Title: **The Wise App Trial for Improving Health Outcomes in PLWH**

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STUDY PURPOSE AND RATIONALE

The United States (US) HIV epidemic continues to be a significant public health challenge affecting 1.2 million Americans [1]. Persons living with HIV (PLWH) confront a range of psychological and behavioral challenges, including adherence to medication regimens, accessing healthcare services, changes in quality of life, stigma, uncertainty about physical and psychological decline, and death [2]. At the same time, the US HIV epidemic is highly concentrated demographically in racial and ethnic minorities [3-5].

Antiretroviral Therapy (ART) adherence is central to therapeutic success for PLWH. Strict adherence to ART is key to sustained HIV suppression, reduced risk of drug resistance, improved overall health, quality of life, and survival [6] as well as decreased risk of HIV transmission [7-10]. Achieving adherence to ART is a critical determinant of long-term health outcomes in HIV-infected patients. For many chronic diseases, such as diabetes or hypertension, drug regimens remain effective even after treatment is resumed following a period of interruption. In the case of HIV, however, loss of virologic control as a consequence of non-adherence to ART may lead to emergence of drug resistance and loss of future treatment options. Developing effective interventions to enhance ART adherence is essential. Currently only about 25% of PLWH in the US are virally suppressed, supporting the urgent need for interventions to engage people in the HIV care continuum and improve ART adherence [11].The shift to simpler regimens alone is insufficient for optimal adherence [12].

mHealth is the use of mobile devices -- such as cellular phones, tablets, smartphones and other wireless devices -- for the delivery of health services and information [13]. **The ubiquitous nature of mobile technologies in daily life creates opportunities for health behavior management tools that were not previously possible [14].** mHealth can rapidly assess and modify health-related behavior and transform patients' decision-making about their health [13]. Smartphones can house mHealth applications (apps) designed to be used by patients and providers for diagnostics, behavioral prompts, reminders, illness monitoring and self-management programs that extend far beyond the limits of a physical clinic. The potential for information and communication technology, such as mobile apps, to enhance medication adherence through the provision of support (information, education, reminders, etc.) for behavior change has been well-documented over the last decade [15-22]. A growing body of research confirms the benefits of empowering healthcare consumers with information and decision-making support [23-25]. Patient participation in their health leads to increased patient satisfaction as well as positive changes in adherence patterns translating into improved clinical outcomes [26-28]. Individuals who use mobile apps to manage their health may perceive these tools as more private, potentially increasing patients' willingness to disclose non-adherence and seek support tools [29,30].

mHealth also has the potential to bridge a divide in healthcare delivery among underserved racial and ethnic minority groups. The use of mobile technology has made a huge impact on communication, access, and information/resource provision to minority and underserved populations [31]. Nearly 2/3 of Americans are now smartphone owners, particularly those from racial/ethnic minority and low socioeconomic groups [32]. Furthermore, emerging evidence suggests that underserved populations use smartphones as their primary method for accessing the Internet [33]. The use of mHealth can reduce geographic and economic disparities and personalize healthcare [34,35], which can be particularly relevant to PLWH since a majority of them are from underserved and minority groups [3-5].

mHealth has the potential to be an efficacious tool for improving the health of PLWH. mHealth tools can promote the management and prevention of chronic illnesses, such as HIV [36] and have the potential to address many of the healthcare needs of PLWH including adherence to HIV medications and retention in HIV care and treatment. Medication reminders delivered via text messaging have been shown to improve ART adherence in a number of studies [37].

Self-report of medication adherence is often criticized since it typically overestimated adherences especially in unmasked trials [38]. **Our study will use real-time, wireless monitoring strategies via the CleverCap™ Lite dispenser, for measuring ART adherence. This will overcome this often cited limitation and provide novel opportunities** to proactively prevent virologic rebound and treatment failure. In contrast, current adherence assessments, such as patient recall, pill counts and pharmacy refill data, typically detect missed doses long after they occur. All of these methods are assessed on an intermittent basis, such that missed doses are detected several weeks to months after they occur, which can lead to treatment failure and drug resistance [39]. Real-time medication adherence monitoring can allow for the detection of adherence lapses and initiation of interventions to resume treatment prior to the development of virologic rebound and drug resistance, which has not previously been possible [40].

CleverCap™ Lite, a smart pill box container, (Compliance Meds Technologies, North Miami Beach, Florida) communicates dosing behavior in real-time by transmission of a patient identifier and date-time stamp over existing cellular networks when the container is opened to take medications. Because cellular network coverage is becoming ubiquitous, the technical infrastructure now exists for real-time adherence monitoring in resource-limited settings. A similar device, called The Wisepill container, was pilot tested in a small sample (N=10) of PLWH in Africa and shown to be useful for providing real-time adherence counseling in PLWH [41]. The Wisepill has also been successfully used to monitor adherence to anti-depressants by Dr. Mohr (Co-I) on this proposed project [42].

The Wise App will motivate and engage participants over time. Although mHealth technology may be promising, several studies have shown that adherence to mHealth interventions is low and decreases over time [43], even though these studies showed a significant effect on health outcomes [44]. Therefore there is a need for strategies that motivate people to use, and keep using, the technologies offered. Gamification, the use of game-like rewards and incentives, paired with desired behaviors, is one such strategy that can be used to increase motivation to sustain habits of individuals over time [45]. Companies have widely accepted and adopted gamification as a means to increase initiation and retention of desired behaviors [46]. In fact, it has been estimated that 60% of health initiatives in workplaces now include gamification elements [47]. PatternHealth Technology's HealthStar mobile app, referred throughout this protocol as "The Wise App," will use persuasive games to motivate end-users [48]. End-users can set health and fitness goals and use persuasive gaming to help meet the goal. In the case of the Wise App, participants will set goals, have a tally bar, and receive reminders to motivate them to complete their goals.

