Stand Alone Protocol Title: Development and Pilot Testing of the Sense2Quit App
MPIs: Drs. Schnall and Huang
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SPECIFIC AIMS

Of the approximately one million persons living with HIV (PLWH) in the United States (U.S.), it is estimated that between 40-70% smoke cigarettes[1, 2], at least three times the prevalence observed in the general U.S. adult population (14%)[3]. Consequently, PLWH experience substantial tobacco-related morbidity and mortality. For PLWH, apart from achieving and maintaining a suppressed viral load, tobacco cessation is the most important health behavior they can undertake to maximize both quality of life and life expectancy[4]. Indeed, PLWH who quit smoking upon entering HIV care gain greater than 5 years of life expectancy as compared to those who enter HIV care and continue smoking[5, 6]. Given the high prevalence of cigarette smoking among PLWH and the benefit of smoking cessation, there is an urgent need to intervene to reduce tobacco use rates. However, the currently available evidence for improving tobacco cessation among PLWH is inadequate. Few tobacco cessation interventions have been tested among PLWH, and of those which have, there is 'very low' quality evidence that they were effective in the short-term and 'moderate' quality evidence indicating similar outcomes to controls in the long-term[7].

Given the few randomized controlled trials (RCTs) examining smoking cessation interventions for PLWH and the major methodological limitations of many of these studies (e.g., lack of randomization, comparison conditions, treatment fidelity assessments, abstinence verification tests), it is critical to develop evidence-based tobacco cessation interventions to address the complex and unique needs of PLWH (e.g., risk factors, treatment needs). Tailored cessation interventions for PLWH need to focus on the factors specific to PLWH which are associated to date with poor success with tobacco cessation efforts. For example, neurocognitive deficits are common among PLWH and are associated with poor quit rates and relapse, supporting the need for unique interventions for PLWH[8]. Additionally, specific factors such as self-efficacy and decisional balance have been shown to decrease the likelihood of relapse[9].

In recent years, use of mobile health (mHealth) technologies for tobacco cessation has gained popularity, such as Text2Quit[10] and the National Cancer Institute's (NCI's) SmokeFree Text[11]. While these programs have demonstrated positive effects in some populations[12-15], their functionality is limited because text messaging is unable to automatically capture instances when assistance resisting cravings is needed or when relapses occur. To address this need, our study team proposes to capitalize on sensor and mHealth technologies to integrate both behavioral assessment and a just-in-time cessation intervention for smokers. Our *Sense2Quit App* builds on the extant evidence that text messaging can be an effective tool for improving smoking cessation in the general population. However, text messaging as a stand-alone intervention has limited efficacy for PLWH who smoke[16]. To address this limitation, our team proposes to develop and pilot test the *Sense2Quit App* which specifically addresses challenges to tobacco cessation for PLWH: slips, relapses, and difficulties associated with neurocognitive deficits[8] and supports both self-efficacy and decisional balance[9]. *Sense2Quit* is a multi-component intervention that links a smartphone app to a smartwatch to provide real-time quit reminders to curtail relapses and avoid potential triggers. The artificial intelligence algorithm (validated by Multiple Principal Investigator [MPI] Huang) interprets time-series wearable sensor data to detect smoking gestures and motions – a technology with more than 98% accuracy in differentiating "lighting up" from other similar motions[17]. *Sense2Quit* leverages low-cost smartwatches to detect when smoking activity occurs so that an intervention message can be sent in real time to the participant via a linked smartphone app to help prevent the slip (a puff or two) from becoming a full-fledged relapse. This real-time feedback is critical especially in the first few weeks of a quit attempt. Additionally, Global Positioning System (GPS) data can help participants deal with geographical triggers (e.g., coffee shops, smoking relatives, friends' homes, etc.). Reminders to take nicotine replacement when around geographic triggers will be sent to participants instead of suggesting complete avoidance (e.g., 'You are now in a trigger area. Please take a moment to have a nicotine replacement/substitute.') Finally, *Sense2Quit* provides information on how well they are progressing through their quit plan as well as motivational tools (i.e., badges). Our MPI team brings unique and complementary expertise in each of the areas necessary (mobile health, health disparities, tobacco cessation intervention, software engineering, human computer interaction, and health behavior change interventions with PLWH) to develop and pilot test an innovative tobacco cessation intervention for PLWH. Participants will be recruited from clinics and community-based organizations in New York City (NYC). The specific aims of the study are to:

AIM 1: Explore and identify, using qualitative methods, acceptable and appropriate app content and features of the *Sense2Quit App* to support smoking cessation and relapse prevention in PLWH who smoke. We will conduct focus groups, design sessions, and usability assessments with HIV-positive daily smokers, former smokers, and usability experts. This feedback will guide tailoring of the app to this population of smokers.

AIM 2: Conduct a pilot randomized controlled trial to examine the feasibility, acceptability, and preliminary efficacy of the *Sense2Quit App*. We will randomize 60 HIV-positive smokers to the *Sense2Quit App* plus the Fossil Gen5E smartwatch, standard smoking cessation counseling, and nicotine replacement therapy (active condition) versus

standard smoking cessation counseling plus referral to NYC Quitline (control) in order to examine group differences in rate of quit attempts, 7-day point prevalence abstinence, and sustained abstinence.

AIM 3: Employ the RE-AIM framework to assess the potential scale-up of the *Sense2Quit App*.
IMPACT: Given the high rates of tobacco use among PLWH, the Sense2Quit App has considerable potential for reducing morbidity and mortality among PLWH who smoke.
AIM 4: Testing with Confounding Gestures. To improve the accuracy of smartwatch smoking detection within the current version of the app, we will perform additional testing on the smartwatch with participants who will complete a set of hand gestures to distinguish them from smoking gestures.

STUDY TIMELINE
We will implement a 2-year timeline to accomplish study specific aims. The details of the study activities, including development of the *Sense2Quit* App and the detailed timeline for the clinical trial, are listed in **Table 1**.

Table 1.

Timing (Year/Month)	Enrollment Target	Milestones
"Just in Time" 1-3		• Protocol & manual of procedures finalized Institutional Review Board (IRB) approvals • Recruitment: Pre-screen potential participants, contact participants from database, advertisements/brochures in local clinics, provider meetings, presentations to community groups about study
Year 1: 4-6		• Aim 1 – Focus Group Sessions • Coding of qualitative data begins
Year 1: 7-8		• Aim 1 – Design Sessions • Code and analyze qualitative data
Year 1: 9-10		• Aim 1 – Usability Testing • Complete qualitative analyses • Disseminate findings from Aim 1 through presentations and publications
Year 1: 11		• Prepare/submit Year 1 progress report & IRB continuing review
Year 1: 12	Begins	• **Pilot Trial enrollment begins** • Prepare/meet with safety officer for every 6-month review (after first patient enrolled)
Year 2: 13-15	20	• Enrollment continues
Year 2: 16-18	40	• Revisit enrollment progress and recruiting strategies; readdress as needed • Enrollment, study visits continue
Year 2: 19-21	60	• Prepare/submit IRB continuing review to complete data analyses • Aim 3 – Follow-Up Interviews
Year 2: 22-24		• **Last participant completes all study procedures** • Data cleaned, code transcripts for Aim 3, data analyses for Aim 1, begin Aim 2, 3 and 4 submit manuscript Dissemination of results • Study completed, results disseminated to the research and participant community • Submit R01 study to test the intervention in fully-powered efficacy trial.

SIGNIFICANCE

Cigarette smoking is highly prevalent among PLWH. The prevalence of smoking in the general U.S. population has gradually declined to 14% in 2017 – the lowest rate ever recorded[3]. However, this has not been true for PLWH who have disproportionately high smoking rates (40-70%)[1, 2]. In our studies across more than 550 PLWH in NYC, 47.1% of our participants are cigarette smokers (see **Table 1**), highlighting the need for interventions to improve tobacco cessation in this group. Tobacco use causes morbidity and mortality in PLWH, and tobacco-related harm is substantially higher in PLWH than smokers in the general population.

Table 1. Sample of Smokers among Studies of PLWH (PI: Schnall)

(Funding)	Period			Owner
Gender Supplement (R01NR015737-02S1)	Apr. 2017 – Mar. 2018	100	44%	94%
Wise App (R01HS025071)	Oct. 2017 – Aug. 2020	172	60%	100%
VIP-HANA (R01NR015737)	Nov. 2017 – Oct. 2018	105	47%	100%
mVIP (R21HS023963)	Sept. 2016 – Feb. 2017	80	23%	100%
InternationalHIV Network	Dec. 2015 – Sept. 2016	101	49 %	92%
Total		**558**	**47%**	

High rates of smoking have grave health implications for PLWH, placing them at increased risk for bacterial pneumonias[18], acute bronchitis and tuberculosis[19-26], early development of emphysema[27-32], and lung and cervical cancers at a younger age than the general population[33-38]. These disparities are partly due to a higher prevalence of tobacco use in PLWH than the general population and partly attributable to exacerbated co-morbidities such as cardiovascular disease, lung cancer, and diabetes in PLWH who smoke compared to non-HIV-positive smokers[39-41].

Smoking cessation efforts have largely been aimed at the general population. Consequently, it is not clear whether they are suitable or effective for cohorts with population-specific concerns and clinical issues such as PLWH[1, 21, 32, 42]. Further, three specific factors have been identified as contributing to poor quit rates and relapse in PLWH. First, ***neurocognitive deficits*** are common among PLWH and are a unique barrier to their smoking cessation, increasing the likelihood of relapse[8]. Mediators to tobacco cessation through nicotine replacement therapy such as self-efficacy and decisional balance have been more effective than motivational interviewing in PLWH. Therefore, ***decisional balance***, or perception of the pros versus cons of smoking[43], and ***self-efficacy*** through the provision of success experiences can do more to support long-term tobacco cessation in PLWH than motivational interviewing. Building on these three factors which contribute to slips, relapses, and poor quit rates in PLWH, our study will develop and test an mHealth intervention, the *Sense2Quit App*, which specifically targets these factors by providing just-in-time feedback through a sensor detection system, reminders, and information about the benefits of tobacco cessation to improve decisional balance[44]. Importantly, mHealth is a feasible platform for delivering this intervention since there is extremely high mobile phone penetration in the U.S.[45], especially among racial/ethnic minority groups[46]. mHealth technology can be used for achieving health equity in vulnerable groups because it is a widely available and relatively inexpensive tool for health behavior change[47] and can be adapted to meet the needs of its end-users[48-51]. **Our work has shown that even the lowest income and most health disparate persons own and use smartphones (Table 1)[52].** Therefore, our mHealth intervention, the *Sense2Quit App*, is timely, relevant, scalable, and likely to improve health outcomes in our health disparate study population – PLWH who smoke. Even when successful, however, there are barriers to widespread adoption and successful scale-up of tobacco interventions[53, 54]. Therefore, we will use implementation science in Aim 3 to understand and address the well-documented gap between 'research' and 'practice'[55]. To accelerate and improve the translation of research into widespread, routine practice, implementation will be actively considered and evaluated during the translational process[56]. Thus, this study will overcome the limitations of incremental, stepwise progressions of research (i.e., efficacy to implementation), reducing the length of the traditional research pipeline and yielding much richer data to directly inform more widespread scale-up efforts of the *Sense2Quit App* for tobacco cessation in PLWH.

INNOVATION

1) The *Sense2Quit App* uses a validated sensor to detect participants' smoking behaviors in real-time. The algorithm for detecting the smoking arm movement can be used to interpret data from a smartwatch[17]. Testing with confounding gestures will be completed as part of aim 4 to improve this algorithm.
2) We will combine biometric data with behavioral interventions specific to smoking behavior, an advancement and innovation not previously tested in PLWH.
3) The *Sense2Quit App* is a multicomponent intervention addressing each slip and craving, having the potential to empower smokers to succeed without relapse.

4) The ability for a mobile app to deliver content that would otherwise require staff and clinician time and resources, as well as burden participants, is an innovative approach to the delivery of a tobacco cessation intervention.

INVESTIGATORS

The investigative team has previously worked together. Formative focus groups were conducted with African American PLWH in NYC, and findings were disseminated by MPIs Drs. Schnall and Huang[57]. Further, Drs. Schnall and Cioe (Co-Investigator) have been long-time colleagues as Editorial Board members of the *Journal of the Association of Nurses in AIDS Care (JANAC)*; additionally, they work closely on a small committee to determine the *JANAC* Article of the Year.

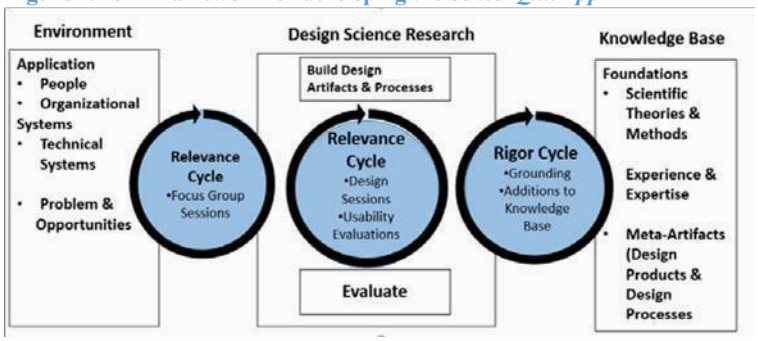
Case Western Reserve University (CWRU). Dr. Ming-Chun Huang, PhD, will commit his effort in the research activities in the CWRU site and will be responsible for designing and optimizing Sense2Quit sensors, app interfaces, and advanced data analytics methodology to improve performance and user-friendly operation of mobile and wearable devices. Our sponsored GRA will focus on the aims including wearable system interfacing, App integration, algorithm development under the supervision of Dr. Huang and also help in research dissemination by publishing research results from this project to peer-reviewed journals, and present at premier conferences. Dr. Huang has an over six-years of dedicated research on wearable sensors and mobile sensing technologies development with 20+ conference and journal publications. He led a well-established research team in terms of solid theoretical, technological, experimental, and societal foundations to contribute to this project.

Brown University. Patricia A. Cioe, PhD, will serve as Co-Investigator and will be responsible for assisting the Principal Investigator with planning and oversight of study procedures, data collection, and use of instruments for measurement of smoking cessation outcomes throughout the course of the study period. Dr. Cioe will assist with interpretation of the study results and will contribute to publications and dissemination of data.

APPROACH

Theoretical Framework for Developing the mHealth Decision Support Tool. This study is guided by the Information System Research (ISR) Framework **(Figure 1)** that will inform the design of the *Sense2Quit App*. The ISR framework has been used to design two mobile apps for ongoing studies (R01HS025071, U01MD011279), and has been cited over 200 times in the past four years to support the design of mobile apps[58]. The ISR Framework employs three research cycles to build a product such as an mHealth app: 1) the Rigor Cycle - to evaluate and update the knowledge base; 2) the Relevance Cycle - to understand the environment of the end-user by determining requirements through a series of focus group interactions with stakeholders (PLWH current and former smokers); and 3) the Design Cycle in which artifacts produced and evaluated[59]. The cycles do not need to be conducted linearly, and it may be preferable to conduct them in an iterative process.

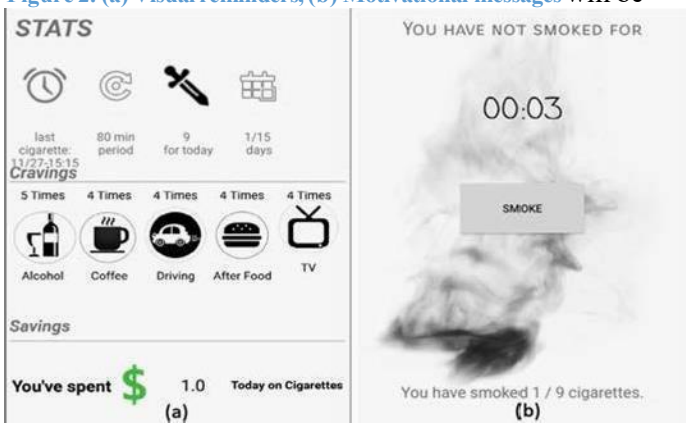
Figure 1. ISR Framework for developing the *Sense2Quit App*



Overview:

A research study involving a mobile technology intervention for persons living with HIV (PLWH). The research activities will take place in New York City, and data collection will take place at Columbia University. Participants will be recruited online and offline through social networking websites and apps and through local community-based

Figure 2. (a) Visual reminders, (b) Motivational messages will be



organizations, health centers, and local events. The study will test the *Sense2Quit App* for smokers living with HIV.

Participants in the intervention arm will receive Nicotine replacement therapy (NRT). Participants will be provided with an 8- week supply of combination NRT that they will begin after the baseline visit. The quit date will be the date of their baseline visit. Participants will be offered all 3 forms of NRT (patch, lozenge, gum) and will be allowed to choose 2 forms (combination: patch/lozenge or patch/gum) to use.

Participants who smoke 10 or more cigarettes per day will receive the following dosage for their NRT patch: one 21 milligram patch per day for 4 weeks; one 14 milligram patch per day for 2 weeks; and one 7 milligram patch per day for 2 weeks. Participants who smoke less than 10 cigarettes per day will receive the following dosage: one 14 milligram patch per day for 6 weeks and one 7 milligram patch per day for 2 weeks. This is considered the standard clinical treatment, and participants will receive additional instructions on usage of the patch. Participants will be told the risks of using the patch, which include skin irritation, itching, dizziness, headache, rapid heartbeat, and nausea. Participants will also be advised that they can curb additional cravings with their choice of Nicotine gum or lozenge available for purchase over-the-counter.

Setting. The study will be conducted at Columbia University which provides HIV care for a diverse group of more than 2,000 PLWH. A recruitment plan, which outlines how participants will be recruited through the clinic and community-based organizations, is outlined below.

Participants.

Inclusion criteria: For Aim 1, (1) PLWH; (2) ≥ 18 years of age; (3) current or former smoker (where smoking is defined as ≥5 cigarettes a day for the past 30 days, past smoker is defined as having at one point smoked a minimum of ≥5 cigarettes per day for a period of at least 30 days) and (4) understand and read English; Aims 2 and 3 follow the same inclusion criteria with the added criteria that (1) PLWH will be confirmed through medical records or pill bottles for ART medications; (2) only current smokers are eligible (where smoking is defined as ≥ 5 cigarettes a day for the past 30 days); (3) own an Android smartphone (if they do not have a phone compatible with the app, they will be provided with one to use during the study); (4) not pregnant or breastfeeding (due to contraindications for Nicotine Replacement Therapy [NRT]); (5) permanent contact information; (6) interested in quitting smoking within 30 days; and (7) blows ≥ 5 CO into a breath analyzer at baseline. For Aim 4) participants will be PWH who smoke cigarettes and will either be 1) enrolled participants at their 12-week follow-up visit; 2) participants who are initially eligible for the study after completing the screener but do not qualify based on eCO levels; or 3) participants who already finished Aim 2 (and 3, if applicable).

Exclusion criteria. For Aim 1, participants will be excluded if they do not meet the defined inclusion criteria. For Aims 2 and 3, the exclusion criteria will be (1) use tobacco products other than cigarettes (i.e., cigars, piped tobacco, chew, snuff); (2) planning to move within 6 months of enrollment; (3) alcohol dependence measured through the AUDIT-C[60]; (4) positive history of a medical condition that precludes nicotine patch use; (5) current use of NRT or other smoking cessation medications (e.g., Chantix or Zyban); (6) current enrollment in another smoking cessation program; and (7) household member is also participating in the Sense2Quit study (due to study contamination). For Aim 4, participants will be excluded if they fail to meet the inclusion criteria.

Inclusion of Individuals

Across the Lifespan: Our study will not include children. All participants in this study will be 18 years or older. Given the current age breakdown of the epidemic with approximately 2.5% or less of new diagnoses of HIV infection occurring in those who are under 18 years of age, children (under 18 years of age) are not a major epidemiologic concern for this study. Further, given that most children 18 years of age are newly diagnosed (within the past 1-2 years) with the infection and there could be many psychological implications of a new HIV diagnosis, tobacco cessation is a secondary concern to sustaining these children and participation in this study may divert their focus from their need to focus on starting HIV treatment.

There is no upper-age limit for participation in this study. Based on our past studies with persons living with HIV, we anticipate that ~5% of our study sample will be over 65 years of age.

Inclusion of women:

The aims of this proposal are geared towards improving tobacco cessation in persons living with HIV (PLWH) who smoke. We will enroll at least 40% women in this study to ensure that we can compare differences in the intervention effect between men and women. Our study team has extensive experience recruiting and enrolling PLWH into study trials. More specifically, Dr. Schnall has experience and success recruiting women living with HIV into her studies

(R01NR015737, R21HS023963, R01HS025071).
We will purposefully enroll a minimum of 40% females and stop enrollment of males at 60% of the sample to force female enrollment. We will also track refusals, reasons, and demographic characteristics of those refusing to participate and examine those data as part of our ongoing data safety and monitoring activities.

Inclusion of Minorities

Dr. Schnall has extensive experience recruiting PLWH of diverse racial and ethnic backgrounds in her prior investigations. It is planned for this investigation that at least 75% of the enrolled participants will be of diverse racial and ethnic backgrounds, largely from Latino and Black/African American backgrounds. In our past work in New York City (NYC), nearly 90% of our study participants are Black, Latino, or Black and Latino.
Several strategies will be employed at both study sites to maximize the potential of enrolling many racial and ethnic minorities in the study. The strategies that will be employed are:

1. Partner with PLWH of diverse racial and ethnic backgrounds at HIV clinics and community organizations to identify successful strategies to promote engagement of diverse populations of PLWH. Dr. Schnall has an ongoing relationship with community-based organizations throughout NYC and has worked closely with these community-based organizations (e.g., Gay Men's Health Crisis, Alliance for Positive Change, LGBT Center, Iris House, Callen Lorde) during her past and ongoing studies to recruit study samples and has consistently met her recruitment goals across all studies per project timelines.
2. Host tables with information about our study at health fairs in diverse neighborhoods and at churches, community organizations, and wellness events.
3. Present an overview of the study at invited patient-centered presentations at HIV community organizations in areas that are comprised of participants of diverse racial and ethnic backgrounds.
4. In addition to posting study flyers, we will use previously successful online recruitment methods such as online postings and social media. Specifically, we will post our study ads on Craigslist, a free online classified service that is one of the most popular websites in the United States. It has been used successfully in online work, including our own current National Institutes of Health- and Agency for Healthcare Research and Quality-funded HIV self-management studies (U01PS003715, R01NR015737, R21HS023963, R01HS025071, R01MH118151; PI: Schnall) which have all been completed per project timelines.
5. Recruitment through clinics and community-based organizations. One of our primary clinic sites is the Comprehensive Health Program of New York-Presbyterian/Columbia (NYP-CHP). The NYP-CHP is a Ryan White funded, bilingual, patient-centered clinic that emphasizes sexual health, hepatitis management, and HIV care. It primarily serves Upper Manhattan and the South Bronx where residents are disproportionately affected by HIV. NYP-CHP's large multidisciplinary team provides HIV care to a population of more than 2,300 children, adolescents, and adults through more than 16,000 visits per year. NYP-CHP clients are 58% male, 40% female, and 2% male to female transgender.

RECRUITMENT AND RETENTION PLAN

Study Settings.

This study will be conducted at the Columbia University School of Nursing in collaboration with the Comprehensive Health Program of New York-Presbyterian/Columbia (NYP-CHP). The NYP-CHP is a Ryan White funded, bilingual, patient-centered clinic that emphasizes sexual health, hepatitis management, and HIV care. It primarily serves Upper Manhattan and the South Bronx where residents are disproportionately affected by HIV. NYP-CHP's large multidisciplinary team provides HIV care to a population of more than 2,300 children, adolescents, and adults through more than 16,000 visits per year. NYP-CHP clients are 40% female. In addition to the clinic, Dr. Schnall has an ongoing relationship with community-based organizations throughout New York City (NYC) and has worked closely with these community-based organizations (e.g., Gay Men's Health Crisis, Alliance for Positive Change, LGBT Center, Iris House, Callen Lorde) during her past and ongoing studies to recruit her study sample and has consistently met her recruitment goals across all studies per project timelines. Recruitment for participation in the study will occur following approval by the CUIMC IRB.

Recruitment Challenges.

If recruitment for this study proves difficult, in addition to posting study flyers, online recruitment methods will be used such as online postings, Recruitme and social media which the study team has used successfully in the past. Specifically, study flyers will be posted on Craigslist (a free online classified service that is one of the most popular websites in the United States) and POZ.com which have been used successfully in online work, including the study team's current National Institutes of Health and Agency for Healthcare Research and Quality-funded HIV self-management studies (U01PS003715,

R01NR015737, R21HS023963, R01HS025071; PI: Schnall) that have all been completed per project timeline. *Craigslist* is widely used in NYC. Each Craigslist has a *Volunteers* section. The research assistant will post numerous ads per week. This will be repeated each week to reach and recruit a diverse sample.

Facebook and Instagram. The study team had great success in recruiting diverse samples from social networking sites, like Facebook and Instagram, where psychographic targeting (in-depth publicly available consumer data such as interests, occupation, and city) is used, as well as boosting posts and asking colleagues to post campaigns to their pages.

Retention Plan

Our study team has developed several successful strategies for retaining study participants during our study period. Strategies used successfully in our previous studies include confirming contact information at each assessment and obtaining contact information of two or more people who will know how to contact them. In addition, a token of appreciation will be provided for completion of all study questionnaires. Importantly, our team has a strong track record of retention of study participants across past trials. Notably these participants are typically those who are most difficult to retain in studies (e.g., low income, unstable housing, co-morbid psychiatric conditions, illicit substance use). We have conservatively estimated an 80% retention rate at the follow-up assessment for each study arm based on our past work with this study population. Specifically, our R21HS023963 study had a 5% attrition rate at 12 weeks, and our current R01NR015737 has an attrition rate of 12% at 3 months and 14% at 6 months.

The foremost important retention strategy will be the personalized attention participants receive from the research staff from the first visit forward. Participants interact with staff members during each of their visits and phone calls, thus providing the opportunity for frequent assessments of engagement with the mobile Health app and to discuss other study related concerns. Information that is to be recorded by the participants (e.g., assessments) is reviewed by staff members (and clarified, if necessary). Participants will be provided opportunities to communicate, either verbally or in writing, any concerns they have regarding participation in the study. During the intervention, an unexpected absence from scheduled assessment appointments generates a phone call to the participant. If contact with the participant is not established after several attempts by telephone or letter, a certified letter is sent. Failure to receive a reply to the certified letter would result in the participant being designated as having dropped from the study.

The retention plan harnesses the previously used retention strategies including phone calls, texts, emails, and/or letters to participant to remind them about their upcoming appointment; providing bus or parking validation/vouchers for study visits; and hiring professional staff with whom many of the participants will have a long-standing and trusting relationship. Additionally, each of our sites will provide compensation (amount determined by site-specific norms and in collaboration with the local Community Advisory Boards) for the additional time to complete the study-specific research procedures.

STUDY PROCEDURES

Intervention: The *Sense2Quit App*

Sense2Quit is a multi-component intervention that links a smartphone app to a smartwatch and addresses tobacco cessation challenges for PLWH, namely providing real-time quit reminders to curtail the urge to smoke and avoid potential relapses (validated by MPI Huang). *Sense2Quit* will be extended through machine learning to interpret data from a smartwatch to detect smoking hand gestures and motions and differentiate them from other common daily activities (e.g., drinking from a cup, answering the phone, etc.)[17] and

Figure 3. Smartwatch screenshots, (a) daily progress summary, (b) detecting smoking motions, (c) motivational messages to show (c) motivational messages to show how long the user has maintained the quit plan

aid with PLWH-specific daily activities such as taking medicines and tracking hygiene habits. Our pilot data has shown that our developed smoking gesture detection algorithm can be used among various wearable brands including Myo, Moto360, Misfit Vapor 2, and Skagen Falster 2 (unpublished). *Sense2Quit* leverages smartwatch data **(Figure 3)** and detects when smoking activity occurs so that a message can be sent in real time to the participant via a linked smartphone app to help prevent the slip (a puff or two) from becoming a full-fledged relapse. This real-time feedback is critical especially in the first few weeks of a quit attempt. The base algorithm for the *Sense2Quit App* has been validated and pilot tested, but the user interface of the App, PLWH-specific daily activities, the alerts, and the just-in-time intervention message delivery service have not been developed or tailored for PLWH. This will be achieved through Aim 1 described below with methods summarized in **Table 2**.

Informed Consent

The study team under the direction of the MPIs will determine eligibility for inclusion, explain the purpose of the study, answer any questions, and obtain written consent from the participants. Informed consent will be obtained for each of the study components in Aims 1 and 2, and 4. Interested volunteers who agree to participate will sign an electronic consent form. Potential risks and strategies for managing risks will be carefully explained as part of informed consent procedures. The study team will use REDCap's E-Consent Framework to electronically collect and store consent documents. REDCap uses survey features to consent research participants and forms can be completed via computer, mobile phone or tablet. CUMC- approved REDCap is secure with restricted access that ensure confidentiality of a participant's identity, study participation and personal information. Additionally, REDCap is easy to navigate, and information will be on one scroll-able page.
There is functionality within the system and to stop and continue at a later time. REDCap also allows for generation of a copy of the informed consent form signed by the study participant, which can be downloaded at any time. In REDCap, all versions of the IRB-approved e-Consent Form and all signed e-Consent Forms can be accessed and retrieved easily.

AIM 1. Explore and identify, using qualitative methods, acceptable and appropriate app content and features of the *Sense2Quit App* for smoking cessation and relapse prevention in PLWH who smoke.

Table 2. Overview of Aim 1 Research Design and Methods

	Cycle I: Relevance Cycle	Cycle II: Design Cycle: Develop/Build	Cycle III: Design Cycle: Evaluate
Sample	• 40 PLWH who smoke or are former smokers	• 10 PLWH who smoke	• 5 experts in human computer interaction for heuristic evaluation • Usability Testing: 20 PLWH who smoke or are former smokers
Instruments	• Focus Group Guide	• Interview guide • Preliminary designs of mobile apps	• Usability Testing Survey • Heuristic Evaluation Survey • Health-ITUES[61, 62]
Procedures	• Four focus group sessions (N=40)	Session 1: 1. Review content, features, & functions from focus group sessions & literature review 2. Discussion based on structured questions 3. Brainstorm functional requirements Session 2: 1. Review potential app designs & confirm/revise them 2. Sketch user interface	• Heuristic evaluation • Usability testing
Analysis	Thematic analysis	Descriptive analysis	Descriptive analysis

The Relevance Cycle:

Procedures. We will conduct focus groups with 40 intended e-users (see inclusion criteria). Prior to the start of the focus group session, we will collect demographic information. Focus groups will be 60-90 minutes. Following informed

consent, sessions will commence and be audio-recorded. Dr. Schnall, who has conducted focus groups for requirements analysis in the past[56, 58, 63-66], will facilitate the sessions with project staff as note-takers.

Sample focus group questions for PLWH who smoke are:

1) What are the barriers to quitting smoking?
2) What messages would motivate you to not light up your cigarette?
3) What information would you like to see included in an app?
4) What messages would deter you if were about to start smoking a cigarette?
5) How frequently do you want to receive reminders about your quit plan?
6) How frequently do you want alerts about your accomplishments?
7) What are your triggers? And what is the best time for you to receive an alert about the trigger?

The team will adhere to qualitative research processes to ensure the *credibility, confirmability,* and *transferability* of the data from these analyses. To support the data credibility, we will conduct peer debriefing and triangulate findings. We will also use member checks, i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance confirmability of the interpretations.
Compensation: Eligible participants will be able to receive $35 for participating in the focus groups.
Data Analysis. All qualitative data will be transcribed verbatim and then coded. Thematic analysis will be used for the development of a coding scheme, which is an integral component of the data analysis process. It enables the systematic examination and interpretation of data related to the primary analytic foci. The coding scheme is conceptualized as a multilevel structure. At the highest level are the primary analytic foci coded as headings. Specific aspects or dimensions of the headings are assigned core codes. Specific aspects or dimensions of the core codes are assigned sub-codes. We will use Nvivo™ (QSR International, Victoria, Australia) software program for qualitative analysis. The following seven steps will be used to develop the coding scheme:

- Step 1: Identify the principal issues discussed by participants;
- Step 2: Construct definitions of the primary analytic themes;
- Step 3: Develop and apply core codes and sub-codes to the initial set of data;
- Step 4: Develop a provisional coding scheme;
- Step 5: Test and refine the provisional coding scheme;
- Step 6: Reconcile coding differences and construct an updated and final coding scheme;
- Step 7: Apply the coding scheme to the full data set and assess inter-coder reliability. After all transcripts have been coded, we will extract and examine the content of text segments linked to core codes and sub-codes relevant to understanding barriers and facilitators to the use of the App and its content.

The Design Cycle: Develop/Build Phase: In this phase, focus is on creation of a highly usable artifact (mHealth app). To achieve this, we will incorporate findings from the earlier parts of our study, including a list of content, features, and functions from the focus groups. We will conduct two design sessions.

Design Session I: We will recruit 10 PLWH who smoke to participate, and each will be expected to attend two sessions.
Sample: Focus group methodology will be used as it permits participants to use their own words to answer open-ended questions and react to each other's responses[67]. This interaction should elicit the most useful information.
Procedures. The goal of the first design session will be to identify optimal features for the *Sense2Quit App*. Each session will be audio recorded and is anticipated to last 60-90 minutes. Building on focus group findings and the extant literature and mobile apps, we will develop an initial list of content, features, and functions prior to the design session. We will ask participants to imagine each of the broad categories, identified from our focus group analysis, as a separate screen on a mobile app. We will present this information and ask participants to discuss the content and features they think should be included as functionality in a mobile app. Because we do not want to stifle creativity, we will not show existing apps or prototypes except when participants have difficulty envisioning the content or features of the app. Participants will be encouraged to draw sketches of the app, which has been successfully completed in our past work with PLWH.
Compensation: Eligible participants will be able to receive $35 for participating in design session I.

Design Session II:
Procedures: The goal is to gain information about the user interface to inform the development of prototypes. We will audio record the session, which is anticipated to last 60-90 minutes. We will divide participants into two groups and ask

each group to sketch a user interface of the desired mobile app. We will present findings from the first design session as categories along with pictures of existing nutrition apps. Participants will be asked to identify the components to include under each topic area and will be reminded that each category would be a screen on the App. They will also be asked to describe the organization of the content and features and the desired "look" of the user interface they would want to see in an app. After participants share ideas, we will follow up with questions to stimulate discussion about the existing apps and the need for refined content, features, and interface design. We will ensure that the App is usable and will ask questions such as, "Are the alerts useful to you?"
Compensation: Eligible participants will be able to receive $35 for participating in design session II.

Data Analysis of the data collected in the design sessions will be the same as the procedures described for data analysis of the Relevance Cycle data.

The Design Cycle: Evaluate: The goal of this phase is to improve the App design and increase the likelihood of technology acceptance[68]. We will evaluate the user interface and system functions of the prototype and assess whether they are consistent with the end-user's needs. We will conduct two types of usability assessments: 1) heuristic evaluation of the prototype using informaticians with experience in interface design and/or human-computer interaction, and 2) end-user usability testing with PLWH. We will use an iterative process in which one heuristic evaluator and four end-users will evaluate the *Sense2Quit App* for PLWH and then changes will be made based on recommendations. Five versions of the app will be created, each building on an earlier version.

Heuristic Evaluation.
Participants. Five experienced informaticians will participate as usability experts, based on the number recommended by Nielsen[69]. Each expert will have training in human-computer interaction, hold at least a master's degree, and have published in the field of informatics.
Procedures. Usability experts will be provided with a description of the full functionality of the prototype App. Each human-computer interface expert will test the prototype user interface with use case scenarios for approximately 45-90 minutes on Zoom alongside research staff. Because the visits will be remote, a research staff member will share their screen so that the experts are able to view the app. Experts will instruct the research staff member which tabs or buttons they should click on to perform specific tasks on the app. They will be asked a series of interview questions regarding the app's usefulness and appropriateness for people living with HIV who want to quit smoking. The process will be audio and video recorded using Zoom. Recording the users' interactions and vocalizations provides additional feedback to highlight problems that would not be identified with static screenshots[70]. Experts will evaluate the App using a think-aloud protocol as they perform the assigned use case scenarios, and then complete a Heuristic Evaluation Survey to evaluate the extent to which the user interface violates a set of usability heuristics. They will indicate specific areas of usability problems and rate the severity of each problem[73, 74].
Compensation: Usability experts will be able to receive $150 for participating in the 2-2.5 hour heuristic evaluation session.
Data Analysis. Mean severity scores will be calculated for each heuristic principle. Evaluators' comments about usability problems on the evaluation form and the recordings will be used to refine the prototype App.

Usability Testing with End-Users (PLWH).
Participants. We will recruit 20 PLWH who are either current or former smokers and have not participated in the earlier phases of the study activities to evaluate the prototype user interface screens. Eligibility criteria will be the same as described above for Aim 1. We will use similar recruitment methods as those used for the other study aims.
Procedures. Participants will be assigned tasks to perform on all screens of the app and their use of the App will be recorded using an audio recording device. After the usability evaluation, participants will rate the prototype's usability using the Health Information Technology (IT) Usability Evaluation Scale (Health-ITUES)[61, 62]. This tool differs from traditional scales as it is designed to support customization at the item level to match the specific task/expectation and health IT system while retaining standardization at the construct level; it has been validated for mHealth technology evaluation[63]. Compensation: Eligible participants will be able to receive $40 for participating in the 2-hour usability testing evaluation. Data Analysis. Analysis will be based on recordings of user sessions, transcriptions, notes, and the user survey. The team will search for critical incidents characterized by comments, silence, and repetitive actions. We will review these using the recordings and summarize incidents and written comments. Descriptive statistics of the Health-ITUES will be calculated.

AIM 2: Conduct a pilot randomized clinical trial to examine the feasibility, acceptability, and preliminary efficacy

of the *Sense2Quit App*.

Purpose: The purpose of this aim is to conduct a pilot feasibility study of the preliminary efficacy of the *Sense2Quit App* for improving tobacco cessation in PLWH who smoke.

Study Design: The study will be conducted with 60 PLWH who smoke and will be randomized to two arms. Participants will be randomly assigned to receive the *Sense2Quit App* (active) or a control condition (standard smoking cessation counseling session). Participants will also receive a survey at baseline, 4, and 12 weeks post-baseline.

Sample Size and Power: The goal of this pilot study is to estimate the cessation rates in each arm to obtain an effect size for future larger studies. To conduct a hypothesis test for the comparison of cessation rates between the two intervention arms will require a minimum 199 people in each arm (total sample=398) for at least 80% power. This calculation was based on a 2-sided test with the type I error of 0.05, and assuming a 20% cessation rate in the *Sense2Quit App* group (intervention) and a 10% cessation rate in the control arm. The 10% difference would be equivalent to a medium effect size (Cohen's d=0.45). In this pilot study, we propose a total sample of 60 (30 per group) of whom we expect there to be 20% attrition. Therefore, this study is not powered to detect a significant difference between study arms. Instead, for the sample size (30 per group), this study will have at least 80% probability that the standard error of the cession rate estimates ≤7%, We assume that the expected cessation rates range from 10% to 20%, and therefore the sample size is sufficient to provide a power estimation for a larger trial with acceptable reliability.

Recruitment and Retention: Strategies for recruitment and retention are described in the Recruitment and Retention attachment. We will enroll 60 PLWH who smoke tobacco. Inclusion/exclusion criteria are described above.

Screening: Potential study participants will provide verbal informed consent by phone or complete an eConsent form through REDCap prior to completing a phone screening process that assesses eligibility. If eligible, participants will attend a baseline session described below.

Procedures: Eligible participants will attend a baseline visit at Columbia University School of Nursing. On the day of their baseline appointment, study participants will meet a study staff member who is trained by a nurse. The study staff member will run the baseline appointment. Upon arrival, participants will be asked to blow into a breath analyzer to complete assessment of their study eligibility. Breath samples will be analyzed for exhaled carbon monoxide (CO) levels (in ppm) using a breathalyzer (Micro$^{+TM\ basic}$ Smokerlyzer®). After providing written consent, participants will complete a baseline questionnaire (See **Table 3**). They will be asked complete a timeline to follow back to track their cigarette use for the previous 30 days and to complete the Fagerstrom Test for Nicotine Dependence. Survey instruments will be collected through Qualtrics at baseline, and 4 weeks, and 12 weeks after baseline.

Following completion of baseline study instruments, participants will be randomized (1:1) to the App arm or the control arm, stratified by sex assigned at birth. Participants in both arms will undergo a smoking cessation counseling session. Notes from the counseling session will be recorded on RedCap. Participants will receive an informational packet during the counseling session which will consist of: 1) an appointment reminder sheet, nicotine patch information, nicotine gum information, nicotine lozenge information and smoking substitution ideas (Intervention) or 2) a reminder sheet, NYS Quitline information, and smoking substitution ideas (control). Participants in the control arm will be referred to the New York State Smoker's Quitline. Through the Quitline, participants in the control arm can receive NRT if desired and receive additional smoking cessation counseling. A study staff member will follow up to see how many participants called, texted and/or visited the Quitline webpage. Participants in the intervention arm (App arm) will be provided with combination NRT. Participants will be given an 8-week supply of combination NRT and will be instructed to begin using their NRT supply directly after their baseline visit. Participants will be offered all 3 forms of NRT (patch, lozenge, gum) and will be allowed to choose 2 forms (combination: patch/lozenge or patch/gum) to use. Also for those in the intervention arm, study staff will provide participants with a Fossil Gen5E or TicWatch smartwatch and initiate the *Sense2Quit App* on the participant's smartphone. If a participant's smartphone is not compatible with the Sense2Quit app, they will be provided with a smartphone to be used during the 12-week long study.

The *Sense2Quit App* will passively collect smoking data, such as when the user smokes (time of day, day of week, before/after eating, after waking up/before going to sleep, before driving to/from work, while driving), where the user smokes, and who is nearby. The *Sense2Quit App* will provide real-time feedback to participants, providing them with tips and messages to urge them to quit smoking when they lift their hand up for a smoke. The *Sense2Quit App* will be paired with the smartwatch so that smoking will be detected by the smartwatch and will be sent directly to the App. The *Sense2Quit App* will reliably predict cravings, target users with notifications to prevent individuals from smoking, refine notifications for each user, and display their change in smoking behavior in a smoking graph and money spent in a cash spent graph. Users will also be able to see their quit plan with their assigned quit date which will be baseline or another set date within a short period after baseline (i.e. within a week of completing the baseline visit), along with smoking trends, supporting tips, videos and games. The study staff member will show the participant how to use the app, and will also help them set up a reminder to take their daily HIV medication and use NRT at their baseline appointment. Participants will wear the smartwatch and

use the app for the duration of the study period. Two days after baseline, a study team member will reach out to the intervention arm study participant to see if they have any questions or issues with the *Sense2Quit App* and/or watch. The study coordinator will be able to access smoking behaviors and subject information through the online dashboard. The study coordinator will also reach out to participants in both arms once a week through phone call to check-in about their quitting process. At 4 and 12 weeks after baseline, participants in both study arms will attend a follow-up visit at the study site. Participants will report a 7-day point prevalence abstinence of smoking cigarettes[76] and provide a breath sample using Micro$^{+TM\ basic}$ Smokerlyzer®. They will also be given a follow-up survey with questions asked at baseline and process questions dictated by the primary outcomes that assess usability and acceptability of *Sense2Quit* (see **Table 3**). We will use skip logic features in our study surveys to identify subjects who select certain responses indicating depression, substance abuse, and/or alcohol abuse and referral information will be presented at the end of the survey. Referral information will include contact information for the Comprehensive HIV Program (CHP) at New York-Presbyterian/Columbia University Irving Medical Center, which offers comprehensive care and services for people living with HIV. Participants completing the survey(s) on-site will be asked if they want to be escorted by staff to CHP.

Table 3. Study Measures

Construct	Measures
Demographics	Gender, age, education, income, employment, health insurance, housing, time since diagnosis with HIV, health literacy (measured by S-TOFHLA),[75] and co-morbid conditions
Tobacco Use History	Age of initiation, current smoking, daily smoking, e-cigarette use, types of products used, history of quit attempts, prior use of quitline/telephone counseling services
Tobacco Cessation	CO lung/blood concentration, 7-day point prevalence abstinence – Timeline follow-back[76, 77] (confirmed with saliva cotinine); number of quit attempts; days of continuous abstinence
Illicit Substance and Alcohol Use	NIDA ASSIST[78, 79], AUDIT-C[60]
Predictors of Tobacco Cessation	Fagerstrom Test for Cigarette Dependence,[80] Readiness to quit[81]
Cravings and Withdrawal	Minnesota Withdrawal Scale[82]
Psychosocial Factors	Depression: CESD score[83]; Anxiety: STAI score[84], Social support[85]
Marker of HIV/AIDS immune status	CD4, viral load (chart review), Case Adherence Index (self-report)[86]
Follow Up Visit Only	
Pharmacotherapy Use	Nicotine replacement therapy Adherence
Intervention Quality	Health-ITUES[63]; Post-System Study Usability (PSSUQ) [87], Intervention ratings

Operationalization of Outcome Measures:

The primary outcome for determining preliminary efficacy will be biochemically (saliva cotinine) validated 7-day point prevalence abstinence.

Subjective Data (e.g., health status, quality of life) and system use will be obtained from subjects for the specific research purposes of this study. Follow-up visits will be completed on-site at the study location.

Carbon Monoxide Monitoring. We will be using a carbon monoxide detector to biochemically verify tobacco use. *Medical Records.* We will be reviewing patient records to assess participants' CD4 and viral loads. For participants who are not patients at CUIMC, they will be asked to bring in their most recent CD4/viral load laboratory data from their last visit to their healthcare provider.

Compensation: Eligible participants will be able to receive $40 for completing baseline study procedures, $50 at the 4-week follow-up study visit, and $60 at the 12-week follow-up study visit.

Data Analysis: This is a pilot study to assess preliminary feasibility, acceptability, and efficacy. Descriptive statistics will be used for all analyses. The rate of quit attempts will be calculated as the proportion of smokers who attempt to quit (i.e., no smoking during a 24 hours period); 7-day point prevalence abstinence will be calculated as the proportion of smokers who are biochemically verified (saliva cotinine) 7-day abstinence at a given time point; and sustained abstinence will be calculated as proportion of days of no smoking starting on the quit date among those who attempt to quit. We will provide point estimates and corresponding confidence intervals of these measures for each arm. Because of our small sample sizes, we will obtain Clopper-Pearson exact confidence intervals based on the binomial distribution. Given the small sample size, the purpose of the arms is to monitor for unexpected, gross differences between the two groups. To determine acceptability, we will ask participants in both arms how useful each of the intervention components were (1 =*Not at all useful* to 7 = *Extremely useful*) and whether they would recommend the program to a friend (1 = *Definitely would not recommend* to 7 = *Definitely would recommend*). For the intervention to be deemed acceptable, the mean level for each of these measures would have to be five or

higher. The efficacy of the intervention will be based on saliva- confirmed 7-day point prevalence abstinence at the final study visit. Lost-to-follow-up participants will be included as smokers.

NOT-OD-15-102: Consideration of Sex as a Biological Variable: In accordance with NIH guidance, we will include sex as a biological variable in the study design (enroll equal numbers of males and females), analyses, and reporting. We will report all primary and secondary outcomes separately by sex to enhance rigor and transparency of our findings in addition to including sex in all multivariate models.

AIM 3: Employ the RE-AIM framework to assess the potential scale-up of the *Sense2Quit App*.

In addition to testing the **E**fficacy of the *Sense2Quit App*, we will concurrently measure the four remaining RE-AIM dimensions[88] as follows:

Reach – 1) percent and demographic and clinical characteristics of those who joined the study based on current national statistics of PLWH, and 2) percent and demographic and clinical characteristics of those randomized to the intervention who used the app compared to those who did not.

Adoption – We will recruit study participants from the intervention arm (N=30) to assess acceptability and perceived usefulness of the *Sense2Quit App* (see **Table 4**). Interviews will be collected until saturation is reached, but we estimate up to 30 participants.

Table 4. Follow-up Sample Interview Guide

- Describe your general perceptions of the ***Sense2Quit App*** and its usefulness for helping with tobacco cessation.
- How helpful was the ***Sense2Quit App*** for improving your tobacco cessation?
- What would you change or improve about the ***Sense2Quit App***?
- How did the ***Sense2Quit App*** help you gain information about your tobacco cessation?
- How comfortable were you in using the ***Sense2Quit App*** in social settings? Probe: where and when did you use it mostly?
- How often did you use the ***Sense2Quit App*** in a typical week? Would you recommend it to a friend?
- Did you stop using the App altogether at some point? (If yes) Why?
- Describe the usefulness of the reminders to overcome your triggers.

Implementation and Maintenance will be evaluated through interview data gathered from intervention arm participants (N=30) (**Table 4**). Finally, we will meet with other key stakeholders (N=10) (e.g., health care payers, city health officials) to determine what they may need to implement the *Sense2Quit App* and their willingness to partner and cost-share; implementation strategies will also be developed with them.

Compensation: Participants will be able to receive $30 for completing an interview session.

In-depth Interview Data Analysis: We will use the same analytic plan as described in Aim 1 for analyzing the qualitative data.

Paradata Data Analysis: At the individual level, we will understand participants' use of the App over time through the collection of paradata[89] which is "free" in that it does not require any additional effort from the user[90]. To explore barriers and facilitators to widespread implementation of *Sense2Quit App*, we will collect data during intervention, implementation, and after the trial has ended. The primary paradata to be collected are page accessed, time stamp, and device type. From these data, we will derive the following use of data for each session: duration on each page, page progression through the application, time from login to result, and total time from login to logout. We will analyze the data at the individual-level (i.e., user-level), application-level, page-level, and session-level and assess how these differ by demographic characteristics, technology use, and outcome measures. Additionally, we will measure the amount in bytes of user data transmitted. Importantly, longitudinal analysis will determine if the user experience changes with repeated use. The paradata collected from each page will be analyzed to generate a "heatmap" of user-interaction (i.e., the distribution of activity for each link/button) that will inform user duration on each page of the App and user interaction with App content, contact pages, and the help page. We will explore usability issues with consideration for how many times users accessed help and what page of the App referred them to the help, implying the need for clarification. We will analyze differences in aggregated data by demographic group (e.g., age) to better understand engagement with the intervention and potential facilitators and barriers to App use.

Plan for Future Fully Powered RCT of *Sense2Quit*. At the end of Year 2, we will write an R01, which will include a full- scale trial of the final *Sense2Quit App* with the same sample. Importantly, process evaluation interviews will allow us to refine the intervention in preparation for the RCT. We will also assess the intervention's sustainability, and with key stakeholders, develop specific strategies to scale up the intervention to reach more PLWH who smoke within additional community-based and clinical settings.

AIM 4: Testing with Confounding Gestures

We recognized confounding effects as a range of gestures and actions that mimic the motion associated with smoking. To enhance the accuracy of smoking detection, the capability to discern these confounding effects is essential. For example, a typical smoking gesture involves the user bringing their hand to their mouth for a puff, subsequently shifting

the hand to a resting position, and then returning it to the mouth for another puff. This particular sequence of actions is not exclusive to smoking, and parallels can be drawn with other activities that we investigate, such as drinking and answering a phone call. To improve precision and accuracy of smartwatch smoking detection, for Aim 4 we will conduct additional testing with PWH who will be performing smoking and additional confounding gestures. This process, which has been demonstrated in past studies[93-96], will help us improve the current algorithm for smoking detection associated with the Sense2Quit app.

Recruitment and Consent:
Aim 4 participants will be PWH who smoke cigarettes. We will enroll 30 people who will consist of 1) enrolled participants at their 12-week follow-up visit; 2) participants who are initially eligible for the study after completing the screener but do not qualify based on eCO levels; or 3) participants who already finished Aim 2 (and 3, if applicable).

All participants will sign informed consent prior to participating in Aim 4 procedures.

Procedures:
Participants who have not yet participated in Aim 2 will complete the baseline survey prior to participating in Aim 4 procedures. All Aim 4 participants will complete the required hand gestures (See table below) as well as smoking gestures for a total of approximately 30 minutes. Study staff will 1) connect the watch with the smartphone; 2) have participant wear the watch on their smoking hand; 3) open the smartphone to start data collection by pressing the start button and assigning the label for the particular activity they are about to perform; 4) repeat each activity listed above in three postures (sitting on a char, standing, walking around) for a duration of 5 seconds; and 5) stop data collection by pressing the stop button after 5 seconds of the activity being performed. Participants will also complete the optional actions with the opportunity to omit some of them.

	Action	**Required?**
1	Drinking a beverage without a straw	Yes
2	Drinking beverages with a straw	Yes
3	Eating a meal with a spoon or fork	Yes
4	Eating a snack with a hand	Yes
5	Talking with a hand gesture	Yes
6	Using a phone (making a phone call)	Yes
7	Adjusting glasses	Yes
8	Arm cross	No
9	Brushing teeth	No
10	Gym activity (e.g. lifting, Zumba)	No
11	Scratching face	No
12	Applying lipstick	No
13	Coughing	No
14	Yawning	No
15	Whistling	No
16	Eating a lollipop	No
17	Playing harmonica	No
19	Pinching the chin	No
20	Wiping the nose	No
21	Massaging somewhere on the head	No
22	Waving	No

Compensation:
Participants will receive $30 in the form of a Bank of America pay card following the completion of the Aim 4 activities.

LIMITATIONS AND ALTERNATIVES

1) An important limitation is that we are relying on self-report of NRT use among study participants, and while we will track our administration of NRT to study participants, we are limited in our ability to validate whether participants have used the NRT.
2) We carefully considered our control condition and although referring control arm participants to the NYC quitline, which will therefore give them access to an NRT supply may underestimate the effect of the *Sense2Quit* App, we believe that it is imperative to offer NRT/access to NRT to both arms since this is standard of care for persons who are trying to quit smoking.
3) While leveraging accessible mHealth technologies is a strength, our study team acknowledges the target population may not have access to smartwatches outside of the research study. Nonetheless, if efficacious, the cost of the smartwatch is half of the cost of purchasing cigarettes for 1 month in NYC, estimated at $320/month[91] and even more minimal in comparison to the annual cost ($170 billion) for direct medical care for persons who smoke in the US[92].

POTENTIAL RISKS AND ADEQUATE PROTECTIONS

The investigators will follow all required policies related to the protection of human subjects. All investigators have fulfilled Human Subjects Protection and Health Insurance Portability and Accountability Act (HIPAA) training requirements (including CITI basic and refresher courses, Good Clinical Practices, and conflicts of interest) and are up to date with these certifications. All prospective participants will be fully informed of the intent of the study, expectations of participants, and risk to participants prior to enrollment using an IRB-approved informed consent form.

Potential Risks

There is no more than a **minimal risk** associated with any of the study activities. The study activities meet the general definition found in Subpart A (46.102) that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The risks of participating in this study are few. Potential risks consist of discomfort with interview questions and potential breaches of confidentiality. It is possible that certain questions on the questionnaires (e.g., drug use) may make participants feel uncomfortable, but the subject is free to decline to answer any questions. Participation in research can involve loss of privacy. All study data including App data will be maintained on CUIMC servers that are completely secure and HIPAA compliant. All signed consent forms and payment receipts used in this study will be kept in locked files which only the investigators can access. We will also apply for a Federal Certificate of Confidentiality, which will protect against attempts by law enforcement or other government agencies to access our data.
Nicotine Replacement Therapy. Participants will be told the risks of using NRT, which include skin irritation (patch), itching (patch), dizziness, headache, rapid heartbeat, and nausea.
FDA Regulatory Pathway. The CUIMC IRB will make the final determination if this App is subject to FDA regulation. Nonetheless, the *Sense2Quit App* is not subject to FDA regulation within the category of Software as a Medical Device because this device does not function as a medical device (meaning such software functions do not meet the definition of a device under section 201(h) of the Federal Food, Drug, and Cosmetic Act), and therefore the FDA does not regulate it as a device. Since the software function does not meet the definition of a device, even though it is deployed on a mobile platform, the FDA oversight would not be applicable. This is consistent with the FDA's existing oversight approach that considers functionality of the software rather than platform, and the FDA will apply its regulatory oversight to only those software functions that are medical devices and whose functionality could pose a risk to a patient's safety if the device were to not function as intended.

Adequacy of Protections Against Risks

Confidentiality and Privacy. Risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting. Reminder text messages will make no mention of HIV. All data will be collected using unique patient identification codes. All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number to maintain participant confidentiality. All records will be stored in a locked file cabinet. Study data from all sites will be collected and managed using Research Electronic Data Capture (REDCap). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (e.g., SPSS, SAS, Stata, R/S-Plus). REDCap data collection projects rely on a thorough, study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process

results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry. Lastly, clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or the National Institutes of Health (NIH).

Plan for Privacy and Data Security of the *Sense2Quit App*. Beginning with the development process and throughout the research project, we will follow the privacy and security principles set forth at healthhit.gov. Our team is familiar with the importance of the privacy and security of personal health information to engender individual trust in the use of health IT applications. We have expertise and experience in this domain as we have developed a number of health IT systems funded through NIH and the Agency for Healthcare Research and Quality for PLWH whose personal health information is usually held to higher security standards than traditional patients as HIV has historically been a stigmatized disease.

The App will be stored on a secure HIPAA compliant server.

Further, CUIMC has an Information Security Office (ISO) that facilitates all aspects of information security risk management at CUIMC, with a particular focus on threat management and HIPAA compliance. This includes administration and enforcement of information security policies on campus. ISO also provides guidance to CUIMC Schools and Departments regarding any information security concerns they may have. The ISO collaborates with the entire CUIMC community to protect the confidentiality, integrity, and availability of our critical information and computer resources. The ISO strives to implement secure computing infrastructure and practices with sensitivity to CUIMC's educational and research environment. Columbia University has an information security charter which is the foundation of all the work carried out by Dr. Schnall and her research team. In specific, the Multiple Principal Investigator (MPI) team will work with the CUIMC ISO to protect the confidentiality, integrity, and availability of participants' data.
Confidentiality means that information is only accessible to authorized users. Integrity means safeguarding the accuracy and completeness of data and processing methods. Availability means ensuring that authorized users, such as research participants, have access to data and associated information resources when required.

To protect the integrity of participants' data, the Project Coordinator will assign an ID number to all participants. The participant ID number will be used to identify data collected. Since the study has repeated follow-up visits, we will maintain a list of participants which link identifying information to study ID numbers. Only a limited number of staff members will have access to this list, which will be kept in locked files and in a password-protected computer file. De-identified data will be accessible by all members of the research team involved in the data analysis, unless study personnel needs access to individually identifiable information to perform their duties. Access to individually identifiable private information about human subjects will be limited to research team members who collect and manage the data, the project coordinator, and the MPIs.

All research personnel will complete extensive training before they are granted access to this identifying information. Study personnel will complete Human Subjects Protection Training which complies with federal guidelines delineated in 45 CFR Part 46. Personnel will also sign confidentiality statements that specify that if the participants' confidentiality is breached unintentionally that personnel will follow the procedures for reporting this breach to the MPIs. The confidentiality statement also indicates that unintentional or deliberate violations of participants' confidentiality may result in demotion or termination depending upon the severity of the event. Personnel will also participate in training with the Investigators and/or Project Coordinator regarding data safety, confidentiality of participants, limits of confidentiality, and proper administration of the study protocol.

We will store all personally identifiable data on secure, HIPPA compliant servers. All electronic forms containing personally identifiable information, including participant locator forms (i.e., containing contact information), will be maintained in a password-protected computer files. Data that are entered into computer files will be de-identified and maintained on a subdirectory of an institutional server with password-protected access. The MPIs will review all requests, current and future, to use the data, and any data files that are provided to other individuals will be de-identified. Data files will contain code numbers in order to make reference to particular cases across multiple assessment waves.

We will maintain a Federal Certificate of Confidentiality throughout the life of the research project. We will inform study participants of the above procedures and the limits of confidentiality during the consent process prior to data collection.

Specifically, we will warn participants that state law mandates reporting of abuse and/or neglect of children, and that threat of harm to self or others requires intervention by clinical staff. We will inform participants that criminal behavior (i.e., drug use) is not reported to authorities, and that the security of this information is protected by the Federal Certificate of Confidentiality.

Plan for Privacy and Security Protections in the Development and Implementation of the *Sense2Quit App* System. Beginning with the development process and throughout the research project, we will follow the privacy and security principles set forth at healthhit.gov. Our team is familiar with the importance of the privacy and security of personal health information to engender individual trust in the use of health information technology applications. We have expertise and experience in this domain as we have developed a number of health information technology systems for persons from high-risk populations, including PLWH, whose personal health information is usually held to higher security standards than traditional patients. We will be housing the App on a secure server hosted by Amazon Web Services. All servers have HIPAA compliant security. Data will be encrypted and stored securely on the Amazon Web Services servers. Prior to consent, study participants will be informed as to what data the Sense2Quit App will collect (including location/GPA information). Study staff will explain to study participants that data will be encrypted and stored securely on the Amazon Web Services servers. As a starting point for ensuring privacy and security, all smartphones will be password–protected. In addition, there will be an additional password for the *Sense2Quit App* so that only study subjects will be able to open the app and/or view their personal health information.

Procedures for Monitoring Adverse Events. Should any physical or psychological manifestation be exhibited at any time during the study, Dr. Schnall will consult with her Co-Investigators regarding clinical situations as they arise. If an urgent clinical situation should arise, Dr. Schnall or a designee will access an urgent appointment at the Columbia University School of Nursing Nurse Practitioners Primary Care Clinic or the emergency department at CUIMC. Dr. Schnall will complete an adverse event form and report it to the CUIMC IRB. If there are any serious adverse events, they will be reported within 48-72 hours to the CUIMC IRB. The CUIMC IRB is responsible for reporting any serious adverse events to the NIH, Office for Human Research Protections, Food and Drug Administration, and other federal, State and local agencies.

BENEFITS

Potential Benefits to Research Participants and Others

The purpose of this study is to test the *Sense2Quit App* for improving tobacco cessation in PLWH. The knowledge gained from the research will enable the scientific community and patients to improve tobacco cessation in communities and persons who are most in need in the United States. There may be a benefit to participants after use of the intervention as they will be more likely to stop smoking and more likely to have sustained tobacco cessation. More broadly, the knowledge gained will contribute to the body of knowledge regarding the use of health information technology for improving the lives of persons with chronic illnesses. Possible risks (i.e., discomfort answering questions, potential confidentiality breaches) are outweighed by the potential for improving tobacco cessation rates in a health disparate group of PLWH.

Importance of the Knowledge to be Gained

The knowledge gained from this research will enable the scientific community, clinicians, and PLWH to improve tobacco cessation. The *Sense2Quit App* is a scalable, low-cost intervention which does not require provider resources. Findings from our study will provide timely and important information on the use of mobile technology for the delivery of an evidence-based tobacco cessation intervention for PLWH.

DATA SAFETY AND MONITORING PLAN

Data Management and Data Quality. Columbia University will be responsible for computerized survey programming, data capture, management, and analysis. All study information will be identified through the Participant Identification Number (PID) on all forms and computerized files. Data files will be exported from the Qualtrics program and imported into the SPSS statistics software database for storage. Computer data files never have any identifying information and are encrypted prior to transfer between study sites.

Data entered into the SPSS database will not include any identifying information. Only authorized users with a login name and password will be able to open the computerized survey, and only those with administrative privileges will be able to

access data. The study research assistant will use a login name and password to gain access to the software in order to administer it to a participant, but they will have no ability to access the saved data. The database, data structure, and data quality will be routinely reviewed by the contact Principal Investigator (PI), Dr. Schnall. Dr. Schnall will work closely to plan analyses for various purposes, including for hypothesis testing and manuscript development and reports. Data quality will be examined before statistical analyses are conducted, including examination of missing data, assessment of distributional assumptions, and identification of outliers. In addition to data quality, the comparability between intervention and control groups will be carefully examined, including baseline balance and differential attritions at all waves of follow-up. While differences are not expected from the randomized design, it is prudent to plan for this contingency so that sufficient follow-up data and appropriate statistical methods can be used for intent-to-treat analyses. The psychometric properties of instruments will also be examined, as will the patterns of missing data.

Training on human subjects and data safety and monitoring. All staff will participate in the National Institutes of Health (NIH) required trainings for the conduct of studies that involve human subjects, and any future study staff will do so upon hiring. Training for all staff includes (but is not limited to) Human Subjects, Informed Consent, Good Clinical Practice, Quality Management, Confidentiality, and Reporting of Adverse Events. If any study staff discovers any untreated condition (e.g., onset of physical or mental health condition), they will refer participants to appropriate treatment immediately.

Data Safety and Monitoring Committee. This study will also have a data safety monitoring committee (DSMC) which will meet yearly *via Zoom*. The DSMC will consist of individuals who are not otherwise associated with the study. The DSMC will meet at least yearly to review study progress, adequacy of randomization, and, at their discretion, adverse events or differential outcomes. For randomization, we will tabulate the number of individuals who have been randomly assigned to each condition at each of the DSMC meetings. Before the DSMC meeting, relevant information will be tabulated to report to the DSMC, and after the meeting, staff of the management core will collect minutes and distribute to the board for sign-off. The final report will be submitted to the Institutional Review Board (IRB) on an annual basis.

Procedures for Monitoring Adverse Events. Per guidance provided by the Office of Human Subjects Research at the NIH, an adverse event (AE) is any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. A serious adverse event (SAE) is defined as an untoward medical occurrence that: 1) results in death, 2) is life threatening, 3) requires (or prolongs) hospitalization, 4) causes persistent or significant disability/incapacity, 5) results in congenital anomalies or birth defects, or 6) is another condition which in the judgment of the investigators represents significant hazards.

Possible AEs that are anticipated include the need to violate the confidentiality of the participants. All study personnel will be trained regarding the limits of confidentiality. The training will include reviewing possible scenarios and knowledge of key questions to assess risk. We will train staff to err on the side of caution and to contact the clinical supervisor as needed. Coordinators will be available on site or via phone after hours should staff need consult regarding an emergency. In this situation, we will train all staff to immediately contact clinical supervisors, and under the guidance and direction of clinical supervisors, study staff will be trained when to either contact police to ensure the safety of participants.

Possible AEs that are unanticipated will be brought to the attention of the Coordinators and reported immediately to both site IRBs. All study staff will be trained to recognize and report AEs and SAEs. Possible AEs will immediately (within 24 hours) be brought to the attention of the Lead at each site by study staff who identify the event. The Site Lead will report the AEs and SAEs to the IRB in writing as soon as possible, but within 7 calendar days for death or life-threatening events and within 15 calendar days for all other AEs or SAEs. The IRBs will determine whether it is appropriate to stop the study protocol temporarily or will provide suggestions/modifications to the study procedures as necessary. Possible modifications include adding these possible adverse events to the consent form and re-consenting all study participants. The PIs will be responsible for monitoring participant safety on a monthly basis at regularly scheduled research meetings. They will keep a written log of all events and ensure that the IRB is contacted immediately. They will also keep a log of the outcome of IRB decisions regarding AEs and apprise the research team of any changes that need to occur because of IRB decisions

STATISTICAL DESIGN AND POWER

Sample Size and Power. The goal of this pilot study is to estimate the smoking cessation rates in each arm to obtain an effect size for future larger studies. To conduct a hypothesis test for the comparison of cessation rates between the two intervention arms, it requires a minimal sample size of 199 per group (total 398) for at least 80% power. This calculation was based on a 2-sided test with the type I error of 0.05, and assuming a 20% cessation rate in the *Sense2Quit* App group (intervention) and a 10% cessation rate in the control arm. The 10% difference would be equivalent to a medium effect size (Cohen's d=0.45). In this pilot study, we propose a total sample of 60 (30 per group). Therefore, this study is not powered to detect a significant difference between arms. Instead, we estimated the minimal sample size for the estimation of cessation rates in each arm with acceptable reliability. For the sample size (30 per group), this study will have at least 80% probability that the standard error of the cessation rate estimates ≤7%, assuming expected cessation rates ranging from 10% to 20%. Therefore, the sample size is sufficient to provide estimation with acceptable reliability.

Statistical Design and Data Analysis: This is a pilot study to assess preliminary feasibility, acceptability, and preliminary efficacy. Descriptive statistics will be used for all analyses. The rate of quit attempts will be calculated as the proportion of smokers who attempt to quit (i.e., no smoking during a 24-hour period); 7-day point prevalence abstinence will be calculated as the proportion of smokers who are biochemically verified 7-day abstinence at a given time point; and sustained abstinence will be calculated as proportion of days of no smoking starting on the quit date among those who attempt to quit. We will provide point estimates and corresponding confidence intervals of these measures for each arm. Because of small sample sizes, we will obtain Clopper-Pearson exact confidence intervals based on the binomial distribution. Given the small sample size, the purpose of the arms is simply to monitor for unexpected, gross differences between the two groups. To determine acceptability, we will ask participants in both arms how useful each of the intervention components were (1 = *Not at all useful* to 7 = *Extremely useful*) and whether they would recommend the program to a friend (1 = *Definitely would not recommend* to 7 = *Definitely would recommend*). For the intervention to be deemed acceptable, the mean level for each of these measures would have to be 5 or higher. The efficacy of the intervention will be based on saliva-confirmed 7-day point prevalence abstinence at the follow-up survey. Lost-to-follow-up participants will be included as smokers.

DISSEMINATION PLAN

Tools developed and evaluated during this project have the potential to extend the impact and reach of tobacco cessation for all smokers but specifically for persons living with HIV (PLWH) who smoke. Per the RFA, this study was designed for dissemination (e.g., feasibility/acceptability of the intervention for PLWH) and suitable for the intended context. Therefore, a multi-faceted dissemination plan targeting various stakeholders is proposed. We will disseminate our findings to technology-oriented and clinical management- oriented audiences. For technology audiences, we will provide enough detail to enable the *Sense2Quit App* to be constructed and used within an appropriate context.
We propose the following dissemination strategies:

1. Members of the research team will present the results of this study in several different venues targeting different audiences, including conferences such as the American Public Health Association and Society for Behavioral Medicine.
2. We will seek out appropriate organizations that are influential in HIV and tobacco cessation public health practice (e.g., International AIDS Society, Society for Research on Nicotine and Tobacco). We will provide these organizations with an executive summary, press releases, and/or published papers and present study findings at local community-based organizations.
3. We plan to publish our results in appropriate high-impact, peer-reviewed academic journals such as the *American Journal of Public Health*, *AIDS and Behavior*, and *Nicotine and Tobacco Research*.
4. We will work with our local community-based organizations (e.g., Alliance for Positive Change, Gay Men's Health Crisis, LGBT Center) to disseminate our study findings to the community.

All informed consent documents for this clinical trial will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov. We will register this study with ClinicalTrials.gov. Finally, the recipient institution (Columbia University) has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements. Specifically, the Human Research Protection Office and Institutional Review Boards have policies to ensure that clinical trials registration reporting occurs in compliance with policy requirements. Specifically, the Human Research Protections Office and Institutional Review Boards have policies to ensure that clinical trials registration reporting occurs in compliance with policy requirements.

Presentations at national scientific meetings. It is expected that we will present our findings at HIV, tobacco-cessation, behavioral health, informatics, and engineering related scientific meetings. We will also disseminate the findings through relevant newsletters and websites of related interest groups.

We will also make de-identified data from our study available. Researchers interested in replicating our methods and study findings will have full access to the study protocol, analytic methods, and codebook of qualitative data analysis. We will deliver versions of our protocol with our first 12-month progress report. We will deliver our final protocol, codebook documents, and instructions regarding how other researchers can access our study documents to the NIH within 12 months of the end of the funding period. In addition to the documents mentioned above, de-identified transcripts from our in-depth interviews will be available at the conclusion of the study. The de-identified transcripts will be archived on the secure network server provided to the Contact PI at Columbia University Irving Medical Center. A Data Use Agreement will be implemented for other researchers interested in using our data for replication of research findings or for additional areas of research. We will request that outside investigators discuss their manuscript ideas with the PIs before proceeding. Furthermore, we will request that manuscripts using data from our project be approved by the PIs prior to submission for publication. Members of this project team may contribute as co-authors when data from this study are used. We will request that manuscripts, abstracts, presentations, and chapters developed by other investigators credit this study and credit NIH as the funding source for the data. This process will allow for a central repository and access point for all papers, abstracts, posters, and presentations by any individual or organization using our data.

Our plan for sharing research data and resources is designed to assure that data generated in this project are made as widely and freely available as possible while safeguarding the privacy of participants and protecting confidential and proprietary information.

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