STUDY PROTOCOL

Piloting a Sequential Multiple-Assignment Randomization Trial to Evaluate AllyQuest: An mHealth Intervention for HIV-Positive Young MSM to Optimize HIV Medication Adherence and Care Outcomes

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PROTOCOL TITLE:

Piloting a Sequential Multiple-Assignment Randomization Trial to Evaluate AllyQuest:
An mHealth Intervention for HIV-Positive Young MSM to Optimize HIV Medication Adherence and Care Outcomes

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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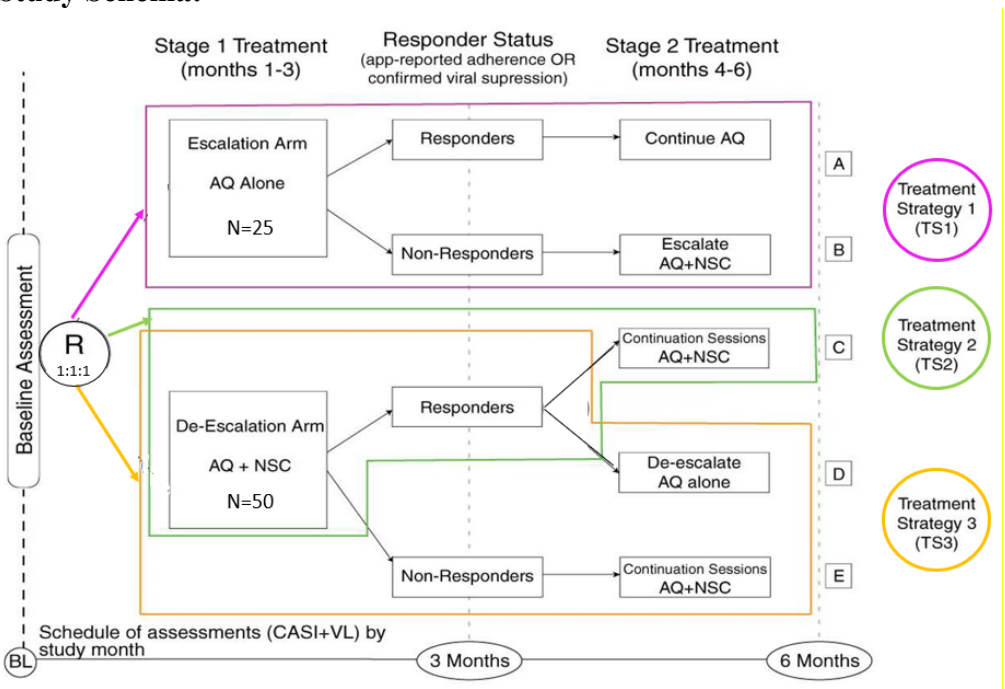
1.0 Study Summary

Study Title	Piloting a Sequential Multiple-Assignment Randomization Trial to Evaluate AllyQuest: An mHealth Intervention for HIV-Positive Young MSM to Optimize HIV Medication Adherence and Care Outcomes
Study Design	This study is a two arm Sequential Multiple-Assignment Randomization Trial (SMART) that will test the feasibility and acceptability of the intervention and trial design in a 6-month pilot intervention study among young men who have sex with men (YMSM) and young transgender women who have sex with men (YTWSM) living with HIV, ages 15-29. Participants will be randomized to one of three treatment strategies: (TS1) AQ alone followed by Continued AQ for Responders and Escalation to AQ+NSC for Non-Responders; (TS2) AQ+NSC followed by Continued AQ+NSC for Responders and Continued AQ+NSC for Non-Responders; and (TS3) AQ+NSC followed by De-escalation to AQ for Responders and Continued AQ+NSC for Non-Responders. Responder status will be assessed at 3 months, based on app reported adherence and available viral load (VL) data.
Primary Objective	To test the feasibility, acceptability, and preliminary efficacy of the AQ/AQ+ intervention app among 75 YMSM and YTWSM, ages 15-29, by conducting a SMART with assessments at baseline (month 0), month 3 (intervention arm reassignment) and month 6 (end of intervention). The primary outcome measures are: (a) Intervention feasibility: Average proportion of days of any app use, average proportion of days of HIV medication tracked and (b) Intervention acceptability: Mean intervention acceptability, composite score AHAA. To analyze app paradata to determine which treatment strategies embedded in the SMART (escalation, de-escalation, and maintenance combinations) are most promising to test for sustained app engagement, self-reported adherence, and VS.
Secondary Objective(s)	The secondary outcome measures (preliminary efficacy) are: (c) Change in ART medication adherence from Baseline to Month 6 (self-report); (d) Difference in ART medication adherence between treatment arms at month 6; and (e) Rate of viral suppression (VS) at 6-month follow-up
Research Intervention(s)/	N/A This project is coming to FSU as data analysis only.

Investigational Agent(s)		
IND/IDE # (see section 5)	N/A	
Study Population	Eligible participants: 1) are aged 15-29 at enrollment visit; 2) were assigned male sex at birth; 3) report sex with men or transgender women (lifetime); 4) are able to speak and read English; 5) have reliable daily access to an Android or iOS smartphone with a data plan during the intervention period (approx. 6 months); 6) are HIV+; 7) Prescribed ART; 8) At least one of the following: Having failed to show up for or missed 1 or more scheduled HIV care appointment in the past 12 months OR Last HIV care visit was more than 6 months ago OR Self-reporting less than 90% ART adherence in the past 4 weeks OR have a detectable viral load measure in the past 12 months OR recently diagnosed with HIV (past 3 months) Not eligible: 1) unable to be consented due to active substance use or psychological condition; 2) participating in another HIV-related study.	
Sample Size	SMART Trial: 71 YMSM and YTWSM living with HIV recruited across 6 SRV sites (Birmingham, AL; Chapel Hill, NC; Charleston, SC; Charlotte, NC; Detroit, MI; and Newark, NJ) and nationally through social media recruitment and online enrollment.	
Study Duration for individual participants	The total duration of study participation and active intervention for each participant was 6 months.	
Study Specific Abbreviations/ Definitions	AIDS	Acquired Immunodeficiency Syndrome
	AHAA	Acceptability of Health Apps among Adolescents
	ART	Antiretroviral medicine
	AQ	AllyQuest
	AQ+	AllyQuest with Integrated Next Step Counseling
	CASI	Computer assisted self-interview
	CFR	Code of Federal Regulations
	CRF	Case report form
	DBS	Dried blood spot
	DHHS	U.S. Department of Health and Human Services
	GCP	Good Clinical Practices
	HIV	Human Immunodeficiency Virus
	iNSC	Integrated Next Step Counseling

	IRB	Institutional Review Board
	MSM	Man (or men) who has sex with men
	NIH	National Institutes of Health
	NIMH	National Institutes of Mental Health
	PrEP	Pre-exposure prophylaxis
	PI	Principal Investigator
	OHRP	Office of Human Research Protection
	SID	Study ID number
	SMART	Sequential Multiple-Assignment Randomization Trial
	SRV	Subject Recruitment Venue
	SSL	Secure Socket Layer
	TW	Transgender woman (or women)
	TWSM	Transgender woman (or women) who has sex with men
	VL	Viral load
	YAB	Youth Advisory Board
	YAC	Youth Advisory Council
	YMSM	Young man (or men) who have sex with men
	YTWSM	Young transgender woman (or women) who have sex with men

Study Schema:



Key terms: AQ: AllyQuest; NSC: Integrated Next Steps Counseling; R: Randomization

2.0 Objectives

2.1 *The* primary objective is to test the feasibility of the SMART and to assess the acceptability of the AllyQuest app.

The secondary objective is to assess the preliminary efficacy of the AQ/AQ+ intervention at improving self-reported ART adherence and viral suppression.

Exploratory research question: Exploratory analyses will assess whether app engagement and adherence vary by possible tailoring variables (e.g. education level, depression, substance use).

Qualitative research questions: We will thematically code and analyze in-app text data (iNSC session transcripts, daily discussion forum posts) and qualitative exit-interview data to assess app engagement and the acceptability and feasibility of the app features.

2.2 H1: The intervention design will be feasible as defined by average app use for the majority of participants on 30% of trial days or more.

H2: The intervention will be acceptable as defined by average composite score on the AHAA.

H2a: Greater app use will be positively associated with higher AHAA scores.

H3: Average self-reported ART medication adherence will show trends toward improvement from Baseline to Month 6 across intervention arms.

H3a: Greater app use will be positively associated with improvement in ART medication adherence.

H4: The proportion of virally suppressed participants will increase from baseline to 6-month follow-up

H4a: Greater app use will be positively associated with achieving viral suppression.

3.0 Background

3.1 In 2015, men who have sex with men (MSM) accounted for 92% of all new infections among people ages 13 to 24. While recent epidemic trends suggest some slowing of new HIV infections among MSM overall, significant disparities still exist for youth and Black and Latino MSM. The United States (US) HIV epidemic future depends in large part on what happens among young MSM (YMSM).

Compared to adults, youth (ages 18 – 24) have worse outcomes across the HIV care continuum. Nationally, 33 to 38% of diagnosed HIV-positive youth aged 13 to 24 achieve VS, with rates lower for Black YMSM (16%). Among 13 sites in the US Adolescent Trials

Network (ATN) only 7% of a predominantly Black YMSM sample of HIV-positive youth achieved VS. In another ATN study, only 59% of VS youth attending clinics with comprehensive supportive services maintained 12-month VS. As most YMSM with detectable viral load (VL) report condomless anal sex, onward transmission is likely to continue. Effective interventions for YMSM are needed to support sustained VS for individual health and HIV prevention.

Sustained antiretroviral (ART) adherence is critical for VS but suboptimal among YMSM. A 2014 meta-analysis of adherence for youth living with HIV found overall low self-reported adherence of 62.3%. Barriers to adherence and VS among youth and YMSM include forgetting or not feeling like taking ART, low adherence self-efficacy, psychological distress (depression, anxiety), substance use, structural barriers (transportation, homelessness, insurance), low social support, and HIV-related stigma. Many YMSM experience multiple barriers, impacting adherence and VS in a dose-response nature.

Despite clear need, few adherence interventions have focused on YMSM. A 2017 systematic review of interventions along the HIV care continuum identified 117 medication adherence interventions; only 9 (8%) focused on adolescents/youth and only 2 (2%) focused on MSM. A 2014 review of adherence-focused Evidence Based Interventions found none exclusively designed for MSM or youth. While several adherence intervention studies for MSM are underway or under development, none appear to utilize smartphone technology and engagement features in the innovative ways we propose.

The flexibility of mobile health (mHealth) platforms and the power of paradata allow real-time assessment of user engagement and adaptive delivery of tailored content to fit individual HIV management challenges. Daily mobile phone-based contact is acceptable to youth living with HIV and is associated with improved adherence. High smartphone ownership among diverse YMSM provides capacity for national scale up and diffusion. With extensive input from HIV-positive YMSM, we developed the AllyQuest (AQ) smartphone app as a tailored adherence and social support intervention. In a 4-week pilot study, AQ was rated highly and greater app use was associated with significant increases in HIV knowledge and self-management.

3.2 Despite these promising results, some participants minimally engaged with the app and daily app use declined over the course of the pilot (from 4.3 to 2.8 days/week). Based on the pilot results, we propose to enhance AQ engagement and effectiveness by adding tailored content, small financial incentives, and personalized text-based adherence counseling. AQ can be programmed to deliver individualized, tailored content through complex algorithms, but a

combination approach (auto-tailoring plus two-way texting) may benefit some YMSM via higher intervention engagement and adherence support. Our ART counseling model is based on Next Step Counseling (iNSC), a brief, client-centered motivational approach to supporting medication adherence. iNSC was developed for the iPrEx pre-exposure prophylaxis (PrEP) trial and was found to be highly acceptable among MSM. iNSC, which is grounded in the Information-Motivation-Behavioral skills (IMB) model of ART adherence, provides flexible, individualized adherence support. Core components of iNSC include: reviewing participant experiences with adherence, exploring adherence facilitators and barriers, identifying adherence needs and strategies, and developing an adherence action plan. Our study team is already adapting iNSC for two-way text chat in a PrEP adherence app for YMSM (U19-HD089881).

Sequential multiple assignment randomized trials (SMART) have numerous advantages over traditional trial designs. In these adaptive interventions, the type or dose of the intervention (app alone vs. app + iNSC) is adjusted based on participant characteristics or response (adherence/VS). Thus, an adaptive intervention is a sequence of decision rules that specify how the intensity or type of treatment should change depending on the patient's needs rather than applying a “one size fits all” approach. SMARTs are an efficient and rigorous way to maximize clinical utility and real-world applicability. A pilot SMART will allow us to estimate an optimal adaptive adherence intervention using a design that more closely mirrors clinical practice.

This study has been previously reviewed and approved by the University of North Carolina at Chapel Hill IRB. All study activities outlined in this protocol, including recruitment, enrollment, data collection, and follow-up with participants were completed while the research team was at UNC-CH. <u>By submitting this protocol to Florida State University, we are seeking IRB approval for purposes of data analysis only.</u> The original protocol, study documents, and approval letters are appended in the IRB submission.

3.3 Improving ART adherence among YMSM is an urgent public health issue. Given estimates that only 7 to 38% of youth/young adults living with HIV achieve VS, advancing innovative ART adherence interventions for YMSM with HIV is a pressing priority. This proposal expands on our existing theory-based app, AQ, which showed promise for engagement and impact on HIV knowledge and HIV self-management, while adding innovative features via enhanced app engagement strategies and SMART adaptive design. Using a SMART design will allow us to evaluate the impact of multiple evidence-based intervention treatment strategies. mHealth

technologies' have an underutilized ability to monitor behaviors in real-time via app paradata (usage metrics) and adapt strategies when a participant is not responding to an initial intervention approach. Adaptive strategies that adjust for intervention non-response and increase in intensity to meet the needs of non-responders represent a more "real-world" approach, which would have a high public health impact and great potential for rapid scale-up and dissemination. Simultaneously evaluating the efficacy of a treatment strategy that de-escalates intervention intensity among responsive participants more closely mirrors clinical practice, follows the scientific rationale that some patients will benefit from a more intensive intervention up-front, and optimally applies resources where and when they are most needed.

4.0 Study Endpoints

4.1 *The* primary study endpoint of 1) feasibility is app use, measured by number of trial days using AQ/AQ+; 2) acceptability is average composite score on the AHAA.

The secondary study endpoint of preliminary efficacy of the AQ/AQ+ intervention is average 6-month self-reported ART medication adherence and end-of-study proportion of viral suppression.

4.2 *N/A*

5.0 Investigational Test Articles or Products

5.1 AllyQuest is not an investigational device as it does not meet the requirements specified in Section 201(h) of the FD&C Act (21 USC 321(h)). However, to provide context, we have included an overview of the intervention and its intended use in the study below:
AQ is a theory-informed, multi-feature medication adherence and social support app. AQ+ adds a component of one-on-one guided support provided through the app by an adherence coach. The intervention app is currently designed to provide six months of educational content and adherence coaching. In the current trial, the app will be tested using an adaptive trial design which will allow participants to move between the two intervention conditions (AQ vs. AQ+) to best meet their current medication adherence and health needs.
AQ development was guided by health behavior change theories including Social Cognitive Theory (SCT), narrative communication (e.g. storytelling), and the principles of persuasive technology. AQ addresses key principles of SCT including: (1) observational learning by doing daily activities; (2) modeling and vicarious experiences (observing and participating in Daily Discussions, exploration of narrative "choose-your-own-adventure" stories); (3) self-efficacy and verbal persuasion from expert sources (multi-media knowledge center, tailored messages) and (4) reinforcements (virtual

rewards, FI, achievements). The Fogg Behavioral Model (FBM) of persuasive technology informed the development of our technology partner Ayogo's Empower™ platform employed for AQ. According to the FBM, the principal factors to promote behavior change using technology include triggers, ability, and motivation. In AQ app notifications are triggers for healthy behaviors while app content also helps participants identify their own daily triggers. Regular self-reported adherence prompts act as additional triggers. Ability is increased through knowledge and by defining steps toward behavioral goals (e.g. coping with side effects, knowing how to fill a prescription). Participants get tips from others dealing with similar issues and through narrative stories that reinforce the consequences of health behavior choices. App motivators include social support, rewards, goal setting, and achievement. Table 1 presents all features of the app along with their purpose and evidence base.

Table 1: Ally Quest intervention components and scientific rationale

Feature: Description	Scientific Rationale
Profile Page	
Privacy features: avatars, pseudonyms, confidential pin number to open app, app time-out after 5 minutes of inactivity, medication tracker allows participant to choose any name (real or made-up) they want for medication reminder.	Work by our team and others identify anonymity and privacy as critical features for YMSM mHealth.
Virtual bank account: Shows $ gained and lost based on daily app use. Account seeded at BL and 3-mo FU with $40. Gain $0.25/day for completing ≥1 in-app activity; lose $0.50/day for <1 activity. At 3- and 6-mo FU, user given account balance amount (possible range at each FU: $0 - $60).	Financial incentives support behavior change. and are being employed to maximize engagement and intervention retention.
App progression meter: Visual display of current app "level" and in-game currency, visible to other participants. YMSM level up and earn in-game currency based on app use. Redeem currency to unlock narratives and other app features.	Game-based elements (e.g. levels, competition) influence intervention engagement and impact.
Daily Discussion	
Social prompts: (e.g. How do you remember your meds?) Daily Discussion prompts foster community, peer sharing, and model and reinforce successful health behaviors. AQ/AQ+ will be optimized by increasing prompts (to 2 per day) to facilitate increased user interaction. Notifications are sent when users comment or "like" posts.	Most engaging AQ feature, users requested >1 daily prompt. Social support and connection are important app features for HIV+ YMSM.
Medication Tracker	
Medication reminder system: Personalized reminders and habit building solutions to promote ART adherence.	Medication reminders improve adherence, but may not be sufficient.

Tailored adherence strategies: Upon set-up, participants enter medication details (doses/day, preferred time of day taken, food restrictions). The app uses this information to provide suggested adherence strategies (e.g. Take when I brush my teeth). Participants who are having adherence difficulties receive tailored feedback on new strategies and adherence tips.	Dynamic tailoring and unique feedback based on frequent assessments effectively promotes behavior change for many conditions, including HIV prevention and ART adherence.
Appointment & refill reminders: Participants can create personalized reminders for ART refills	Requested by AQ usability and pilot YMSM. Feature of "ideal" apps.
Adherence dashboard: Provides study team with an easily interpretable, real-time overview of each user's ART tracking and app use. Automated and tailored messages can be delivered to provide support and encouragement. AQ+ arm can communicate 1:1 with iNSC counselor between sessions.	AQ pilot participants wanted more personalized reminders, messages and additional accountability regarding medication taking.
Daily Challenge	
Daily Quest: Actionable routine tasks help users set goals, build knowledge/skills.	Rated highly by usability and pilot participants. Gamification increases intervention engagement & impact.
Brain games: Articles, quizzes and interactive exercises help users check knowledge and skills.	
Knowledge Center	
Multimedia: Presentation of information that includes HIV-related, safer-sex, relationships and general health and wellness. Users prompted with a reflection question after articles to apply the material to their lives. Visual meter shows progress toward completing each section.	Formative work of our team and others has identified that HIV+ YMSM desire information on both HIV-related issues and general health and wellness.
Tailored Content Sets: Participants receive tailored daily content (quests, quizzes, articles) based on creation of an initial profile at app set-up (e.g. high vs. low HIV literacy and ART adherence, and health areas of interest). Level and preferences are reassessed monthly to adjust tailored content.	AQ pilot trial users wanted articles most relevant to them. Content sets allow prioritization of information based on each user's life situation.
Character-based Narratives	
Text and video-based narratives feature HIV+ YMSM navigating situations that impact care engagement and adherence (e.g. unstable housing, substance use, disclosure). Stories facilitate self-reflection on contexts and choices that impact health; problem solving; and visualizing relevance in one's own life.	Narrative communication through role modeling facilitates health behavior change.
AQ+ iNSC	
Two-way chat based iNSC (AQ+): Ability to deliver iNSC-based adherence counseling sessions via in-app two-way text-based chat.	Connection to provider/counselor and iNSC support ART adherence.

5.2 AQ+ Integrated Next Step Counseling Description

Integrated Next Step Counseling (iNSC) is an interactive, client-centered motivational intervention that was developed and implemented during the iPrEx PrEP trial and was found to be highly acceptable among MSM. The intervention is based on the IMB model and provides flexible, individualized counseling with the goal of supporting adherence and the accurate reporting of adherence. The key components of iNSC counseling include: review of participant experiences with adherence, exploration of adherence facilitators and barriers, identification of adherence needs, identification of strategies to meet needs, and development of an adherence action plan. Our team has adapted iNSC for use as a two-way text-based intervention to support ART within the context of the AQ app. Those assigned to AQ+ for 3 months will receive 7 iNSC sessions; those who do not de-escalate at month 3 and are thus assigned to AQ+ for all 6 months will receive 15 iNSC sessions. Depending on when escalation occurs (due to VL testing window), time between chats may vary but will not exceed 1 chat per week. Table 2 outlines the goals, components, and timing of iNSC sessions based on participant study trajectories. Coaches will conduct brief text messaging "check ins" with YMSM in between sessions using AQ's provider dashboard. Text check ins are an evidence-based method to keep participants engaged and can provide reminders of personal goals set during sessions. During the pilot SMART, staff will document all iNSC sessions and the study team will regularly review session transcripts for protocol fidelity.

Table 2: Schedule of iNSC sessions

Week	Type of Contact	Session Description	Key Takeaway
1	Session 1	Coach (C) will introduce the concept of adherence counseling while answering participant's initial questions. AC will work with participant to articulate what they hope to get out of participation.	Rapport building. C will learn participant's motivation for participating in Ally Quest.
2	Session 2	C will introduce SMART (Specific, Measurable, Achievable, Realistic, Timely) goals. C will guide participant in brainstorming goals.	Participant will learn what SMART goals are and how to set them.
3	Session 3	C will guide participant in goal solidification. Participant will verbalize a clear path forward.	Participant will set a SMART goal.

4	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
5	Session 4	C will work with participant to evaluate progress toward goal. C will guide in goal maintenance or reshaping, as needed.	Evaluate SMART goal progress.
6	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
7	Session 5	C will guide in goal maintenance or reshaping, as needed. Participant will assess their progress.	Participant will be able to successfully evaluate SMART goal progress independently.
8	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
9	Session 6	C will assist in goal maintenance or reshaping, as needed. Participant will begin to discuss post-intervention plans and will verbalize potential obstacles and ways to overcome them.	Participant will begin making plans for continuing progress post-intervention.
10	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
At this point, we will be assessing intervention non-response through a combination of daily app-reported adherence and VL measurement. Non-responders will remain on AQ+ and receive refocused iNSC support, while responders will either remain on AQ+ or de-escalate to AQ (depending on the treatment strategy they were randomized to at Baseline). De-escalated participants will still have access to the counselor but will not be asked to schedule sessions Among those initially assigned to AQ, non-responders will be escalated to AQ+ and will begin their intervention at 'Week 1' as listed in this chart.			
11	Session 7	(Non-responders) C will prep participant to begin contemplating whether or not they want to continue with the same goal.	Assess progress on SMART goal and determine factors that prevented participant from meeting the goal.
		(De-escalators) C will guide participant in creating a maintenance plan. The two will address any final concerns.	Participant will have a plan for maintaining their progress.
12			
13	Session 8	C will answer questions and address concerns from participants, if any. Examine the previous 12 weeks and goal. The two will examine victories, challenges, and lessons learned.	C and participant will identify past challenges and strengths of the participant. Participant will be able to identify past goals they successfully met.
14	Session 9	C will guide participant in setting new goal or revising their previous goal.	Participant will be able to differentiate their new SMART

			goal from their previous SMART goal.
15	Session 10	C will explore any concerns that the participant expresses, if any. C will work with participant to create a clear path forward for their SMART goal.	Participant will set plan for SMART goal.
16	Session 11	C will lead participant in exploring and expressing the similarities and differences that they're experiencing from the previous goal.	C will evaluate participant's mindset and reframe as necessary.
17	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
18	Session 12	C will work with participant to evaluate progress toward goal. C will guide in goal maintenance or reshaping, as needed.	Evaluate SMART goal progress.
19	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
20	Session 13	C will guide in goal maintenance or reshaping, as needed. Participant will assess their progress.	Participant will be able to successfully evaluate SMART goal progress independently.
21	Check In	C will contact participant for the purpose of rapport building. C will check in on concerns.	
22	Session 14	C will guide participant in creating a maintenance plan.	Participant will have a plan for maintaining their progress.
23	Session 15	C will address any final concerns.	Participant will leave with a sense of their strengths and abilities.
24	Check In	C will send well wishes and reiterate the participant's strengths.	

5.3 N/A

5.4 N/A

6.0 Procedures Involved

6.1 Sequential Multiple Assignment Randomized Trial (SMART) Design

We conducted a 6-month pilot SMART of the AQ intervention to test trial design feasibility and app acceptability. This was a two stage SMART including AQ and AQ+, with 71 YMSM and YTWSM living with HIV with assessments at baseline (month 0), month 3 (escalation/de-escalation) and months 6 (end of

intervention). Progress through the trial was dependent on the participant's responsiveness as determined by self-reported daily adherence in the app and/or viral load status. As presented in Table 3 below, at 3 months, among those initially assigned to AQ, non-responders were escalated to AQ+ and responders remained on AQ; among those initially assigned to AQ+, non-responders remained on AQ+ and received refocused iNSC support, while responders either remained on AQ+ or de-escalated to AQ depending on the treatment strategy they were randomized to at baseline. The primary outcome measure is the feasibility of the SMART and the acceptability of the AllyQuest app. Secondary outcomes include self-reported ART adherence and viral suppression. As a secondary analysis, we will compare escalation/de-escalation decisions based on in-app reported ART adherence to month 3 viral loads. We also piloted home DBS collection for all participants. Qualitative exit interviews were conducted with a subset of participants (up to 25 total).

Table 3: Escalation/De-Escalation Treatment Decision Guidelines

Baseline	Treatment strategy decision rules at 3-month follow up	Status	Action
AQ	<80% past month app-reported adherence OR ≥5 consecutive days non-adherence; OR detectable VL	Non-responder	Escalate to AQ+
AQ	≥80% past month app-reported adherence AND do not have ≥5 consecutive days non-adherence; AND are VS	Responder	Continue AQ
AQ+	<80% past month app-reported adherence OR ≥5 consecutive days non-adherence; OR detectable VL	Non-responder	Continue AQ+ Revise adherence strategies as needed
AQ+	≥80% past month app-reported adherence AND do not have ≥5 consecutive days non-adherence; AND are VS	Responder	Assign to AQ+ or AQ based on treatment strategy randomized to at baseline

Table 4: Schedule of Visits and Procedures (completed while staff was at UNC)

	Baseline/enrollment (in-person or remote)	Month 3 (in-person or remote)	Month 6 (in-person or remote)
Visit-specific procedures	Informed Consent Randomization App install & tour	SMART decision (re-randomize, escalate, de-escalate, maintain)	Exit interview (optional)
Visit window	30 days from screening	14 days before and 30 days after	14 days before or 30 days after
Viral load	Chart review or blood draw or self-collected DBS or participant	Chart review or blood draw or self-collected DBS or participant	Chart review or blood draw

	shared (either by documentation or showing result to SRV staff)	shared (either by documentation or showing result to SRV staff)	or self-collected DBS or participant shared (either by documentation or showing result to SRV staff)
ACASI survey	Qualtrics	Qualtrics	Qualtrics
Remuneration	$75 (survey, app download) $25 (self-collected DBS)	$50 (survey) $25 (self-collected DBS) Up to $60 (app use)	$50 (survey) $25 (self-collected DBS) Up to $60 (app use) $50 (interview) $50 (bonus for participants who completed all 3 study visits)
Long chain referral (up to 5 referral coupons per enrolled participant)	$10 provided to the participant for each referred contact who screens eligible and presents for a baseline study visit. Total possible $50 additional remuneration.		

6.2 We conducted a 6-month pilot SMART intervention trial with 71 HIV-positive YMSM/YTW on ART with detectable viral load (VL) or poor adherence. Participants were randomized to one of three treatment strategies (TS): (TS1) AQ alone followed by Continued AQ for Responders and Escalation to AQ+NSC for Non-Responders; (TS2) AQ+NSC followed by Continued AQ+NSC for Responders and Continued AQ+NSC for Non-Responders; and (TS3) AQ+NSC followed by De-escalation to AQ for Responders and Continued AQ+NSC for Non-Responders. Daily app-reported adherence and 3-month VL were used as decision rules to escalate, de-escalate, or maintain intervention intensity. Participants completed surveys and VL tests at baseline, 3- and 6- months. We will measure the trial procedures' feasibility and acceptability via surveys, in-depth exit interviews, and study records (e.g. attrition, staffing needs, and completeness of VL data). We will utilize 3 types of paradata to assess intervention feasibility, acceptability, and preliminary efficacy: 1) frequency and total time spent on each AQ feature; 2) in-app daily adherence reports; and 3) user-contributed content (adherence counseling chat logs, user-entered daily discussion content and adherence strategies). We will use paradata sources 1 and 2 to determine which treatment strategies embedded in the SMART (escalation, de-escalation, and maintenance combinations) result in sustained app engagement, self-reported adherence, and VS. Exploratory analyses will assess whether app engagement and adherence vary by possible tailoring variables (e.g.

education level, depression, current substance use). We will thematically code and analyze paradata source 3 to assess app engagement and the feasibility of two-way text-based adherence counseling.

Feasibility and Acceptability analyses

To determine the SMART procedures' feasibility we will adapt Thabane et al.'s framework for assessing pilot studies across 4 domains: study Processes (e.g. recruitment rates, escalation procedures); Resources (e.g. retention, appropriateness of eligibility criteria); Management (e.g. staff capacity, time to deliver NSC); and Science (e.g. completeness of VL data, frequency of app use; estimated intervention effect, variance of intervention effect). To measure the SMART procedures' acceptability we will use a combination of survey measures Acceptability of Health Apps among Adolescents (e.g. AHAA), open-ended interview questions, and paradata metrics (Table 5). CASI surveys will also measure moderators (Table 5) associated with adherence to assess feasibility of using these as tailoring variables in a future fully-powered SMART.

Paradata overview: AQ's Empower™ platform captures timestamped usage metrics (paradata) that can be compiled and analyzed by app feature and user across time. We will utilize three types of paradata to assess intervention feasibility, acceptability, and preliminary efficacy:

Source 1: frequency and total time spent on each AQ feature;

Source 2: in-app self-reported daily adherence; and

Source 3: user-contributed content (adherence counseling chat logs, user-entered in-app content, including social wall posts and adherence strategies).

We will assess AQ intervention feasibility by thematically coding and analyzing paradata source 3 to assess the nature of user-contributed content and delivery of two-way text-based adherence counseling via AQ+. We will code whether adherence strategies are identified within the chat sessions and then implemented within the user's in-app reported adherence strategies, and whether a user's in-app daily adherence reports (paradata source 2) increase after an NSC session. We will use paradata metrics as a proxy measure of AQ intervention acceptability by creating usage variables for each AQ feature (paradata source 1). We will supplement paradata with participant-reported intervention acceptability using an app acceptability questionnaire (BL, 3M, 6M) and the Acceptability of Health Apps among Adolescents (AHAA) via CASI at 3- and 6-

months and open-ended exit interview questions (6-months) regarding each app component.

Table 5: SMART Pilot Study Measures

Primary Outcomes	Measures
Feasibility	Adaptation of Thabane et al. framework for assessing successful pilot studies: Processes, Resources, Management, Science.
Acceptability	Acceptability of Health Apps among Adolescents (AHAA): 22-item measure of global intervention satisfaction; In-depth exit interviews (intervention features, study protocols); and App use paradata: frequency and time and participant-contributed content (social wall posts; iNSC adherence counseling chat logs).
Secondary Outcomes	
Self-reported ART adherence	BL, 3 & 6-months CASI: Missed doses (Last 30 days, Visual Analog Scale and 7-day recall) Daily: in-app reported adherence.
Viral suppression	BL, 3 & 6 months: clinic/diagnostic VL, VS defined as VL below limit of detection per assay used.
Moderators	Measures (BL, 3 & 6 months)
Sociodemographics	Education, income, race/ethnicity, age, housing stability.
Depression	Patient Health Questionnaire (PHQ-8): 8-item measure to identify probable depression.
Anxiety	General Anxiety Disorder scale (GAD-7): 7-item measure to screen for and measure anxiety.
Substance use	Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): 8-item measure that screens for all levels of problem or risky substance

	use.
Social support	Medical Outcomes Survey- Social Support Scale: 19-item scale to measure perceived support including emotional/informational, tangible, affectionate, and belonging support.
HIV stigma	HIV Stigma Scale: 40-item measure (4-point Likert scale) of perceived stigma among HIV+ persons.

More details on the analysis plan are provided later in the protocol (see Section 17.0)

All data used for analysis will be stored securely in HIPAA-compliant, cloud-based storage systems such as Microsoft Teams or OneDrive hosted by FSU.

6.3 To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures and will sign a confidentiality agreement before receiving access to any participant data.

All study-related information will be kept in double-locked, limited access areas at each study site. SIDs will not be entered into the mobile app and instead a unique app ID will be assigned to each participant and used when logging into the app. These unique App IDs will be provided by the developer and recorded into CRFs during enrollment. Original source documents (e.g., Contact Information Worksheet) for individual participants will be maintained at the respective SRV and will be accessible only to the study staff. Data from original source documents will be transcribed on CRFs as applicable.

6.4 N/A

6.5 N/A

6.6 N/A

7.0 Data and Specimen Banking

7.1 N/A

7.2 N/A

7.3 N/A

7.4 N/A

8.0 Sharing of Results with Subjects

8.1 After completion of analyses, overall study results will be shared with participants in the form of a lay summary and/or infographic. This information will be sent to participants via the email they consented to using for study purposes.

Any manuscripts for academic publication or other publicly available materials generated as a result of this work will not individually identify participants in this study.

9.0 Study Timelines

9.1 Primary analyses of previously collected study data are expected to be completed within 6 months.

10.0 Inclusion and Exclusion Criteria

10.1 The SMART included 71 youth (YMSM and YTWSM) who met one of the following five conditions 1) one or more detectable VL test result (above the lower limit of detection for the clinical assay if medical-chart verified) in the past 12-month while on ART for at least 3 months; 2) having failed to show up for or missed 1 or more scheduled HIV care appointment in the past 12 months; 3) last HIV care visit was more than 6 months ago; 4) self-reporting less than 90% ART adherence in the past 4 weeks; 5) newly diagnosed with HIV in the past 3 months).

10.2 Inclusion Criteria

- Ages 15-29, inclusive at enrollment visit
- Male sex at birth
- Report sex with men or transgender women (lifetime)
- Able to speak and read English
- HIV-positive status (self-report)
- Reliable daily access to Android or iOS smartphone with a data plan during the intervention period (approximately 6 months)
- Prescribed ART
- Meet one of the follow five conditions
    - One or more detectable VL test result (above the lower limit of detection for the clinical assay if medical-chart verified) in the past 12-month while on ART for at least 3 months
    - Having failed to show up for or missed 1 or more scheduled HIV care appointment(s) in the past 12 months
    - Last HIV care visit was more than 6 months ago
    - Self-reporting less than 90% ART adherence in the past 4 weeks
    - Newly diagnosed with HIV (in the past 3 months)

Exclusion Criteria

- Aged younger than 15 years or older than 29 years at enrollment visit

- Not available to meet (in person or remotely) with study staff for baseline study visit
- Non-English speaking
- Unable to be consented due to cognitive impairment from active substance use or psychological condition
- HIV-negative (self-report)
- Not currently prescribed ART
- Anticipate not having reliable access to a smartphone with a data plan for 2 or more days during field testing or 1 or more weeks during the SMART intervention period
- Unwilling or unable to comply with protocol requirements.
- Participating in any other experimental HIV interventions
- Does not meet any of the following criteria by medical chart or self-report:
  - One or more detectable VL test result (above the lower limit of detection for the clinical assay if medical-chart verified) in the past 12 months while on ART for at least 3 months
  - Having failed to show up for or missed 1 or more scheduled HIV care appointment(s) in the past 12 months
  - Last HIV care visit was more than 6 months ago
  - Self-reporting less than 90% ART adherence in the past 4 weeks
  - Newly diagnosed with HIV (in the past 3 months)

10.3 Special populations:

- This study does not include adults who are unable to consent
- This study DOES include teenagers who are 15 years or older
- This study does not include pregnant women
- NIH has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subjects research and should NOT be considered by local IRBs for the recruitment of prisoners. Subjects enrolled who subsequently become incarcerated or are placed in detention may not continue study participation. Study visits cannot be conducted during the period of incarceration or detention

For all participants, study staff reviews the informed consent/assent to make an assessment of the youth's decisional capacity and ability to provide consent/assent prior to signing, using a 2-step process. First, staff determines if the person understands the study goals by asking "Can you tell me what this study is about?" In step 2, potential participants will be asked questions designed to assess their capacity to understand, appreciate, reason with, and express a choice about participation in our specific protocol. Participants will be asked to: name things they will be expected to do during the study;

explain what they would do if they no longer wished to participate in the study**;** explain what they would do if they experienced distress during the study; and identify potential risks for participating in the study. For youth who cannot answer these questions, the study staff will go back and review the relevant elements of consent with the participant again and repeat the process. Youth who appear not to understand after repeated review will not be enrolled in the study. If the enrollment process occurs online, research staff will talk with potential participants via phone or online teleconference software such as Zoom or other comparable platform to assess for decisional capacity and to address any questions or concerns the person may have.

As this is a minimal risk study, we sought a waiver of parental consent for individuals under age 18. A request for a waiver of the requirement for parental permission is requested for 2 reasons: 1) many youth would be reluctant to participate in this study – which focuses on HIV and risks for poorer medication adherence – if they are required to get parental permission; and 2) many of the youth in our study are likely to be gay, bisexual, or have an attraction to persons of the same gender, but may not be out to their parents; requiring parental permission may place participants at risk for outing themselves as part of the LGBT community or having HIV. For these reasons, we believe it is important to be granted a waiver for parental permission for this study population.

11.0 Vulnerable Populations

11.1 Waiver of parental consent: Participants under 18 years of age were enrolled with a waiver of parental consent granted by UNC-CH IRB as the central IRB (IRB of Record at the time of enrollment) to participate in this research study for youth participants who were 15 to 17 years of age. The research team has been granted waivers of parental permission for prior studies with sexual minority youth. Under 45 CFR 46.408 (c), an IRB has the authority to waive parental permission if it determines that "a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects" and "an appropriate mechanism for protecting the children who will participate as research subjects is substituted" and "that the waiver is not inconsistent with Federal, State, or local law." A waiver of parental permission for studies with lesbian, gay, bisexual, transgender, and questioning (LGBTQ) youth that do not involve greater than minimal risk is a common practice among researchers working in the area of gay and lesbian health/mental health. This is done to avoid the selection biases operating in only recruiting youth whose parents are both aware of and comfortable with their sexual

orientation. Commonly these youth have explored their sexual orientation without their parents' knowledge as the youth struggle with issues of disclosure and its consequences within the social, religious, and economic context of their families. A requirement for parental permission in this type of study could not only affect a person's willingness to participate, but could also potentially impact the ability of researchers to engage in this type of research with sexual minority youth. Additionally, minors can often seek sexually transmitted infection (STI) and HIV prevention services without parental/legal guardian permission, depending on each site's state laws.

If the purpose of requiring parental permission as stated in CFR is to protect the minor subject, then requiring parental permission for youth in these circumstances is not a reasonable requirement.

12.0 Local Number of Subjects

12.1 *N/A*

12.2 *N/A*

13.0 Recruitment Methods

13.1 We worked closely with the participating SRVs to engage youth. This included utilizing in person, venue-based (including recruitment from locally specific HIV clinics/providers) and online recruitment mechanisms. All participating SRVs either provided ART or had close relationships with sites in their community that prescribe. Recruitment procedures varied slightly depending on the SRV. This study requested a limited waiver of HIPAA to allow clinical sites to review patient medical records for recruitment purposes. We also followed respondent-driven sampling (RDS) methods and used a long-chain referral method to supplement recruitment, especially with the adolescents (15-17) who may be harder to reach than young adults (18-29). Online recruitment was also conducted, including but not limited to recruiting via online social media outlets (e.g., Facebook, Instagram, Snapchat, etc.). In addition to recruitment and enrollment through the SRVs, recruitment also happened nationally through national online recruitment, including but not limited to social media recruitment.

13.2 Participants were sourced from venue-based and online recruitment methods implemented at Medical University of South Carolina, Wayne State University, University of Alabama Birmingham, University of North Carolina at Chapel Hill, Rutgers University, and RAIN Inc.

13.3 Potential participants recruited in any of the aforementioned ways were directed to the study screening survey (hosted on a HIPAA-compliant online software program, e.g. Qualtrics). The screening

survey included information about the study. Those who expressed interest in the study were asked to provide informed consent/assent for eligibility screening. Those who provided consent/assent viewed the aim-specific eligibility screener questions. The screener survey could be viewed on participants' own device or on a computer or tablet located in a confidential room at the SRV to determine if they meet eligibility criteria. Screening happened onsite and remotely. Study staff also administered the screener to participants by phone if desired. The participant's clinical provider could also provide clinical information to complete the screener on behalf of the participant or with study staff.

For those who expressed interest in participating, we asked for and recorded the first name, e-mail, and phone number of the individual via the online screener. We also collected preferred means of contact (e.g. call, text, email) and permission to leave a message. We used SSL encryption for transfers of information online and data were stored in secure, HIPAA-compliant servers. The study staff accessed the screener database to determine eligibility. Eligible individuals were contacted by study staff and scheduled for an enrollment visit. Screening and enrollment happened during one visit if possible. Enrollment and follow up visits happened in person or remotely.

13.4 *N/A*

13.5 *N/A*

13.6 *N/A*

14.0 Withdrawal of Subjects

14.1 The principal investigator has the authority to withdraw any participant at any time if it their opinion it would be in the best interest of the participant. The participant will be informed of this withdrawal and explained the rationale. Withdrawal will be documented in the study tracking system.

Subjects will be prematurely discontinued from the study if any of the following occurs:

- The subject withdraws consent/assent;
- The participant is unwilling or unable to comply with study procedures;
- The investigator believes that ongoing participation may cause harm to the participant or study staff;
- The investigator believes that ongoing participation may impact the integrity of the study data;
- The study is cancelled by the *NIH*;
- The study is cancelled for other administrative reasons;

- The participant repeatedly posts hostile or inflammatory information on the app (see Section 8.3)
- The subject becomes incarcerated or placed in detention during the study; or
- Death of the subject.

14.2 Participants may end their participation in the study at any time. A study CRF will be completed for any participant who is prematurely discontinued from the study. No further data collection will occur from the date the decision is made to permanently discontinue the subject from the study. Participants who experience distress during the study while in the SRV clinic will be offered counseling on site. Participants who experience distress during the study and do not come to the SRV clinic for a visit will be provided a list of community referrals via phone or e-mail.

14.3 N/A

15.0 Risks to Subjects

15.1 We identified the following 4 items as possible risks to subjects and describe how we plan on addressing those risks:

Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout the trial. Files – audio, paper, and electronic – will not have any identifying information about the study participants and will be tracked through a unique SID and participant code. All audio recordings will be downloaded and stored on a password-protected, encrypted computer in locked offices. Transcription of audio files will be conducted using a HIPAA compliant transcription service. Any names mentioned in the audio files will be redacted during transcription. Hard copies will be kept in locked files. This research specifically includes a vulnerable population, children (YMSM ages 15-17). We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, we have a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human's subjects. Third, the study will safeguard against the risk of the linking information being stolen by keeping such information in a locked Excel file stored on a secure server to which only essential study personnel who have completed CITI certification for human subjects' research ethics training (http://citiprogram.org) will have access. We have also included numerous features to ensure app security and privacy. All relevant app communications (e.g. those

between participants or those between participants and staff) will be secured via industry standard encrypted SSL communications links. These connections will ensure that all communications are inaccessible to unauthorized third parties. Furthermore, the app can be updated regularly to address any unforeseen security updates to the software libraries underlying the secured communication links. Beyond encrypting communication, we will allow users to enable an extra PIN to secure the app within their phone beyond the PIN required to unlock the phone itself. This will allow the user to share their phone generally with others without granting access to the AQ study app. These software security solutions will provide the layers of both communications security and physical access security to ensure that only authorized users have access to the information stored on the phone as well as the information being shared over communications links. We will take special care to ensure that AQ addresses participant privacy. We have chosen the app name, AQ, because it does not relate to health care and is therefore designed to be non-stigmatizing and un-interpretable by anyone observing a participant using the app on their mobile phones. During app onboarding, study staff will assist youth in choosing a discreet and anonymous username. Moreover, mobile phone screens themselves are also constructed to prevent surreptitious observation.

Emotional discomfort: It is possible that the study may precipitate discomfort and/or an emotional response when YMSM/YTW who have sex with men answer questions about potentially sensitive topics such as living with HIV and HIV medication adherence. Further, participants may feel embarrassed about discussing sensitive issues. All participants will be told during the informed consent process that their participation is voluntary and that they can chose to stop participating at any time without any consequences. Based on our experiences using similar data collections methods with YMSM/YTW who have sex with men in past studies, the likelihood and seriousness of this risk is minimal and we will strive to create a safe and comfortable environment for all study participants.

Discomfort related to blood draws for viral load testing: Participants will require three viral load measures during the study: at baseline, 3 and 6 months. Staff will make every effort to align participants' data collection time points with standard clinic viral load measures. When these do not align, an additional blood draw or participant self-reported VL(via participant shared documentation or participant showing SRV staff a VL test result from their online health portal) or self-collected DBS will be needed. The risk of discomfort due to blood sample collection is considered minimal – and no greater than regular standard of care diagnostics. For both standard VL testing and DBS, physical harms are minimal. The type of safety lancet selected for use in the study was designed to minimize the potential

for infection or significant injury. Cleaning the area with an alcohol pad first lowers the already low infection risk further; pads are included in every kit. The spring-loaded lancet retracts fully after one firing, and thus does not pose a risk for "needle stick" injury to anyone after the device has been used. Subjects could experience dizziness, diaphoresis and nausea associated with the procedure but in prior clinical studies using dried blood spots, adverse events have been rare.

Protecting against hostile interactions and inaccurate information from one participant to another. participants will be informed during the consent process of the "group rules" regarding interactions with one another (e.g., "Honesty is important; however, hostile or abusive language will not be tolerated and may be grounds for immediate removal from the study"). These "terms of use" will also be available with a link on the app for review by participants at any time. The project coordinator and/or research assistant will manually review participants' posts on a daily basis to identify any hostile interactions or inaccurate information. Hostile interactions between participants will be handled by, first, reminding the participants in the interaction of the "group rules" regarding appropriate interactions. If the hostility continues, the offending participants will be given a warning that the continued hostility will result in withdrawal from the study if it continues. On the third offense, the offending participant will be withdrawn from the study. Text containing hostile exchanges will be removed from the study app and unavailable to view. In cases in which inaccurate information is found, project staff will be guided by experts on the team to post a comment that provides accurate information on the topic. In extreme cases, the PI may decide to withdraw a participant before the third offense. We will ensure all SRVs have a clear clinical protocol to address major issues that may come up at study visits or in online interactions. The major issues addressed in the procotol will be suicidal ideation, homicidality or violent ideation, emotional and cognitive disregulation, violent/aggressive or disruptive behavior, and intoxication. If research staff see concerning comments or messages online from participants regarding self-harm or harm of others, they will contact clinicians at the site and take immediate precautions.

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a participant should experience any adverse reactions resulting from study procedures.

While participants will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions

may indicate distress on the part of the participants. If at any time during the study, a participant divulges that they are at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states they are suicidal/homicidal, measures will be taken to ensure their safety. Reporting will be done as appropriate to the situation and the legal statutes, including reporting to child protection agencies or other appropriate agencies, and referrals will be provided to appropriate support, counseling, or treatment resources.

15.2 *N/A*

15.3 *N/A*

15.4 *N/A*

15.5 *N/A*

15.6 *N/A*

16.0 Potential Benefits to Subjects

16.1 The risk to individual participants is small and the potential benefit to both the individual and society is substantial. The main benefit of the proposed study to society is the development of a potentially feasible and acceptable mobile app that improves HIV medication adherence, retention in HIV clinical care, and increased social, emotional and informational support among YMSM/YTWSM that can be scaled up for use in a variety of clinical and community settings. Participants may experience improvements in their own ART adherence, retention in ART clinical care, and social and emotional well-being thereby potentially reducing their risk for poor health outcomes related to HIV (e.g. opportunistic infection, detectable viral load) and risks and costs to society (i.e. forward HIV transmission, expense of additional medical care, loss of productive workforce labor). Therefore, the risk/benefit ratio is favorable. Study participants will be compensated for their time.

YMSM and YTWSM account for nearly two thirds of all new HIV infections in the US and YMSM are the only risk group experiencing a significant increase in HIV incidence. Youth are also less likely to link to care, and become and maintain consistent viral suppression. Given this high potential impact and low potential hazards to participants, we find that a clear examination of these research questions outweighs the previously mentioned risks. The effectiveness of a novel, scalable, technology driven, intervention to address ART adherence and retention in clinical care is understudied with this population. Given the significant health sequelae associated with HIV infections, and the paucity of intervention programs for this population of young adults, the knowledge to be gained from

this research is significant. The risks to participants are reasonable in relation to the importance of the knowledge to be gained.

16.2 N/A

17.0 Data Management and Confidentiality

17.1 Statistical analyses for preliminary intervention efficacy

Using the variables created from paradata sources 1 and 2, we will determine which Treatment Strategies (TS) embedded in the SMART (escalation, de-escalation, and maintenance combinations, Figure 1, TS1 – TS3) result in sustained app engagement, daily app-reported ART adherence, and VS. First, we will assess VS at 3 months. While pilot SMARTs are not intended to determine efficacy, we expect to see increases in VS at 3- and 6-months that vary by app use. We will calculate the change in the proportion of VS in the AQ and AQ+ arms from baseline to month 3. At a significance level of 0.05, using a Bonferroni correction for multiple comparisons, and assuming 20% attrition (conservatively assumed to occur at baseline), the proposed sample size has 85% power to detect a medium effect size (Cohen's h=0.5) and over 99% power to detect a large effect size (Cohen's h=0.8). Second, using AQ paradata and participant profiles, we will compare the 3 TS embedded in the SMART to determine optimal intervention engagement approaches for maximizing app use, daily in-app reported ART adherence, and VS. We will compare the following TS which are embedded in the trial design: (TS1) assign AQ initially, escalate non-responders to AQ+, and have responders continue AQ; (TS2) assign AQ+ initially for 3 months, and continue AQ+ regardless of responder status; and (TS3) assign AQ+ initially, de-escalate responders to AQ, and have non-responders continue AQ+. TS comparisons will be made in terms of total app use (minutes and days), in-app daily reported adherence, and the rate of VS at 6 months. For VS, at a significance level of 0.05 and adjusting for all pairwise comparisons using a Bonferroni correction there is 80% power to detect a medium effect size (Cohen's h=0.50).

Exploratory analyses

The pilot SMART design creates a unique data resource that facilitates hypothesis-generating analyses including the estimation of an optimal adaptive treatment strategy (TS) that maps individual patient characteristics to treatment recommendations so as to maximize ART adherence/VS. While the pilot study is not powered for these analyses, we will conduct them in order to assess feasibility and generate hypotheses and estimates for full SMART sample size calculations. To estimate an optimal adaptive TS, we will use an estimation method known as non-parametric Q-learning with policy-search. This method uses a sequence of regressions to estimate the

marginal mean outcome under any possible adaptive TS and subsequently searches for an optimal TS within a parsimonious and clinically interpretable class of candidate TS, e.g., those that can be expressed as flow-charts or as a sequence of if-then statements. For example: if a patient meets clinical criteria for depression at baseline screening, then recommend AQ+ initially, otherwise recommend AQ; if the patient starts on AQ and responds, then recommend continuing on AQ; if the patient starts on AQ but does not respond, then recommend escalating treatment to AQ+; if the patient starts on AQ+ and responds, then recommend de-escalating to AQ if the patient does not report depression in the past 3 months, otherwise recommend continuing on AQ+; if the patient starts on AQ+ and does not respond, then recommend continuing on AQ+.

In addition to generating new clinical hypotheses about how patient characteristics should be used to tailor treatment, estimation of an optimal adaptive TS can be used to conduct moderation analyses. An intermediate step in the Q-learning with policy-search estimation algorithm is that one must postulate and fit a model for the regression of the outcome on covariates and treatment. This model can be used to conduct standard moderation analyses, e.g., test for a differential effect of AQ relative to AQ+ among subjects with depression. Furthermore, these models can be used to test whether moderators are tailoring variables, i.e., those that would be important for choosing a TS. Continuing the example of depression, to test if depression is a tailoring variable, we would test if the optimal TS that does not make use of depression status results in significantly lower adherence/VS rates compared with the overall (unconstrained) optimal TS. We will test for moderation and tailoring among known risk factors for non-adherence (depression, substance use, unstable housing, low social support, and HIV-related stigma) as well as additional variables identified during model building for the Q-learning with policy search algorithm. The results of these analyses will inform the design of our full SMART.

To augment the primary quantitative analyses, we will evaluate participants' app usage and engagement by measuring app usage (e.g. numbers of times per week participants access app, completion of daily quests, and average daily use of app), number and content of social wall posts, amount of virtual currency collected and rewards unlocked. The research team will have access to these data as they are transferred from mobile phones to the secure server, which will occur any time the participant is connected to the internet via broadband or Wi-Fi. For AQ+ we will collect data on number of sessions, and content of sessions.

Missing Data

Several procedures will be used to conduct data analysis when data for either outcomes or covariates are missing. The first step will be to assess the extent and pattern of missing data. If data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants, or if this approach would lead to biased or inaccurate results, the multiple imputation scheme for sequential multiple assignment randomized trials proposed by Shortreed et al. (2014) will be used to account for the missing data.

17.2 All laboratory specimens, questionnaires, evaluation forms, reports, transcripts, and other records will be identified by SID and participant code only, to maintain participant confidentiality. All paper records with personally-identifying information will be kept in a locked file cabinet in a limited secure access area at each SRV site. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by NIH.

Every effort will be made to ensure that study participants are protected from risks.

Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout all research procedures and data management and analysis.

Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. The research team has significant experience developing security protocols for Internet-based studies, and we will take a variety of steps to ensure participant security, including using a dedicated server behind a firewall, encryption of data, separation of identifiers from responses, and password-protected access to data. Therefore, we believe that this risk will be minimal. As described above, the AQ app includes a number of features to ensure app security and privacy.

Participants will create a unique username that does not contain any identifying information but will be their username on the AllyQuest app. Intervention participants will choose an anonymous avatar (cartoon superhero head) to represent themselves on the app and are told at the enrollment visit and in multiple places on the app that it is a violation of community guidelines to reveal identifying information including name, address, phone number, email address, social media handles, places of employment, or locations to meet for

personal or business use. Participants will not be able to privately communicate with each other on the app - all conversations are viewable on the main feed. Trained research staff will monitor the app daily to ensure violations to privacy, even through self-disclosure, are addressed. The AllyQuest app is also password-protected.

17.3 Certificate of Confidentiality:
This research specifically targets a vulnerable population, children – YMSM/YTWSM ages 15-17. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, per Section 2012 of the 21st Century Cures Act as implemented in the 2017 NIH Certificates of Confidentiality Policy, all ongoing or new research funded by NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information is automatically issued a CoC. As noted on the NIH website (http://grants.nih.gov/grants/policy/COC/faqs.htm#187), a Certificate of Confidentiality will help the research team "...avoid compelled 'involuntary disclosure' (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect."

17.4 To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Any identifiable data will either be stored on secure servers or will be on fully encrypted laptops. CASI assessments and online eligibility screening will take place on an encrypted commercial survey website, Qualtrics. This site has been used by the investigators for thousands of online surveys with MSM with no data security breaches. Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data.

We will also develop procedures to minimize indirect disclosure that a participant is participating in an HIV- related research study, or a study that enrolls MSM/TWSM. For each mode of contact information, we will ask specifically whether anyone else potentially has access to that mode of communication, and if it is acceptable to leave a non-specific message about participation in a health study. No study-related messages will ever mention HIV or the nature of the research study. Additionally, all scripts for email, text message,

and telephone contact with participants will be reviewed and approved by the IRB before being used for contact with participants.

The research team will use Dedoose software to perform all qualitative analyses. Dedoose is a web-based application for organizing and analyzing textual, audio, and video data (qualitative) along with outstanding functionality for their integration with survey, test score, ratings, and demographic data (quantitative). Dedoose employs the highest levels of data encryption available for a web application in all data storage, back up, and transmission. Dedoose allows for project specific encryption feature. When using this feature, only Dr. Muessig or her designee will hold the additional encryption key needed to be entered in order to view the project. This gives Dr. Muessig exclusive control over who can view the project under any circumstances.

REDCap - a HIPAA-compliant web-based platform – for participant management. REDCap was supported by UNC's TraCS Clinical Research Data Management Service. As specified in their user manual: "Standard features of electronic clinical research data management systems are available in the web-based systems provided with REDCap. These include interactive data entry with real-time field validation, lab data imports, audit logs to record database modifications, database integrity checks, security (in logins, permissions based on need, and encryption), reporting, forms inventory, and exports to common statistical packages for analysis. Logging tracks all data entered in REDCap so that it can be traced back to the person who entered it. No data can be changed without showing who has made the changes. This allows the study team to ensure the security and integrity of the data collected and submitted; therefore, there are controls surrounding this aspect. REDCap also provides for principle investigator sign-off on data, as required in FDA studies. Although users can modify data based on their permissions, they cannot delete the subject or history of that subject. Requests to delete a subject must be made to the REDCap system administrator. The data is encrypted during transmission. The servers are located in a secure campus area with all appropriate physical security measures in place. Access is by individual user id, and is restricted to the forms and/or functions that the user needs to have. The applications themselves are written using open source tools, and have also been scanned by the campus security office to ensure that the applications are also protected from known exploits. The data is backed up to electronic media on a daily basis. The electronic media is secured by ITS stored in a secure area separate from the servers.

The team will use Zoom or a comparable, HIPAA-compliant platform to remotely conduct study visits and the qualitative exit

interviews at 6-months. When using Zoom, participants will have the option to use Zoom in several formats: face-to-face video chat, video chat in which they can see the interviewer but the interviewer cannot see them, audio chat only, or a text based conversation. Zoom is compatible on PCs, tablets, and smartphones; as well as maintains the option to conduct an audio conference without the video component. All SRVs will be asked to use a HIPAA-compliant version of Zoom or a comparable video conferencing platform for study visits and qualitative exit interviews.

End-to-end encryption. Zoom encrypts all presentation content at the application layer using the Advanced Encryption Standard (AES) 256-bit algorithm. Zoom end-to-end (E2E) chat encryption allows for a secured communication where only the intended recipient can read the secured message. Zoom uses public and private keys to encrypt the chat session with Advance Encryption Standard (AES256), and session keys are generated with device unique hardware ID to avoid data being read from other devices. This ensures that the session cannot be eavesdropped or tampered with.

Cloud Control Infrastructure. A distributed network of low-latency multimedia routers (software) resides on Zoom's communications infrastructure. With these low-latency multimedia routers, all session data originating from the host's device and arriving at the participants' devices is dynamically switched — never stored persistently through the Zoom communications infrastructure. Zoom's communications infrastructure for real-time video, audio, and data communications resides on Zoom dedicated servers, which are housed in SSAE 16 SOC2 compliant datacenters on opposite sides of the US. Zoom sessions are completely temporary and operate analogously to the popular mobile conversation over the public mobile network. In addition to unique security benefits, Zoom's communications infrastructure also enables an extremely scalable and highly available meeting infrastructure unrestricted by the limitations of physical data centers.

The Zoom client communicates with the multimedia router to establish a reliable and secure connection. At the time of instantiation, the Zoom client will determine the best method for communication, attempting to connect automatically using udp and tcp port 8801, 8802 and 8804 or HTTPS (port 443/TLS).

The Zoom sessions will contain identifying information, but this information will be stripped form the recorded Zoom sessions before they are sent to the analysis team for content analysis.

Qualtrics may be used for study surveys, online informed consent/assent forms, and online HIPAA waivers.

Qualtrics uses Transport Layer Security (TLS) encryption (also known as Hypertext Transfer Protocol Secure (HTTPS)) for all transmitted data. Survey data are protected with passwords and HTTPS referrer checking. The data is hosted by third party data centers that are Statement on Standards for Attestation Engagements (SSAE)-16 Service Organization Control (SOC) II certified. All data at rest are encrypted, and data on deprecated hard drives are destroyed by U.S. Department of Defense methods and delivered to a third-party data destruction service.

Qualtrics deploys the general requirements set forth by many Federal Acts including the Federal Information Security Management Act (FISMA) of 2002. They meet or exceed the minimum requirements as outlined in Federal Information Processing Standards (FIPS) Publication 200.

Health Insurance Portability and Accountability Act (HIPAA) Statement: With some restrictions, Qualtrics may be designated as a Business Associate when the Qualtrics BA Agreement is signed with a Covered Entity—those organizations that are required to comply with HIPAA privacy rules. All client data are considered confidential, and treated as such.

Related to HIPAA, Health Information Technology for Economic and Clinical Health Act (HITECH) are updated assessment rules to ensure that data are properly protected and best security practices are followed. By using secure and certified data centers, Qualtrics ensures the highest protection and testing as per HITECH requirements.

Back Up Recording

All qualitative interviews may also be recorded using a back-up digital audio recorder. Audio files will be erased after being transcribed and quality control checked and transcripts will be de-identified. All audio files will be kept confidential and stored in a locked/limited access folder on secured servers, which are only accessible to designated study staff. All members of the research team will be trained in confidentiality and have signed confidentiality agreements. A professional transcription service, experienced in the handling of confidential data, will be used to fully transcribe verbatim all audio files. Prior to receipt of the first audio file, the transcription service will be instructed to redact from the typed transcript identifying information (e.g., a name) that may have been verbalized during the course of the interviews.

App paradata

Ayogo (technology partner and creator of AQ) servers can be hosted on Amazon Web Services or ClearDATA (HIPAA compliant)

services. The server-side app is built on a scalable architecture using Ruby on Rails, MySQL, Redis (for caching) and Node.js for analytics functions. Ayogo's infrastructure has been certified as secure and private by IT departments of large pharmaceutical companies and hospital systems. Ayogo uses storage encryption for personal identifying information, SSL and VPN for transport encryption, firewalls to protect access to unapproved ports and IP addresses, centralized key management for system administrator authorization and authentication, hourly backups, and regular HIPAA and security training for all employees. Ayogo's client side architecture is web based and runs on the Web and on Mobile devices. The client-side app uses Typescript, ES6 modules, Webpack, npm, and Apache Cordova. The client communicates securely with the server over HTTPS. Ayogo's client side infrastructure has undergone security and privacy certifications with NowSecure. Analytics de-identification occurs within the Ayogo VPC and outputs de-identified data to make analytics reports with software such as Tableau. De-identified data is stored in Ayogo's data warehouse; users are identified by a 36-character unique identifier linked to a study ID via a secure access code.

17.5 *N/A*

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects.

18.1 Site research staff must first follow both the FSU IRB and their own IRB's procedure for reporting and managing untoward effects.

There are three types of untoward effects to be identified: 1) those related to the participant, 2) those related to the study staff, and 3) those related to the neighborhood/community (if applicable).

First, the study will catalogue any untoward effect related to the participant. Reporting is required for occurrences including social harms, psychological distress, and serious life-threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset state requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will record these untoward effects in the site study log, notify the protocol team, and complete appropriate CRFs to document adverse events and social harms. Study staff will be briefed during the training on the scope of possible untoward effects and instructed to report events.

Second, study staff may encounter untoward events during sessions that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well.

The protocol chairs should be notified of these events so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other study staff.

Third, a critically important area any community-based study intends to evaluate is the impact, including untoward effects, of the project on the community. This will be done informally for this protocol with untoward events being reported to the protocol team.

All untoward effects/adverse events/unanticipated problems will also need to be reported to the FSU IRB if they meet all three of the following criteria:

"Unanticipated problems involving risks to subjects or others" (UPIRSO) refers to any incident, experience, or outcome that: is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; is related or possibly related to a subject's participation in the research; and

Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events that meet the criteria for an UPIRSO and are also serious adverse events should be reported to the FSU IRB within one (1) week of the investigator becoming aware of the event. Any other events that meet the criteria for a UPIRSO should be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem.

If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 *N/A*

19.2 To minimize the risk of participants feeling uncomfortable about answering personal questions, we used Computer Assisted Self Interview (CASI) methods for the study's assessments. In CASI, participants read assessment questions on a laptop computer or mobile phone and use a combination of mouse click and keyboard/touchscreen entry to input the answers themselves. Study staff were available to assist participants with questions or technical difficulties on the CASI. Participants were also able to refuse to answer any question that makes them uncomfortable. In-depth

interviews were conducted face-to-face or online depending on the research project. Descriptions of procedures were provided in each study projects' human subjects sections.

19.3 Participant-related study information will be identified through a study ID number (SID) and participant code on all participant CRFs, audio files, transcripts, lab specimens, and CASI files. Participant names or other personally-identifying information will not be used on any study documents other than the Contact Information Worksheet (stored in double-locked office separate from other study information only accessible by designated study staff) and will be redacted from field trial interview transcripts.

19.4 *HIPAA* Waiver: Clinical SRVs asked participants to sign a HIPAA waiver to access their medical records at the clinical SRV to check for viral load test results in the eligible time period prior to each study visit. SRVs also asked participants to sign medical record releases for any external clinical sites where participants report having had a viral load test in the past month or plan to have a viral load test during the 6-month intervention period. Participants were asked to sign a paper or online HIPAA waiver. Qualtrics was used for the online HIPAA waiver.

CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

Each site was responsible for adherence to their individual institution's HIPAA policies and procedures.

20.0 Compensation for Research-Related Injury

20.1 *N/A*

20.2 *N/A*

20.3 *N/A*

21.0 Economic Burden to Subjects

21.1 There are no costs to participants for completion of analysis of data collected during the study.

22.0 Consent Process

22.1 This protocol is for data analysis only, no new/additional participants will be enrolled in the study.

23.0 Process to Document Consent in Writing

23.1 All data analyzed under this protocol has been collected using UNC-CH IRB approved documentation and procedures.

23.2 *N/A*

23.3 N/A

24.0 Setting

24.1 Analysis of study data will be completed by research staff employed by Florida State University.

25.0 Resources Available

25.1 All proposed study staff have participated in the required trainings in participation and conduct of studies that involve human subjects, and any future study staff will do so upon hiring. Research staff at individual SRVs who interact with AllyQuest participants at assessments do not need to be clinicians. A research assistant (RA) level position should be sufficient to verify eligibility (obtain informed consent, be available for questions during the CASI, and explain the AllyQuest intervention. Research staff at SRVs will be trained via videoconferencing on the intervention components and will be given a script and checklist to review with participants.