mHealth tools, including mobile apps, for PLWH have not been well-developed or evaluated. Currently there are a number of mHealth apps for PLWH [49] but few have been developed by using information gathered from potential end-users (PLWH) or healthcare providers regarding desired content and features of a mobile app. Of the limited number of studies specifically focused on mobile apps for PLWH, one study identified the preferences for a mobile app in HIV positive young mothers [50], but did not rigorously evaluate the app after its development. In another study, researchers developed a mobile app consisting of a music program to improve adherence to ART for adult PLWH, but did not engage the intended end-users in the development of the intervention [51]. Although mobile phone apps are increasingly being used for the care of HIV and other sexually transmitted diseases, most available apps have failed to attract user attention and positive reviews. In a review of existing HIV apps, researchers found that apps were infrequently downloaded (median 100 to 500 downloads) and not highly rated (an average customer rating 3.7 out of 5 stars). Based on this 2012 review, less than 0.3% of the more than 29,000 health-related apps available for iPhone and Android consumers were dedicated to HIV/STD information and prevention[49].

Our proposed study is timely and relevant since there is currently a dearth of evidence on the use of mHealth interventions for improving health outcomes in PLWH. Of the relevant research including text messaging to support HIV care, studies have largely been developed and tested outside the US in low and middle income countries [52]. Two systematic reviews on the use of text messaging for treatment adherence in PLWH have been conducted, but the studies were focused on populations outside the US [37,52]. In another systematic review on the use of health tools for PLWH, all of the US studies in the review focused on the use of mobile technology as a data collection tool for targeting smoking cessation in PLWH [53].

Given the dearth of useful and likeable apps [54], the need for improving medication adherence in PLWH and the great promise that mHealth holds, we propose to test a smartphone app linked to a smart pill box called CleverCap™ Lite (The Wise App) for PLWH targeting ART adherence and guided by a rigorous and relevant theoretical framework[55]. The feasibility of the Wise App is supported by data demonstrating that use of mobile devices is nearly ubiquitous in the U.S. with persons from underserved groups being more likely to own a smartphone and more likely to use a smartphone (as compared to a computer) to access the Internet. The current trial is significant in representing one of the first principled and systematic efforts to build a mHealth app intervention based on user-centered design work and linked to a smart pill box for improving health outcomes. Our proposed study, based on our empirical findings from our preliminary work [56-61], uses rigorous methods and a theory-based approach [55] to develop and test a mHealth intervention (Wise App) for improving ART adherence for PLWH.

STUDY DESIGN

The goal of this study is to test the efficacy of The Wise App for improving health outcomes (as measured by improving ART adherence) in PLWH. Our secondary outcomes are: (a) healthcare access (b) technology

acceptance (c) technology use. Table 1 presents and overview of the design, participants and data analysis plan for each aim.

Table 1. Overview of Design, Methods, Participants, and Data Analysis			
Aim	**Design/Methods**	**Participants**	**Data Analysis**
1	Cognitive Walkthrough, and user testing using think-aloud protocol	Cognitive Walkthrough: human-computer interaction experts (N=5); User testing: PLWH (N=30)	Quantitative and qualitative summary of heuristic violations; thematic analysis of think-aloud protocol, quantitative summary of mouse clicks, time, etc.
2	Randomized controlled design	PLWH (N=200; intervention=100, control n=100) for 6 months	Descriptive statistics; Linear regression model
2b	In-depth Interviews	PLWH (N=100; intervention group only)	Qualitative coding of in-depth interviews related to CleverCap device; thematic analysis to examine CleverCap experience and acceptability
3	Descriptive: focus groups	Focus groups: Participants in the intervention arm of the RCT (N~50)	Descriptive, thematic analysis to examine post-intervention perceptions related to The Wise App use, usefulness and impact on overall health
3b	Descriptive: focus groups	Focus groups: Participants in the control arm of the RCT (N~60)	Descriptive, thematic analysis to examine post-intervention perceptions related to the Fitness Tracker use, usefulness and impact on overall health
3c	Descriptive: in-depth interview	In-depth interview: Participants in the intervention and control arms of the RCT (N~20)	Descriptive, thematic analysis to examine perceptions related to the recruitment process and research participation to the RCT

C. Aim 1: Build a functional app for HIV self-management linked to a smart pill (Wise App) for PLWH and assess its usability

C.1. Intervention Components.

Medication adherence can be monitored using the CleverCap™ Lite bottle, which emits a cellular signal when it is opened, allowing for near real-time acquisition of data regarding patient pill taking activity. The CleverCap™ Lite adherence monitor (see Compliance Meds Technologies, North Miami Beach, Florida) communicates dosing behavior in real-time by transmission of a patient identifier and date-time stamp over existing cellular networks when the container is opened to take medications.

The primary intervention component will include:

- Medication Reminders – Reminders will be tailored to participants' medication schedule (*Figure 1*). To avoid notification fatigue, a cellular signal is sent to the phone when the servers detect a pill bottle opening, which prevents the launching of the reminder notifications on the phone. The app will launch an in-phone pop-up alert before a scheduled dose time is missed. If the Wise App does not receive notification that the pill bottle has been opened, additional reminders will be launched on the phone after the scheduled dose, asking the patient to taken their medication.

Additional app components are listed below and organized according to Fogg's Functional Triad:

Figure 1. Medication Schedule

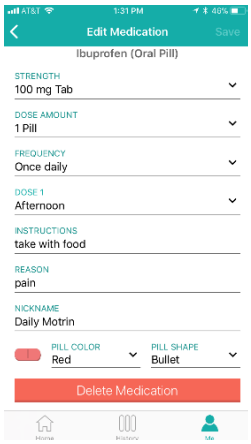


Figure 2. Mobile App Screen of User History

• Missions (Tool) – Missions are intended to help users keep track of activities they enjoy. This feature will display a checklist of tasks participants aim to complete (e.g. go to the gym, text/email a friend, etc.)

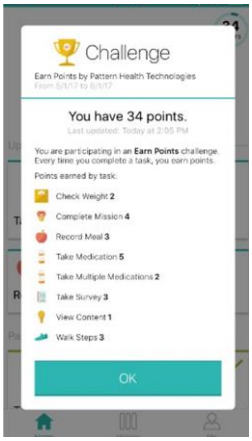
• Fitness Tracker (Medium) – This feature will allow users to track their daily steps. Each user will receive a fitness tracker, which will be synced to the Wise App. A daily step goal will be set for all users and progress will be tracked on the app, allowing users to see the effects of their physical activity.

• History (Medium) – Informed by the CleverCap™ Lite dispenser, users will be able to view their medication adherence over time through a graphical representation *(Figure 2).* The CleverCap™ Lite dispenser uses cellular technology to transmit information on time of pill bottle opening. Users will also be able to view trends of step goals and other app features.

• Games (Medium) – Wise App supports two types of gamification: 1) A virtual pet that reacts to a user's medication adherence, and 2) Challenges that can be designed to award/deduct points to users based on select activities completed (*Figure 3*).

- Chat (Social Actor): This feature will allow study participants to anonymously chat with other users under specific discussion topics. To ensure privacy protection, only study participants will be a part of this chat and all posts will need to be approved by an app administrator prior to being posted.
- Testimonials of Lived Experiences (Social Actor) – Videos of PLWH who share their experiences which has the potential to provide social support.Videos will include topics such as a new diagnosis, living with HIV for 20 years or longer, and disclosing HIV status.

Figure 3. Mobile App Screen of Challenges



After the Wise App has been built, we will conduct usability testing at the Columbia University School of Nursing.

C.2. Usability Testing.

The goal of usability testing is to improve the design and increase the likelihood of technology acceptance. To achieve this goal we will evaluate the user interface of the Wise App developed at Pattern Health Technologies. We will conduct two types of usability assessments: A) Cognitive Walkthrough and B) End-User Usability Testing.

C.2.1.***Cognitive Walkthrough:***

The purpose of a CW evaluation is to evaluate the ease with which users can perform a task with little or no formal instruction or informal coaching.[62] The CW has historically been conducted by experts or researchers[63] and it is highly structured with a goal of understanding a technology's learnability.[64] A CW session's input should include 1) a detailed design of the user interface 2) a task scenario 3) explicit assumptions about the user population 4) the context of use and 5) a sequence of actions that would allow the user to successfully complete the task.[62] For the purposes of this study, we chose the tasks outlined in the procedures section to analyze.

There are four steps in the context of a task that the user will need to complete using scenarios: 1) The user would set an end goal to be accomplished, 2) The user would inspect available actions on the user screen (e.g. menu items, buttons, etc.), 3) The user would select one of those actions as the next step that leads to the end goal, and 4) The user would perform the action and evaluate system feedback for evidence that progress is being made toward accomplishment of the user's goal.

Sample: Five informaticians will be recruited as usability experts with training in human-computer interaction and who have published in the field of informatics. We will recruit the evaluators through direct contact from the Informatics Departments at Columbia University and/or Weill Cornell Medical College, both of which have large cadres of informatics researchers.

Procedures: Each of usability experts will be provided with a beta version of the Wise App, a Clever Cap, and a fitness tracker to conduct the study. Each expert will be provided with a set of user scenarios utilizing the

Wise App. The expert will be asked to simulate a novice user and assess a user interface by analyzing the cognitive processes a user would go through to effectively accomplish each of the high-level tasks within the app. While they are performing the tasks required for the scenarios, the expert will be asked to say aloud what they are thinking, seeing and trying to do and will be asked to explicitly document each step that they deem necessary to successfully complete each task in the user scenarios, if needed. The expert will then asked to answer aloud the following four questions for each of the tasks identified in the user scenarios: 1) Will the user try and achieve the desired effect?, 2) Will the user notice that the correct action is available?, 3) Will the user associate the correct action with the desired effect?, and 4) Will the user notice that progress is being made toward the final goal?. The process will be recorded using Morae software™ (Techsmith Corporation, Okemos, MI),[65] which allows the researcher to record and analyze the audio recording and screen shots that are captured during the heuristic evaluation. Participants will also complete an electronic survey. Participants will be compensated $150.00 for their time.

Data Analysis: Verbal commentary, answers to the four questions from the CW, and screen-recordings from the Morae software will be reviewed and evaluated to determine if any potential usability concerns have been identified. If there are positive answers to all of the questions, then it can be determined that there are not any usability concerns at this stage; if there is a negative answer to any of the four questions, the specified action is not free of usability problems.[64] Specific comments and recommendations will be discussed by the researchers and any concerns will then be aggregated and summarized for presentation to system developers for improvements.

C.2.2.End-User Usability Testing:

We will conduct usability testing to examine task performance by our end-users, persons living with HIV (PLWH). It is intended to identify usability problems and any potential obstacle to their effective use of the Wise App. This is an iterative process that involves testing the system and then using the test results to change it to better meet users' needs.

Sample: 30 PLWH will be recruited to identify usability concerns within the Wise App. Of the 30 PLWH, 15 will be iPhone users and 15 will be Android users. In usability testing the minimum percentage of problems identified rose from 82% up to 95% when the number of users was increased from 10 to 20.[66]

Procedures: Participants will be provided with a beta version of the Wise App, a Clever Cap, and a fitness tracker. They will be also provided with the same set of user scenarios used for CW by experts. Each participant will be asked to perform tasks which should closely mirror the intended end users of the app. Each participant will be also encouraged to verbalize their thoughts about the tasks they are performing. The process will be audio- and screen-recorded using Morae software™ (Techsmith Corporation, Okemos, MI).[65] After the usability evaluation, participants will be asked to complete an online survey including a demographic questionnaire and user satisfaction assessment via Qualtrics®. Participants will be compensated $25.00 for their time.

Data Analysis: The analysis will be based on the Morae recordings of user sessions, transcriptions, and notes. Dr. Schnall will search for critical incidents which will be characterized by comments, silence, and repetitive actions. Dr. Schnall will review these incidents in detail using Morae software. The incidents identified and the users' written comments will be summarized. Content analysis, a technique for making replicative and valid inferences from data, will be performed by the research assistant under Dr. Schnall's supervision. The comments will be categorized according to the positive characteristics, negative characteristics, and recommendations made by PLWH. Results from the user satisfaction assessment will be analyzed using SPSS (IBM, Armonk, NY) to calculate the descriptive statistics to complement the findings from the usability assessment in which the PLWH will be using the Wise App. Using the findings from these activities, we will refine the components of the app for use in the RCT (Aim 2).

D. Aim 2: Evaluate the impact of the Wise App on medication adherence in underserved PLWH

D.1. Design Overview.
A randomized controlled trial will be conducted with 200 PLWH over 6 months. Participants will be randomly assigned to the Wise App (intervention) or a control arm. Details on the differences between the two groups can be found in Table 2.

Table 2. Comparison of Intervention vs. Control Group

	Intervention	Control
The Wise App	✓	✓
• **Medication reminder**	✓	
• **Step Goal reminder**		✓
CleverCap™ Lite dispenser	✓	✓

D.2. Eligibility Criteria for Participants.
Participants must be at least 18 years old, have a diagnosis of HIV, speak and understand English or Spanish, and live in the US. Participants must have a smartphone and be on ART medications. Our participants will all be Medicaid eligible and most of our participants, as can be seen from our preliminary work, are from racial and ethnic minority groups.

To comply with the AHRQ Policy on the Inclusion of Priority Populations (NOT-HS-03-010), our study participants are chronically ill, inner-city, low-income and minority. We anticipate that about 40% of our study participants will include women.

In addition, participants must report past 30 days adherence of 80% or less as measured using the Visual Analogue Scale (VAS) [67] (Appendix) or have a viral load of over 400 copies/mL. Exclusion criteria are: participation in any other mobile app study for PLWH, not including text messaging studies, and any clinical problems that would not allow someone to use a cell phone. Prior to participating in any study procedure, participants must voluntarily provide informed consent.

D.3. Recruitment Plan.
We will post flyers at each of the recruitment sites listed below and will provide compensation for time that it takes to complete the study questionnaires. The flyer will have the name, contact number, and e-mail for the study coordinator. PLWH from these sites are almost exclusively from low socioeconomic backgrounds. If we are unable to recruit participants after posting flyers, we will then hand distribute flyers to potential participants in the waiting rooms of our sites. We will also be using advertisements through social media that will lead users to a short Qualtrics survey, The Wellness Study Interest Survey, asking for contact information and some eligibility criteria. The purpose of this short survey is to attract more individuals towards our study, provide them with necessary study-related information, and to determine initial eligibility before a staff member reaches back out to screen for enrollment eligibility. Our main sites for recruitment are those where we have previously conducted our studies (HRSA H97HA08483, NINR P30NR010677-03S1 and CDC U01PS003715-01).

1) The Comprehensive Health Program at Columbia University/NewYork-Presbyterian Hospital provides primary care, HIV specialty care and care coordination services to over 2,000 PLWH. 95% of individuals are of either Black or Latino background and women represent half of the overall population. In addition, the program has 28 direct clinical providers, 8 social workers, and 10 additional care coordinators. Of note, Dr. Olender (Co-I) is an attending physician at the Clinic.

2) AIDS Service Center (ASC) is a community based organization for PLWH and persons at risk for HIV. ASC has more than 90 staff, 85 peer interns, and more than 1,800 clients who come for services each year. In addition, another 18,000 people are reached through the peer education and community outreach initiatives of ASC. Given our past experience and success in recruiting participants and using the recruitment strategies described above, we are confident that we will be able to recruit the number of participants needed to conduct the study within the study timeframe. See details in Section A.3.3. Preliminary Work.

STATISTICAL PROCEDURES

D.4. Power and Sample Size.
We will recruit 200 individuals and have greater than 80% power to detect a less than 10% difference in adherence to ART medications between the Wise App and the control group. We assume a 25% attrition rate by the end of trial for both arms. The power calculations are based on the analysis of main outcome, ART adherence. All calculations are based on 2-sided test with alpha at 0.05 level. Our calculations are based on the assumption that each person is on a once daily regimen and the adherence rate is ≤ 80% at baseline.

Many of our participants will be on regimens that are two or three times per day which will provide greater power for our study since we have a greater number of measurements (e.g., 180 for once daily vs. 360 for twice daily regimen). To illustrate, if the adherence rate for the control group does not change, we will have 90.7% power to detect a 6% increase in ART adherence for the intervention group (e.g., from 80% to 86% at

the end of the trial). If the adherence rate for the control group increases 4%, from 80% to 84% at the end of the trial, we will have 88.6% power to detect a 5% difference in adherence between the intervention and control group. In this case, the intervention group's adherence rate increased an additional 5% (or 4%+5%=9%) from 80% to 89% at the end of the trial.

D.5. Baseline Screening and Assessment.
Potential study participants will complete a phone screening that assesses eligibility. If eligible, participants will attend a baseline session described below.

D.6. Randomization.
Study participants will be randomized (1:1) to Wise App intervention or control arm. We will use a variable permuted randomized block design [68] where the block size itself is randomly selected (i.e., blocks of four to eight). The advantage of the permuted block design is that treatment assignment is pre-determined before the trial begins and then assignment remains static throughout the course of the trial [69]. Participants will be randomized based on the use of computer-generated random numbers at baseline. The randomization database will be stored on a password protected computer at Columbia University and will only be accessible to Dr. Schnall.

D.7. Procedures.
Upon enrollment in the study, participants will come to the study site, Columbia University School of Nursing to complete consent forms. Following informed consent, study participants will complete a number of baseline questionnaires including socio-demographic characteristics, physical health measurements, behavioral data, health status and social desirability (See Table 3) [70]. Survey instruments will be collected through Qualtrics, a secure, Web-based application designed to support data capture for research studies, providing an intuitive interface, audit trails, and automated export. Qualtrics is a free service offered through Columbia University Medical Center.
Following the completion of the baseline study instruments, study participants in both arms will be given a CleverCap™ Lite dispenser and trained on how to use it, as well as a fitness tracker that will be synced to Wise App. Study participants in both arms will be trained by study team members on how to use the different features of the Wise App. Those in the intervention group will receive medication reminders while those in the control group will receive reminders about completing their step goal. Participants in both arms will be given a document that includes contact information for the project team, information about compensation, study reminders, and will also receive a telephone call from a research assistant 1 week after enrollment to assist with any technical problems with the app or the CleverCap™ Lite dispenser and biweekly thereafter. Participants will be texted appointment reminders for study visits via Qualtrics. Hard to reach participants will also be sent scheduling reminders through the Qualtrics system and encrypted e-mails from the study's secure CUMC e-mail address.
Token of appreciation: Participants will be given $40 at the baseline visit, $50 + up to an extra $25 for app challenges completed at the 3 month visit, and $60 + up to an extra $25 for app challenges completed at the 6 month visit (up to a total of $200 for participation) and for providing a blood sample (or recent lab results) for viral load/ CD4 testing and completion of study questionnaires. Participants will also have the option to have the cost of their transportation to and from the study site paid for, through a ridesharing service.

D.8. Operationalization of Outcome Measures.
The primary outcome will be ART adherence, measured by the CleverCap™ dispenser. The CleverCap™ dispenser will automatically record each time a participant opens the dispenser. We will collect adherence data each day from the start to the end of trial (day 1 to 6 months), and it is a count response (number of times taking medication each day). Frequency of app use will be counted each time a participant opens the app.

Table 3. Study Measures

Tool		Measurement Time Points
Demographic Variables and Potential Confounders		
Socio-demographic characteristics	Gender, age, education, income, employment, health insurance, housing	Baseline
Behavioral Data	Use of condoms, tobacco, alcohol, substance use	Baseline, 3 and 6 months
Health Literacy	Newest Vital Sign[71]; Short Test of Functional Health Literacy in Adults (S-TOFHLA) [72]	Baseline
Health Status	RAND-36; Symptom Distress Module;[73] PROMIS-29;[74] Self-Management Scale[75] Baecke Questionnaire for the Elderly[76]	Baseline, 3 and 6 months
Social Desirability	Social desirability scale[70]	Baseline

Mental Health	Patient Health Questionnaire (PHQ-9);[77] Mood Disorder Questionnaire (MDQ);[78] Prodromal Questionnaire (PQ-16);[79] APA Severity Measures for Generalized Anxiety Disorder[80]	3 and 6 months

Physical Health Measures	Height, weight, hip, and waist measurements	Baseline, 3 and 6 months
Housing Status	Housing Status Assessment Tool	Baseline, 3 and 6 months
Primary Outcome		
ART Adherence	Primary Measure: CleverCap™ Lite Dispenser	Daily
	CASE Adherence Index[81]	Baseline, 3 and 6 months
	CD4 and viral load	Baseline, 3 and 6 months
Secondary Outcomes		
Health Care Access	Number of Primary Care Visits	Baseline, 3 and 6 months
	Engagement with Health care Provider Scale	Baseline, 3 and 6 months
	Caregiver Survey	6 months
System Use	Automated Log Files	Ongoing
Technology Acceptance	Health-ITUES;[82] PSSUQ;[83] Perceived Ease of Use and Potential Usefulness Questionnaire[84]; eHEALS: the Health Literacy Scale[85] Trust in Health Information Sources	Baseline, 3 and 6 months
Physical Activity Measures	Neighborhood Environment Survey, Social Capital Scale, & Self-Efficacy Scale	6-months

We will also use additional measurements of medication adherence to validate the findings from the CleverCap™ Lite dispenser. We will do blood draws at baseline, 3 and 6 months to measure CD4 and viral load data on each study participant; alternatively, participants will be given the option of providing recent lab results of their CD4 and viral load data The blood draw at baseline will also be tested for genotyping, GSA chip and qPCR, Hormone blood levels (Estrogen and FSH), and cytokine blood levels (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, TNFα, and CRP). The genotyping with GSA chip and qPCR, cytokine blood level and CRP, and hormone blood tests will only be collected once during the course of the study, at Baseline or at the 6-month follow-up if not completed at Baseline. The genotyping, GSA chip and qPCR will be performed by the Feinstein Institute for Medical Research at Northwell Health. We will also ask participants to complete the Center for Adherence Support Evaluation (CASE) Adherence Index, a simple composite measure of self-reported antiretroviral therapy (ART) adherence [81]. The CASE Adherence Index consists of three unique adherence questions. Past research has shown that the CASE Adherence Index correlated strongly with the three-day self-reported adherence data ($p<0.001$) and was more strongly associated with HIV outcomes, including a 1-log decline in HIV RNA level (maximum OR=2.34; $p<0.05$), HIV RNA<400 copies/ml (maximum OR=2.33; $p<0.05$) and performed as well as the three-day self-report when predicting CD4 count status. The CASE Adherence Index is an easy to administer instrument that provides an alternative method for assessing ART adherence in clinical settings. Items are scored such that higher values indicate better adherence, and the maximum total score is 16. Scores of 11 or higher on this index indicate good adherence (Cronbach's α= 0.79) [86].

Our primary outcome is ART adherence. The CleverCap™ Lite dispenser is our objective measure of ART adherence and the CASE Adherence index as a subjective measure. We are including the subjective measure since there is potential bias in that participants' in the control group may not use the device or may not use the device for the entire study period.

We will assess for contamination between the study groups at the end of the trial by asking control group participants whether they had used any HIV or medication related apps in the past 6 months. In addition, participants will return at 3 and 6 months to complete the remainder of the measures listed in Table 3 and included in the Appendix. We will also collect data on app use through automated log files so there will not be response burden associated with this measure.

Secondary Outcome Measures: Our measures are listed in Table 3 and included in the Appendix.

D.9. Data Analysis.

We will use intention-to-treat principles for the primary outcome analysis. Intention to treat implies all subjects are considered in analyses. The outcome variable y_i will be the total number of times the CleverCap™ Lite dispenser is opened at day t (from day 1 to day 180) for person i, so y_i follows binomial distribution with parameter of p_i and n where p is probability of taking medication (adherence rate) and n is number of medications to take each day. We use a generalized linear mixed model (GLMM) with logit link function to analyze adherence rate. The basic form of the model is: $\log(p_i/(1-p_i))=\beta_0+\beta_1\times t+\beta_2\times t\times INT+\mu_i$. In the model, μ_i is person level random effect and follows normal distribution. This model is also called individual growth model. Independent variable INT is an indicator for intervention group (INT=1 for the intervention group and INT=0 for the control group). Regression parameter β_1 is change in adherence rate for the control group and β_2 is the difference in change in adherence rate between the intervention group and the control group.

This model can include personal level factors as covariates so we can test for potential confounding by covariates (i.e., age, gender, and health literacy) in this model and inspecting for changes in the point estimate of the relation between study group and adherence.

We will use GLMM for analyzing secondary outcomes. In our analysis of the surveys related to the SDT framework, the variable time (t) will be at 3 time points (baseline, 3 month, and 6 month) and the link function will be identified for continuous outcomes. In the analysis of app use, the unit of analysis will be at daily level for each participant, and system use will be analyzed using a GMMM with log link function (Poisson model). For the analysis of CD4 and viral load, we will analyze difference-in-difference using GLMM with identity or log link function when these variables are treated as continuous outcomes. Viral load will also be treated as a binary outcome (detectable vs. undetectable) and analyses of viral suppression will use the GLMM with logit link. In a secondary "as treated" analyses, missing adherence and viral load data will be ignored. The genotype analysis will be run by the Feinstein Institute for Medical Research at Northwell Health. Finally, we will assess the relationship between adherence (independent variable) and virologic suppression (dependent variable) using GLMM logistic regression and including missing viral load as detectable. This model will include personal level factors as covariates so we can test for potential confounding by covariates (i.e., age, gender, and health literacy) in this model and inspecting for changes in the point estimate of the relation between study group and adherence.

E. Aim 2b: Assess the acceptability of the CleverCap™ dispenser through In-depth interviews, which will focus on the individual experience of PLWH with the device.

E.1. Sample. At the 3-month follow-up visit, semi-structured in-depth interviews will take place with participants in the intervention group. These participants will be the same participants from the intervention study arm, if they choose to participate (N=100)

E.2. Procedures. The in-depth interviews will be approximately 20-30 minutes in length. This will be an optional activity for participants in the intervention group and no additional compensation will be provided. Once participants complete the informed consent process, all interviews will be audio-recorded. The in-depth interviews will be conducted by the study coordinator and research assistants, the members responsible for conducting follow-up visits. The brief interview guide will be informed by past studies focusing on the use and acceptability of electronic pill dispensers.[87-89] This interview will aim to fill gaps in the literature by taking a qualitative approach to understanding how our population of interest engages with the CleverCap device, which captures our primary measure for change in medication adherence. Some of the questions the questionnaire will include are: 1) Please tell me a little bit about your experience using the electronic pill bottle, 2) What have you used in the past for storing and receiving reminders about your medications? How does this compare? 3) What are some of the things that you like about using your pill bottle? 4) What do you dislike about the pill bottle? 5) How has the pill bottle changed how you take your medications 6) If a friend asked you about your experience using the clevercap, how would you describe your experience so far? and 7) At the completion of this study, would you want to keep using the device, why or why not?

The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses[90]. To support the credibility of the data, we will conduct peer debriefing and triangulate findings across multiple data sources (surveys, focus group data). In addition, we will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance the confirmability of the interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts.

E.3. Data Analysis. All in-depth interviews will be transcribed verbatim and then coded. The development and application of a coding scheme is an integral component of the data analysis process. It enables the systematic examination and interpretation of the 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 use ATLAS.ti, a software program for qualitative analysis, to facilitate the analysis.

The following 7 steps will be used to develop the coding scheme:

Step 1: Identify the principal issues discussed by interviewees.

Step 2: Construct definitions of the primary analytic themes.
Step 3: Develop and apply core codes and sub-codes to the initial set of interviews.
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 the technology acceptance of the CleverCap and barriers and facilitators to its use. Based on the coded data, we will propose ways in which certain themes are analytically related. A careful examination of the coded text will reveal the associations among these themes, and may lead to more refined data searches. Once we establish patterns of relationships among themes and issues, we will identify participants' accounts that support or refute these patterns. Identifying and accounting for cases that deviate from an interpretative pattern enables us to test and confirm the pattern's validity and robustness. Schnall has done extensive work understanding technology acceptance with particular emphasis on end-users' needs [91-94]

E.4. Triangulation of Findings. The research team will use the findings from our quantitative data analysis of medication adherence and technology acceptance in Aim 2 to understand use and perceived usefulness of the CleverCap. Field notes and transcripts will be analyzed by the researchers using NVivo™ (QSR International, Victoria, Australia) software. Participants' statements will be captured using memoing and then sorted into the following categories of interest: predisposing, enabling and reinforcing. These activities will result in a greater understanding of the use of the CleverCap based upon the predisposing, enabling, and reinforcing factors identified in the in-depth interviews. Each interview recording will be transcribed; transcripts will be analyzed by Dr. Schnall, who is experienced in qualitative analysis and a research assistant. The research team is experienced with these methods [91,95-97].

F. <u>Aim 3:</u> Assess PLWH perceptions of the predisposing, enabling, and reinforcing factors for Wise App use through theoretically-guided focus group sessions.

F.1. Sample. Post-intervention, we will conduct five focus group sessions with approximately 8-10 participants per group. Focus group participants will be drawn from the intervention study arm (N~50).

F.2. Procedures. The focus groups will be 60-90 minutes in length. We will include $30 reimbursement for participants' time. Following completion of the informed consent process, all focus group sessions will be audio-recorded. The PI, who has conducted focus groups for a number of studies in the past, will convene the groups with the study participants and will act as a facilitator [93,96,98,99]. The focus group guide will be informed by the predisposing, reinforcing, and Enabling Constructs in Evaluation (PRECEDE) portion of the PRECEDE-PROCEED Model of health program planning and evaluation [100]. The integration of these frameworks for application in HIT implementation evaluation has been proposed by a number of authors as a strategy for assessing predisposing, enabling, and reinforcing factors for use and acceptance of HIT [97,99,101].The following structured questions related to Wise App use will be posed: 1) What are some of the ways that your overall health might benefit through the implementation and dissemination of the Wise App (reinforcing factors)? 2) What do you perceive as barriers to implementation and use of the Wise App? (predisposing factors) 3) What do you perceive as barriers to implementation and use of the Wise App? (predisposing factors) 4) What are your ideas about strategies for overcoming these barriers? (enabling factors).

The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses[90]. To support the credibility of the data, we will conduct peer debriefing and triangulate findings across multiple data sources (surveys, focus group data). In addition, we will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. Triangulation of findings, along with reflexivity, will enhance the confirmability of the interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts

F.3. Data Analysis. All focus groups will be transcribed verbatim and then coded. The development and application of a coding scheme is an integral component of the data analysis process. It enables the systematic examination and interpretation of the 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 use ATLAS.ti, a software program for qualitative analysis, to facilitate the analysis.
The following 7 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 interviews.
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 the technology acceptance of the Wise App and barriers and facilitators to its use. Based on the coded data, we will propose ways in which certain themes are analytically related. A careful examination of the coded text will reveal the associations among these themes, and may lead to more refined data searches. Once we establish patterns of relationships among themes and issues, we will identify participants' accounts that support or refute these patterns. Identifying and accounting for cases that deviate from an interpretative pattern enables us to test and confirm the pattern's validity and robustness. Schnall has done extensive work understanding technology acceptance with particular emphasis on end-users' needs [91-94]

F.4. Triangulation of Findings. The research team will use the findings from our quantitative data analysis of medication adherence and technology acceptance in Aim 2 to understand use and perceived usefulness of the Wise App. For example, if a participant uses the app component of appointment reminders but does not score well on the Health Care Climate Questionnaire, then further exploration through the focus group sessions will be conducted to determine whether the appointment reminder component is improving health behaviors. Field notes and transcripts will be analyzed by the researchers using NVivo™ (QSR International, Victoria, Australia) software. Participants' statements will be captured using memoing and then sorted into the following categories of interest: predisposing, enabling and reinforcing. These activities will result in a greater understanding of the use of the Wise App based upon the predisposing, enabling, and reinforcing factors identified in the focus groups. Each focus group recording will be transcribed; transcripts will be analyzed by Dr. Schnall, who is experienced in qualitative analysis and a research assistant. The research team is experienced with these methods [91,95-97].

G. <u>Aim 3b:</u> Assess PLWH perceptions, experience, and satisfaction on the use of the Fitness Tracker that was synced to the HealthStar app through focus group sessions.

G.1. Sample. Post-intervention, we will conduct up to eight focus group sessions with approximately 8-12 participants per group. Focus group participants will be drawn from the control study arm (N~60).

G.2. Procedures. The focus groups will be 60-90 minutes in length. We will include $30 reimbursement for participants' time. Following completion of the informed consent process, all focus group sessions will be audio-recorded. The PI who have conducted focus groups for a number of studies in the past, and her research team members who are pre/post docs will convene the groups with the study participants and will act as a facilitator [93,96,98,99]. This will be an optional activity for participants in the control group. This focus group will be to understand participant's experience, perception and satisfaction on the use of the fitness tracker which was synced to the HealthStar app during the 6 month duration of the study. Some of the prompts in the focus group include: 1) What are some of the things that you liked about using the fitness tracker syncing to the Healthstar app? 2) Please describe your experience using the fitness tracker. 3) Please describe your experience monitoring your daily activity. 4) How do you think that your physical activity (i.e., daily step goal completion) changed after using the fitness tracker for 6 months? 5) What are some of the ways that your physical activity may change through the use of the HealthStar app linked with the fitness tracker? (Focus groups guide included as attachments entitled "WiseApp Fit Bit Focus Group Guide")

The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses[90]. We will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts

G.3. Data Analysis.
Each focus group recording will be transcribed. Transcripts will be analyzed independently for content by research team members experienced in these methods.

H. Aim 3c: Assess PLWH perceptions and experience on the recruitment process and research participation to WiseApp study through in-depth interview.

H.1. Sample. We will conduct in-depth interview with 20 participants. Interview participants will be drawn from both control and intervention arms.

H.2. Procedures. The in-depth interview will be 30 minutes in length. We will include $20 reimbursement for participants' time. Following completion of the informed consent process, all interviews will be audio-recorded. The PI who have conducted interviews for a number of studies in the past, and her research team members who are pre/post docs will convene the groups with the study participants and will act as a facilitator [93,96,98,99]. This will be an optional activity for participants. This in-depth interview will be conducted to understand participant's experience and perception on the recruitment process and research participation. Some of the questions in the interview include: 1) How comfortable were you with the recruitment and screening process for the study? 2) How would you modify the recruitment process to improve it or make it easier? 3) Please describe your experience in the enrollment process. 4) Would you prefer the recruitment and enrollment process to be online or in-person? 5) What motivated you to participate in this research study? (Interview guide included as attachments entitled "WISEAPP_Interview Guide on Recruitment ")

The team will adhere to qualitative research processes to ensure the credibility, confirmability, dependability, and transferability of the qualitative data from these analyses[90]. We will use "member checks," i.e., sharing of initial data interpretations with participants to ensure accurate interpretations. The investigators will carefully record an audit trail and keep extensive field notes to facilitate transferability of study findings into other contexts.

H.3. Data Analysis.
Each interview recording will be transcribed. Transcripts will be analyzed independently for content by research team members experienced in these methods.

RISKS, BENEFITS & MONITORING

The study protocol will be reviewed and ultimately receive approval of the Columbia University Medical Center (CUMC) Institutional Review Board (IRB). As a principal investigator (PI) of a number of funded studies for persons living with HIV, Dr. Schnall has experience securing IRB approval with this special study population.

Risks to Human Subjects

a.***Human Subjects Involvement, Characteristics, and Design***

Characteristics of Subject Population:

We anticipate two categories of research subjects in our study: 1) persons living with HIV/AIDS and 2) experts in human computer interaction.

Persons living with HIV/AIDS in this study will be recruited from the HIV clinic at CUMC/NewYork-Presbyterian Hospital and AIDS Service Center.

There is no more than a **minimal risk** associated with any of the proposed 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.

Following IRB approval, all study participants will provide informed consent prior to their participation in this study.

b. ***Sources of Materials***

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.

b.1. Access to Individually Identifiable Private Information about Human Subjects

Access to individually identified private information about human subjects will be limited to research team members who collect and manage the data, the project coordinator, and the PI. De-identified data will be accessible by all members of the research team involved in the data analysis.

c. ***Potential Risks***

The risks of participating in this study are few. Some of the questions on the questionnaires may make the subject uncomfortable or upset, but the subject is free to decline to answer any questions. Participation in research can involve loss of privacy. Information about the subject will be handled as confidentially as possible. All study data will be maintained in a completely secure and HIPAA compliant environment. All CUMC servers have HIPAA compliant security. All signed consent forms and payment receipts used in this study will be kept in locked files so only the investigators will have access to the files.

Adequacy of Protection against Risks

a. Recruitment and Informed Consent/Assent

Recruitment for participation in the study will occur following approval by the CUMC IRB. The PI will determine eligibility for inclusion, explain the purpose of the study, answer any questions, and obtain written consent from the participants.

Patients who agree to participate will sign a consent form. Recruitment strategies will be developed in collaboration with clinics and community centers. Potential risks and strategies for managing risks will be carefully explained as part of informed consent procedures. All HIPAA requirements will be applied to this study. The study plan, advertisements or recruitment letters, lay description of the study and all consent forms will be submitted to the IRB at CUMC following proposal acceptance and prior to study initiation. Dr. Schnall will be responsible for obtaining IRB approval for this study.

b. **Protections against Risks**

This study will be submitted to the IRB of CUMC before starting the study. We will be careful to ensure that no coercion occurs during the recruitment periods by ensuring that the healthcare providers and patients are voluntarily participating. All participants will be screened to assess for study eligibility.

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 designee will access an urgent appointment at the HIV clinic at NewYork-Presbyterian Hospital or the emergency room at CUMC. Dr. Schnall will complete an adverse event form and report to the CUMC IRB. **If there are any serious adverse events, they will be reported within 48-72 hours to the National Institute of Health (NIH), AHRQ and the CUMC IRB.**

Patient volunteers will be told that they can withdraw from study at any point without any effect on their healthcare treatment or status as patients. During the usability testing, the participants might become frustrated with the system; however, all efforts will be made to provide a comfortable environment. Data will be stored in password-protected computers or double locked file cabinets. All reported data will be de-identified.

Non-participation will not affect patients' medical care in any way. Each group of participants will be made aware of the nature of the questions prior to consenting to participate, but nonetheless may become upset by some of the questions. Participants may opt to omit or not answer any questions at any time.

There are no benefits to participants. However, if a previously unrecognized problem is observed, the participant may access appropriate services for evaluation and treatment.

Subjects will be informed of the potential risks in the consent form. All subject names and medical data will be kept confidential, and all data will be identified only by a code number. The list matching names and code numbers will be kept locked in the PI's office and will be destroyed at the end of the study period.

Loss of confidentiality. All study data will be stored in password protected computers or file cabinets in locked offices. All research team members will pass the protection of human subjects and research HIPAA exams and sign a protocol-specific conflict of interest.

All procedures have been designed to protect each participant's privacy and allow for anonymous participation. All study data will be maintained in a completely secure and HIPAA compliant environment. All CUMC servers have HIPAA compliant security.

Potential Benefits of the Proposed Research to Human Subjects and Others

This study has not been designed for the direct benefit of its participants. However, there are a number of ways in which they may derive benefit. The proposed research will inform the delivery of care for persons living with HIV. The knowledge gained will contribute to the body of knowledge regarding the use of health information technology for improving the lives of persons living with HIV.

Importance of the Knowledge to be Gained

The research has the potential to improve patient-centered outcomes for persons living with HIV.

Data Safety and Monitoring Plan

The Data and Safety Monitoring Plan for the proposed study incorporates the Policies on Data and Safety Monitoring specified by Columbia University. Data safety and monitoring will be the responsibility of the PI.

This trial does not pose more than minimal risk and therefore requires the establishment of a Data and Safety Monitoring Board (DSMB).

The project team will meet weekly during the project period and minutes will be taken. All adverse events will be reported per the requirements of the CUMC IRB.

The PI will report any of the following to AHRQ and NIH in a timely fashion:

a. