptive analyses. Measured outcome variables will be summarized overall and by relevant demographic and baseline variables. Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data (e.g., histograms, boxplots, scatterplots).

Aim 1: Multi-site RCT1 – Evaluate the accrual efficiency of the Remote vs. In-Person Intake Groups. A standard operationalization of intention-to-treat (ITT) will be employed, in which all participants randomized to Remote vs. In-Person Intake (Randomization #1) in RCT1 will contribute to Aim 1 analyses. In the primary analysis, observed differences in intake completion rates between randomized groups will be statistically assessed using the Cochran-Mantel-Haenszel test. Rather than utilizing the asymptotic null distribution associated with this test for group differences, an exact permutation testing approach will be utilized. The randomization mechanism at work is a crucial component in this study in that it will be used to create the randomization distribution by which statistical significance will be determined. The reported p-value will be obtained from the permutation distribution of the test statistic based on 10,000 Monte Carlo simulations. This conditional approach accommodates the sampling scheme implemented in Aim 1 where participants will be enrolled until 200 have initiated treatment at Clinic 1 (modified ITT for Randomization #2; see sample size justification below). The Mantel-Haenszel estimated difference between groups will be computed along with the corresponding exact 95% confidence interval.

Because accrual efficiency beyond Intake is also of interest, supplemental analyses will use the approach described above to evaluate rates of Clinic 1 completion among those eligible at Intake and randomized to Remote vs. In-Person Treatment and Assessment (Randomization #2). We will also characterize overall accrual efficiency (# participants eligible at Phone Screen/# participants who initiate treatment at Clinic 1 visit). For these analyses, we will explore and characterize the separate and combined impact of randomization to Remote vs. In-Person Intake x Remote vs. In-Person Treatment and Assessment.

Since the comparability of assigned groups may be questioned due to chance imbalances in confounding variables, participant covariates will be

statistically adjusted for in a series of secondary analyses using fitted logistic regression models with parameter estimation based on maximum likelihood methods. Standard diagnostic plots will be used to assess model fit and transformations of variables may be considered to meet statistical assumptions. Testing will be performed in this case using likelihood ratio procedures. In addition, associated 95% confidence intervals will be produced based on Wald methodology. The interaction of participant covariates and randomized assignment will also be examined to identify possible differential effects.

Aim 2: Multi-Site RCT1 – Examine key metrics of trial quality in Remote vs. In-Person Treatment and Assessment Groups. To evaluate the impact of remote treatment and assessment on measures of retention, biospecimen completion, and treatment adherence/utilization, it is important to focus on participants who initiate treatment (otherwise, some number of participants will have missing data on all trial quality outcomes). For this reason, primary Aim 2 analyses focus on a modified ITT112 cohort (i.e., the 200 participants who initiate treatment at Clinic 1; see sample size justification below). For comparison, supplemental standard ITT analyses will be conducted with all participants randomized to Remote vs. In-Person Treatment and Assessment.

Most trial quality outcomes are non-normal in nature (e.g., biospecimen completion rates range of 0-5 and will be negatively skewed; see Preliminary Studies). Thus, statistical group comparison will be done utilizing the stratified Wilcoxon rank sum test with van Elteren weights. As for Aim 1, an exact permutation testing approach will be implemented for p-value calculation. Secondary, covariate-adjusted analyses will be based on use of fitted generalized linear models with an appropriately selected link function and parameter estimation based on maximum likelihood methods. Statistical inferences will be based on likelihood ratio and Wald methodologies. These model-based analyses will assist in statistical adjustment for any covariate imbalances. In addition, this approach allows for exploration of the individual and joint effects of the two different randomization stages on trial quality outcomes.

(NOTE: Aims 3 and 4 are not part of the present UG3 trial; they are dependent on yet-to-be-funded UH3 Phase activities.)

Exploratory Aim 5: - Examine the impact of remote vs. in-person trial efficiency and quality for members of select health disparities groups and characteristics. We will incorporate race/ethnicity and their corresponding cross-products with randomized group assignment (which allows for the estimation and testing of differential effects) into logistic regression models (for accrual efficiency, Remote vs. In-Person Intake; see Aims 1, 3) and generalized linear models (for metrics of trial quality, Remote vs. In-Person Treatment and Assessment; see Aims 2 and 4). Our primary analyses will focus on black and white participants because these are the two largest racial groups. We will also provide descriptive information

(including effect sizes) for smaller sub-populations (e.g., Hispanic participants).

We will similarly explore the role of each of the SDOH and related measures (Exploratory Aim 5) by incorporating the SDOH predictor and its' interactions with group assignment. When both race and one or more SDOH exhibit parallel effects, we will run follow-up models including both race and the SDOH metric(s) to characterize the role of SDOH in effects of participant race (i.e., overlapping variance) and, more generally, the impact of remote trial methods as a function of SDOH. For example, if race, internet access, and medical mistrust each interact with remote vs. in-person intake in predicting accrual efficiency, a follow-up model would include the interactions of Race x Remote vs. In-Person Intake, Internet Access x Remote vs. In-Person Intake, and Medical Mistrust x Remote x In-Person Intake. If none of the three interactions were significant when all are included in the model, it would suggest that racial differences in the impact of remote intake on accrual efficiency were fully accounted for SDOH. Follow-up models would address the extent to which racial differences are accounted for internet access or medical mistrust individually. These analyses may suggest targeted approaches for enhancing trial efficiency and/or quality among Black participants and/or as a function of SDOH more generally.

A parallel approach will be taken to examine moderation of remote trial methods as a function of participant age and the role of SDOH in understanding the degree to which Remote vs. In-Person trial methods differentially impact younger vs. older participants. If sample sizes permit, we will similarly examine other participant characteristics that are under-represented in clinical trials (e.g., rurality)[23,131]. Where sample sizes yield inadequate power for inferential tests, we will provide descriptive information (including effect sizes) for smaller sub-populations.

Supplemental: Qualitative Analysis. Qualitative interviews will be transcribed verbatim. The CFIR/HE provides a framework for analyzing qualitative data from a multiple case-study design to identify common themes across trials. Summaries will be created immediately following each interview and reviewed with the team during regular study meetings to allow for high-level analysis throughout the trials. These summaries will also be used to update sampling procedures and interview guides and to inform potential modifications to the UH3.

Formal qualitative analysis procedures will take place at the conclusion of the trial. All transcribed interview data will be uploaded into MaxQDA for analysis. Dr. Allen's team will initially code all interviews using an a priori codebook based on the CFIR/HE constructs to develop an initial analytic framework and develop trial-specific summaries. Emergent codes will be added to areas of transcripts that do not fit the initial coding structures. The coding team will iteratively code 2-3 transcripts at a time, discussing coding, adjusting the codebook, and creating a working

analytic framework by grouping codes into categories or themes until they have reached a static analytic framework. Codebooks and the analytic framework will be reviewed and cross-checked during project meetings. We will triangulate these findings with quantitative results using a rapid analytic coding matrix[132–134]. Findings will contribute to our understanding of trial implementation, especially related to health equity issues, as well as dissemination and sustainability efforts. Moreover, the qualitative data from the UG3 Phase (RCT1) will inform potential modifications to the UH3.

Supplemental: Cost Analysis. We will use standard micro-costing techniques[99] to estimate the costs of implementation of remote vs. in-person trial methods, accounting for both healthcare and non-healthcare costs incurred for researchers and patients[100]. Expenditures will be assessed via time and motion study[101,102] administered periodically to staff and interview with key staff, with expenditures classified in four categories shown in the table below. Brief patient surveys will gather information on time, work/productivity loss, transportation costs, child care costs, and any other forgone resources needed for their participation.

Cost analysis outcomes: Cost per trial outcome			**RCT1**	**RCT 2**	**RCT 3**
Expenditures	*per*	Trial outcome of interest			
Personnel		Recruited patient	X	X	X
Recurring costs		Retained patient	X	X	X
Capital expenditures		Study visit	X	X	X
Overhead costs		Biomarker completed	X	X	X
		Treatment received	X	X	X

Expense documentation will be used in this cost analysis. Our cost analysis outcomes will include the total implementation cost per trial outcome of interest (see table above) for remote vs. in-person trial methods. We will explore drivers of the cost analysis outcomes and conduct sensitivity analyses to assess the uncertainty of these outcomes.

19.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response:

Preliminary considerations. Sample size determinations focused on adequate power to evaluate Aims 1 through 4. As proposed, enrollment continues until 200 participants begin treatment at T/A Visit 1 in RCT1

(i.e., modified ITT for Randomization #2, as described in Aim 2 analyses) and 100 participants begin treatment at T/A Visit 1 in RCT2 and in RCT3.

Unlike the fixed modified ITT sample size for Randomization #2, the sample size for Randomization #1 (standard ITT) must be estimated because the true sample size for Randomization #1 will depend on the degree to the remote intake yields higher attendance rates (our hypothesis for Aim 1). Based on our in-person trials [55–57,59,60,62,77,78], we estimate that: only ~50% of participants invited to Intake (Randomization #1) will attend Intake; with the proposed exclusion criteria, about 80%, will be eligible at Intake; and about 95% of Intake eligible participants will attend T/A Visit 1. Under these assumptions, we would estimate the sample size for Randomization #1 to Remote vs. In-Person Intake is approximately 526 (200/.5/.8/.95) in RCT1 (Aim 1) and 263 (100/.5/.8/.95) in each of RCT2 and RCT3, for a total sample size of 1052 for evaluating accrual efficiency in Aims 3 and 5. However, if intake attendance is 65% in the Remote Intake Group, as assumed in Aim 1 power calculations, then the sample size for Randomization #1 would be approximately 458 (200/.95/.8/[[.5+.65)]/2]) in RCT1 (Aim 1) and 229 (100/.95/.8/[[.5+.65)]/2]) in each of RCT2 and RCT3, for a total sample size of 916 for evaluating accrual efficiency in Aims 3 and 5.

Aim 1: Multi-site RCT1 – Evaluate the accrual efficiency of the Remote vs. In-Person Intake Groups. As just described, power calculations for statistical comparison of accrual efficiency between Remote and In-Person intake groups incorporate projected participant loss at steps leading up to Clinic 1. Although an exact stratified procedure will be used in testing, for the sake of simplicity, power calculations corresponding to the test are approximated by those of Fisher's exact test, calculated at the estimated total sample size of 458 as above. In this context, power is 90.7% to detect a realistic but meaningful difference (15 percentage points) in accrual efficiency between the Remote and In-Person Intake Groups (65% and 50%, respectively).

Aim 2: Multi-Site RCT1 – Examine key metrics of trial quality in Remote vs. In-Person Treatment and Assessment Groups. Power estimates regarding the proposed assessment of the impact of Remote vs. In-Person Treatment and Assessment on metrics of trial quality (retention, biospecimen completion rate, and treatment adherence/utilization) were based on the proposed sample size of 200 ITT participants after

Randomization #2. Although the analyses will be based on a rank-based procedure, power calculations are those corresponding to a two-sample t-test. Given the novelty of the proposed study, effect size estimates are not available in the literature. However, power will be adequate (80.4%) to detect group differences as small as 0.4 standard deviations. Although post-Randomization dropout could differ for the two groups, resulting in an unbalanced number of participants in the Remote compared to In-Person Treatment and Assessment Groups, power will be relatively

unaffected, remaining ~80%. Since the actual analyses to be performed will be based on approaches which incorporates stratification factors which will account for some of the unexplained variability in the dependent variables, the calculations above may be viewed as conservative.

RCT 1 IP rate	RCT 1 Remote rate	RCT 1 N	RCT 2&3 IP rate	RCT 2&3 Remote rate	RCT 2&3 N	Power for R vs IP Main Effect	Power for R vs IP x RCT Interaction
50%	65%	458	50%	70%	440	99.7%	11.5%
50%	65%	458	50%	75%	422	100%	37.7%
50%	65%	458	50%	80%	406	100%	74.1%
50%	65%	458	50%	85%	390	100%	95.3%
50%	65%	458	40%	60%	526	100%	11.8%
50%	65%	458	40%	65%	502	100%	33.1%
50%	65%	458	40%	70%	478	100%	66.9%
50%	65%	458	40%	75%	458	100%	89.2%
50%	65%	458	60%	80%	376	100%	22.2%
50%	65%	458	60%	85%	364	100%	63.0%
50%	65%	458	60%	90%	352	100%	94.1%
50%	65%	458	60%	95%	340	100%	100%
50%	57.5%	490	50%	65%	458	93.4%	20.6%
50%	57.5%	490	50%	70%	440	98.8%	51.2%
50%	57.5%	490	50%	75%	422	100%	80.2%
50%	57.5%	490	50%	80%	406	100%	97.9%
50%	57.5%	490	50%	85%	390	100%	99.8%
50%	57.5%	490	40%	55%	554	95.0%	25.2%
50%	57.5%	490	40%	60%	526	98.8%	47.3%
50%	57.5%	490	40%	65%	502	100%	80.1%
50%	57.5%	490	40%	70%	478	100%	95.3%
50%	57.5%	490	40%	75%	458	100%	99.5%
50%	57.5%	490	60%	75%	390	94.4%	25.8%
50%	57.5%	490	60%	80%	376	99.4%	61.4%
50%	57.5%	490	60%	85%	364	100%	91.4%
50%	57.5%	490	60%	90%	352	100%	99.6%
50%	57.5%	490	60%	95%	340	100%	100%

(NOTE: Aims 3 and 4 are not part of the present UG3 trial; they are dependent on yet-to-be-funded UH3 Phase activities.)

Exploratory Aim 5: - Examine the impact of remote vs. in-person trial methods on efficiency and quality for members of select health disparities groups and characteristics. Power estimates regarding differences in the impact of remote vs.in-person intake on accrual efficiency for sub-groups of participants facing health disparities and who are underrepresented in clinical trials follow the framework for Aim 3. Our power analyses focus on participant race as a moderator and on black and white participants because these are the two largest racial groups. We will also provide descriptive information (including effect sizes) for smaller sub-populations (e.g., Hispanic participants). Given that there is no solid evidence base for estimating differences in the impact of remote screening

across racial groups – indeed, the proposed research will establish the needed translational science evidence base – we considered a range of possible outcomes. For all scenarios considered, we began with observed data from our recent work, which yields an estimated intake attendance rate that favors white participants (56%) over black participants (46%) and estimated that about 65% of the total sample would be white. We then varied widely the projected rate of attendance by white and black participants in the Remote Intake Group; to keep the power estimates manageable, the overall rate of attendance for remote visits was maintained at 65% (see Aim 1). As can be seen in the table below, the proposed work is adequately powered (>80%) to detect outcomes in which the benefit of remote intake on intake attendance is observed primarily in black participants (the top 6 rows of the table) or white participants (the bottom 3 rows of the table).

IP Rate Black	IP Rate White	Remote Rate Black	Remote Rate White	Power for IP vs R x Race Interaction
46%	56%	93%	50%	100%
46%	56%	87%	53%	100%
46%	56%	82%	56%	100%
46%	56%	78%	58%	99.8%
46%	56%	74%	60%	96.2%
46%	56%	71%	62%	81.2%
46%	56%	65%	65%	31.2%
46%	56%	60%	68%	5.6%
46%	56%	58%	69%	4.8%
46%	56%	55%	70%	11.9%
46%	56%	49%	74%	65.7%
46%	56%	45%	76%	89.9%
46%	56%	41%	78%	99.5%
46%	56%	37%	80%	100%

Power estimates for evaluating racial differences in the impact of remote vs. in-person treatment/assessment on continuous metrics of trial quality were computed in parallel to the power estimates for Aim 4. Although power to detect the Remote vs. In-Person x Race interaction is modestly attenuated by the different sample sizes for black and white participants, power remains adequate (>80%) to detect interactions of moderate-to-large effect size (0.6-0.7 standard deviations) for samples in which black participants make up 20%-40% of the sample.

19.3 Describe any procedures that will be used for quality control of collected data.

Response:

Most data collection is computerized and collected using Research Electronic Data Capture (REDCap). This allows real-time validation that data is complete within pre-specified field formats and ranges. As part of the data and safety monitoring process, the team will ensure that all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP). Any inconsistencies/deviations will be

documented. The Project Manager, with assistance from other staff, will conduct quality control reviews of data on an on-going basis.

20.0 Confidentiality*

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*20.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response: The confidentiality of participant data is maximized by several aspects of the proposed work. Physical barriers to violations of confidentiality include the use of secure facilities (all rooms in our unit can be individually locked; access to our facilities is protected by swipe card access).

Most data collection is computerized and collected using Research Electronic Data Capture (REDCap), a secure web-based application used by more than 240 academic institutions, housed on a UB server. REDCap is HIPAA-compliant, has an SSL certificate (Secure Sockets Layer, a cryptographic protocol that provides communication security over the Internet), and uses https (Hypertext Transfer Protocol Secure, a widely used communications protocol for secure communication over a computer network, with especially wide deployment on the Internet). No identifying subject information is directly linked to biological specimens. We have not experienced the unauthorized use of study data.

User access privileges will be limited to study personnel and tailored to fit the access needs of the particular team member. Privileges will be reviewed and updated with each staffing change. In addition, REDCap logs every keystroke of every user, and Box maintains previous versions of every file. All computers used in the acquisition of study data are maintained and serviced by the CAS IT group. Together, these safeguards protect against the three major sources of data security problems: unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. We do not anticipate having any paper-based records. However, if there are any, they will be maintained in locked filing cabinets in 306/307/308 Diefendorf Hall and/or Farber Hall, Room 155; keys are maintained in a safe in the office of the project-coordinator.

Summary data files for data analysis will exclude participant names, contact information, and other unique identifiers.

20.2 A. How long will the data be stored?

Response: We do not anticipate collecting any paper records containing identifying information. Paper records, if collected, will be stored for 3 years after completion of the project; they will then be destroyed. Electronically-captured data will be maintained indefinitely in REDCap, and deidentified data will be stored indefinitely in statistical software and, as mandated by the NIH, in a publicly available repository.

20.3 A. Who will have access to the data?

Response: Access to source documents, identifying information, REDCap databases, and statistical software databases will be limited to project investigators and staff. As noted above, consistent with NIH policy, deidentified data will be made available in a public repository.

20.4 A. Who is responsible for receipt or transmission of the data?

Response: Study investigators and staff.

20.5 A. How will the data be transported?

Response: N/A Data will not be physically transported.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☒ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 21.0)*

NOTE: The only biological specimen that will be collected in the UG3 phase of the study is breath carbon monoxide. This kind of specimen is not something that can be stored.

20.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response:

20.7 B. How long will the specimens be stored?

Response:

20.8 B. Who will have access to the specimens?

Response:

20.9 B. Who is responsible for receipt or transmission of the specimens?

Response:

20.10 B. How will the specimens be transported?

Response:

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

21.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response:

Given that the study medication (NRT) is OTC and has been used safely for decades, there will be no formal Data Safety Monitoring Board.

The site PIs (in consultation with the study statistician and other Co-Investigators) will be responsible for monitoring the trials, reviewing the frequency of AEs reported on the side effect checklist quarterly to see if any are being endorsed more frequently than normal for NRT.

We anticipate, given prior research, that most side effects will be mild-to-moderate. The research staff at each site will report to the site PIs any scores of "severe" on the side effect checklist and any FDA-defined SAE within 24 hrs so that they can decide on the appropriate action (e.g., dose reduction or suspension of treatment).

Given the large number of participants (N=200) and duration of participation (~3-4 months), we do expect some SAEs to occur, all of which will be reported to the UB IRB (the reviewing IRB within our single IRB plan) within 72 hrs. However, given that we are providing OTC NRT, we do not anticipate SAEs attributable to study medication.

We will also report SAEs to NCATS within 72 hrs of learning of any such occurrence, using a standardized SAE Report Form (NCI Standard Adverse Event-Serious Adverse Event CTCAE V5 0). Any significant actions taken by the IRB requiring protocol changes will be relayed to the funding agency. We estimate the SAE rate will be less than 5%.

See also RISE AE/SAE Manual.

Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Standard assessments of side effects, detailed records of serious adverse events, and overall rates of smoking cessation.

21.2 Describe any safety endpoints.

Response: Standard assessments of side effects, detailed records of serious adverse events.

21.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Primarily through the side effect checklist at study visits, but also as reported by participants during any other contacts by phone, email, or text.

21.4 Describe the frequency of safety data collection.

Response: At each of the 5 treatment/assessment visits, which will be from 1-6 weeks apart.

21.5 Describe who will review the safety data.

Response: Study staff will review side effect reports at each study visit; standard decision rules are used to trigger reporting to the PI/Study Physician within 24 hours (often within minutes), as described in 21.1.

21.6 Describe the frequency or periodicity of review of cumulative safety data.

Response: Quarterly

21.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: N/A. The base rates of serious adverse events are too small to be detected by statistical tests in the proposed sample size.

21.8 Describe any conditions that trigger an immediate suspension of the research.

Response: We anticipate that the only potential reason to stop the RCT prematurely would be a significant rate of adverse events, which seems higly unlikely with OTC NRT.

22.0 Withdrawal of Subjects*

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*22.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response:

As described in the informed consent document:

The principal investigator of the study can remove you from the research study without your approval. Possible reasons for removal include:

- The Principal Investigators feel it is necessary for your health or safety. Such an action would not require your consent, but you would be informed if such a decision was made and the reason for this decision.
- You have not followed program requirements.
- The Sponsor, University, or Investigators have decided to stop the program.

22.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: PI or designee will attempt to inform participants (by phone; if unable to contact, then by postal service) of the reason for withdrawal. No additional follow-up is necessary; however, in some situations it may be reasonable to provide alternative referral information.

22.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: If participants choose to withdraw from the research, their already collected data will be retained.

23.0 Risks to Subjects*

23.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response: Overall, there will be modest risks to participants in this RCT, and participants can choose, as an alternative, to not enroll in the trial.

Withdrawal symptoms following cessation. Most participants will experience some withdrawal upon quitting smoking. Symptoms include craving, anxiety, irritability, problems concentrating, appetite change and weight gain, and insomnia. Withdrawal symptoms typically decrease markedly within 1-2 weeks.
ii. Nicotine replacement therapy. The research protocol calls for the recruitment of people who currently smoke who are seeking assistance with quitting smoking. The intervention consists of 8 weeks of nicotine patches and lozenges, supplied to participants in 2- to 4-week allotments; both are over-the-counter products that have received extensive support for their efficacy and safety, as well as evidence that the combination is more efficacious[84]. Nonetheless, there are potential for risks for each product alone, as well as when used concurrently. We believe these risks, described below, will be minimal and mild.

Nicotine lozenge. In a prior trial clinical trial, 68% and 71%, respectively, of 2 and 4 mg users of nicotine lozenge reported an adverse event (AE) vs. 54% of placebo users [121,122]. With both active doses of the lozenge, 7% dropped out due to AEs and 7% dropped out due to AEs on placebo. With both active doses, 1.6% reported a serious AE which was not different than that for placebo. There were no deaths or irreversible injuries deemed possibly due to lozenge. The most common AEs were nausea, flatulence and upper respiratory tract infection (113). Participants will be provided with the current labeling on OTC lozenge, which states that those using a prescription medication for depression or asthma or a smoking cessation medication and those with heart disease, recent heart attack, irregular heartbeat, high blood pressure not controlled by medication, stomach ulcers or diabetes should consult a provider before using the lozenge.
In a recent trial of placebo vs. single vs. multiple medications for smoking cessation123, the three most common adverse events within the lozenge group were 1) nausea: 7.8%, compared to 4.4% within placebo group, 2) mouth/throat irritation: 6.7%, compared to 3.3% within placebo group, and 3) hiccups: 6.2%, compared to 0.3% within placebo group. All other adverse events occurred <5%.

Dependence on the lozenge and harm from concurrent use of lozenge and cigarettes has not been reported but has not been studied. The pharmacokinetics of the lozenge most closely matches that of nicotine gum. With gum used for abrupt cessation, the estimated incidence of dependence is 1-3%[124]. Although an early anecdotal report suggested concomitant use of NRT and smoking could induce heart attacks, several large empirical studies since then have failed to confirm this observation[125]. For example, in the LHS study[126] and in our prior study[127], large numbers of smokers concurrently smoked and used nicotine gum or other NRT products and the incidence of any significant AEs was < 1%. Moreover, most hospitals treat smokers who are admitted with cardiac symptoms/suspected myocardial infarction using NRT as a standard of care.

Nicotine patch. The most common side effects from nicotine patch are skin irritation, insomnia, headache or nausea. In an early but seminal placebo-controlled test of patch[128], there were few systemic side effects of patch use: 21% vs. 15% of smokers in the patch and placebo groups respectively reported a side effect during the treatment period. The most frequent symptoms with the patch as compared with the placebo patch were headache (4 vs. 4 percent), nausea (4 vs. 1 percent), and vertigo (4 vs. 0 percent). Transient mild itching was reported by 14% of the subjects in the patch group and 1% in those in the placebo group after the first week (P<0.001). At each visit, 4.5% to 7.3% of the remaining subjects in the patch group reported erythema, as compared with 2.3% to 6.7% of those in the placebo group. Acute site irritation persisting for several days in the area of the patch caused 1.4% of the subjects in the nicotine group and 0.7% of those in the placebo group to stop using the patch.

Finally, in a large trial of placebo vs. single vs. multiple medications for smoking cessation[123], the two most common adverse events within the patch group were 1) skin irritation: 14.7%, compared to 2.7% within placebo group, and 2) disturbed sleep: 11.3%, compared to 5.6% within placebo group. All other adverse events occurred <5%. Seven percent of patch users vs. 4% of placebo users discontinued medication due to adverse events.

Combined nicotine patch and lozenge. As supported by recent reviews, we believe combined use of NRT medications is safe. One review in particular[129] provides significant rationale by which combined NRT should not incur significant risks, since NRTs provide lower doses per unit or per hour than are typically obtained by cigarette smoking, and the rate of nicotine administration for all NRT products is substantially slower than that from an inhaled cigarette.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation[123] (92), the four most common adverse events within the combined patch/lozenge group, were 1) disturbed sleep: 9.0%,

compared to 5.6% within placebo group, and 2) skin irritation: 8.9%, compared to 2.7% within placebo group, 3) nausea: 7.9%, compared to 4.4% within placebo group, and 4) mouth/throat irritation: 5.7%, compared to 53.3% within placebo group. All other adverse events occurred <5%.
It is possible that smokers could be using NRT products concurrently (same day) while continuing to smoke cigarettes. This could result in nicotine intoxication (e.g., nausea, dizziness, headache, stomachache)[125]. In a prior study, participants completed a nicotine intoxication scale, and we found no evidence of nicotine intoxication when gum and cigarettes were used concurrently. In addition, a review of prior smoking reduction studies found most participants did not have higher than normal cotinine levels with concurrent use of cigarettes and NRT, and there were few AEs reported[130].
***Threats to privacy/confidentiality. Since self-report and biological data will be collected and stored, it is possible that subject privacy or confidentiality can be threatened. However, given the protections against risk described below, the level of risk is judged to be low.

23.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response:

Informed consent. Verbal consent for initial brief eligibility screening will be obtained and documented by a trained staff member at the beginning of the screen. At the subsequent intake visit, a staff member will review all study procedures and requirements, answer any questions, and obtain informed consent. If the participant has concerns that the staff member is not able to address, or the staff member has concerns about the person's capacity to provide informed consent, the staff member will consult with the Project Manager, a Co-Investigator, or one of the Principal Investigators before continuing. Alternatives to participating in this study will be presented (e.g., standard care, state quit line) so there is no coercion to participate.

Participants will be provided with a signed copy of the informed consent document completed at the intake session. Participants will be reminded that they can opt out of or withdraw from the study at any time without any penalty. A signed copy of the informed consent document will be stored in REDCap and/or stored in a locked room in a locked filing cabinet in the lab/clinic.
Oversight and monitoring. As per our single IRB plan, the UB IRB will serve as the reviewing IRB for the proposed RCT. The UB IRB will assess the study before study initiation and then review protocols annually, ensuring the scientific, technical, and statistical soundness of the research and that methods for the ethical and safe treatment of human subjects are in place. The UB IRB will monitor the protection of human subjects,

including SAE reporting for all sites, and the safe and secure collection and storage of data. The UB IRB will provide an objective and ongoing assessment of the study's scientific and ethical integrity.

Minimization of risks.

Withdrawal symptoms following cessation. Because both treatment groups in this RCT (remote and in-person) will be provided with NRT (patches and lozenge) and instructions for use, withdrawal severity should be reduced. Provided self-help materials advise participants of these symptoms and discuss methods to cope with them.

Nicotine replacement therapy. As described above, dual NRT involves two over-the-counter medications that are safe and effective, alone and in combination. Nevertheless, as in our previous pharmacotherapy trials, we will use a rigorous system to minimize the risk for side effects and adverse events and to detect and manage those that do occur. As discussed above, potential participants will be screened for the few NRT contraindications. Participants will receive detailed information on the proper use of study medication, and adherence and side effects will be rigorously and repeatedly assessed. The Study Physician will oversee any need for medication reduction or elimination, as well as adverse event assessment, reporting, and management.

Threats to privacy/confidentiality. To protect privacy, participants must actively contact us in response to an advertisement or referral to be considered for the study, and all study screenings and procedures will be conducted in secure, private rooms.

Participants will be informed of their right to withhold any information they wish to keep private, with the knowledge that refusal to provide samples or answer questions may make the person ineligible for further participation in the study. Finally, staff electronic/verbal communications about participants will refer to the participant's unique study ID number rather than name or other identifying information that might threaten participant privacy.

The confidentiality of participant data is maximized by several aspects of the proposed work. Physical barriers to violations of confidentiality include the use of secure facilities (all rooms in our unit can be individually locked; access to our facilities are protected by swipe card access) and storage of any physical records containing personally-identifying information in locked filing cabinets within these secure facilities.

Most data collection is computerized and collected using Research Electronic Data Capture (REDCap), a secure web-based application used by more than 240 academic institutions, housed on a UB server. REDCap is HIPAA-compliant, has an SSL certificate (Secure Sockets Layer, a cryptographic protocol that provides communication security over the Internet), and uses https (Hypertext Transfer Protocol Secure, a widely used communications protocol for secure communication over a computer

network, with especially wide deployment on the Internet). No identifying subject information is directly linked to biological specimens. We have not experienced the unauthorized use of study data.

*23.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: Though each of the procedures employed in this study have been used in many previous studies, there may be risks that we do not know about at this time. Should such a risk become evident, we will report the information to the IRB and, as warranted, notify participants of any new information that may affect their willingness to continue participation in this study.

23.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: N/A

23.5 If applicable, describe risks to others who are not subjects.

Response: N/A

24.0 Potential Benefits to Subjects*

24.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: All participants receive free combination NRT, 8 weeks of nicotine patches and lozenges, as well as a self-help and resource "quit kit" booklet to assist them in quitting smoking.

25.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*25.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response:

The research procedures described carry modest risk to participants. The University at Buffalo has no program to pay for medical care for research-related injury.

25.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A – There is no contract other than the consent form.

26.0 Economic Burden to Subjects

26.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response: Participants are responsible for their own transportation to/from study visits. (Free parking is provided at the UB site. See below for travel reimbursement at UPenn)

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

27.0 Compensation for Participation

27.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: Remuneration of up to $180 for each participant with complete data, with the participant receiving $30 after each completed visit (Intake and 5 treatment/assessment visits). Participants will receive $10 for providing an expired-air CO sample and $20 for completing the rest of each Treatment and Assessment visit. For UPenn ONLY: Due to the difficulty and cost of traveling to and parking at UPenn's site for in-person sessions, UPenn participants will be reimbursed $10 for any in-person session completed (up to $60). People who are selected to do a qualitative interview will receive an additional $50 after completing the interview.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 29.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 29.0)*

28.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: Consenting will take place in our clinical research lab (UBHEART) on the third floor of Diefendorf Hall (for participants randomized to in-person Intake) or over zoom (for participants randomized to remote Intake). On-site consent will take place in individual rooms with the door closed, and the unit is on a secure, locked floor. For remote consent, participants will be asked to go to quiet, private place to complete the intake appointment.

28.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: After the overview, participants will be invited to take as much time as they like to read the consent form and to ask any questions that they may have. Participants may also take the consent home with them to review and/or discuss with family, physician, etc.; in this case, the participant would contact us to re-schedule their intake visit, where we would complete the consent process. Data collection will not continue until the participant has agreed to participate and signed the consent form.

28.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: Although we will obtain written consent only once in this relatively short-term study (each participant is active in the study for ~3-4 months), participants who raise concerns about continuing participation will always be reminded that they are free to withdraw from the study at any time.

28.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are involved in the consent process*

- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response: We do not read the consent aloud to participants. We give them ample time to read the consent and ask any questions they have about the research. Then study staff ask participants a few questions to assess their understanding of the requirements of the study and staff provide corrective feedback if needed.

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☒ **N/A:** This study will not enroll Non-English speaking subjects.
(Skip to Section 28.8)

28.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 8.4 of this protocol.

Response:

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response:

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 28.9)

28.8 Describe the process to determine whether an individual is capable of consent.

Response:

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 28.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 28.9 and 28.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 28.11 and 28.12).*

28.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

28.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

28.11 Describe the process for ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects.* ***If some, indicate which adults will be required to assent and which will not.***

Response:

- ***If assent will not be obtained from some or all subjects, provide an explanation of why not.***

Response:

*28.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 29.0)*

*28.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response:

*28.14**For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

28.15 Describe whether parental permission will be obtained from:

Response:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

*28.16 Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

*28.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

28.18 When assent of children is obtained, describe how it will be documented.

Response:

29.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

29.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

29.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient

information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

30.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 31.0)

30.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response: All informed consent documents will be electronic, using e-consent within REDCap.

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

31.0 Multi-Site Research (Multisite/Multicenter Only)*

☐ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

31.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:.

See update in section 7.1 above. We are increasing the accrual goal to 102 per site.

Note that this protocol is for the UG3 phase and data will be collected only at the University of Pennsylvania and UB. The University of Pennsylvania will rely on the UB IRB.

The UH3 phase will be comprised of studies at the Medical University of South Carolina and at the University of Alabama at Birmingham. We will submit all materials for the two subsequent studies before those studies begin.

*31.2 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as the following.*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately in accordance with applicable federal regulations and local laws.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response: There will be weekly PI/coordinator meetings at the UB site and biweekly or monthly meetings between the UB and UPenn investigators and coordinators. The UB project manager, CeCe Duerr) will lead cross-site Coordinator meetings (monthly) and co-lead bi-weekly staff meetings.

The project will use single IRB, with UB as the IRB of record.

All consent, measures, and SAE reports will be contained within a common REDCap instance for both sites. This ensures that any changes made through IRB modifications will be consistent across sites.

31.3 Describe the method for communicating to engaged participating sites.

- *Problems (inclusive of reportable events)*
- *Interim results*
- *Study closure*

Response: All problems, interim consideration of AEs/SAEs, and study closure will be discussed in our regular team meetings (see above) and related email. Ad hoc communication by email, phone, and/or videoconference will supplement the regularly scheduled meetings as needed.

*31.4 If this is a multicenter study **where you are a participating site/investigator**, describe the local procedures for maintenance of confidentiality.*

- *Where and how data or specimens will be stored locally?*
- *How long the data or specimens will be stored locally?*
- *Who will have access to the data or specimens locally?*
- *Who is responsible for receipt or transmission of the data or specimens locally?*
- *How data and specimens will be transported locally?*

Response: N/A

31.5 If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described elsewhere in the protocol.

- *Describe when, where, and how potential subjects will be recruited.*
- *Describe the methods that will be used to identify potential subjects.*
- *Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response: **N/A**

32.0 Banking Data or Specimens for Future Use*

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*32.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

NOTE: If the UBIRB has approved this study to bank data and/or specimens for potential future use outside the scope of this research study, any future use or

disclosure of the data that is not described within the approved study must be submitted for review to the UBIRB.

Response: No biospecimens will be stored for phase 1 (UG3).

However, per NIH requirements, we plan to make the full **de-identified** data set (with metadata) available to the research community. Specifically, we plan to archive the data through the National Addiction and HIV Data Archive Program (NAHDAP), a NIDA-funded platform for data sharing/archiving, with a topical focus on behavioral health data. NAHDAP operates under the umbrella of the Inter-university Consortium for Political and Social Research (ICPSR), based at the University of Michigan. Per the ICPSR website, the ICPSR is "the largest social science data archive in the world". To protect participant privacy and confidentiality, shared data will be de-identified by removing PHI.

Consistent with NIH and Institute of Medicine recommendations, the data will be deposited no later than the publication of the primary study data or one year after the completion of this RCT, whichever comes first. We anticipate that data from this RCT will be archived in Year 3.

NAHDAP will determine how long archived data will be preserved. Given the size and longevity of NAHDAP and ICPSR, we anticipate the data will be available into the foreseeable future. One advantage of this repository is that it provides a unique digital object identifier (DOI) for the dataset.

32.2 List the data to be stored or associated with each specimen.

Response: We are not banking specimens, just data.

32.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: See above.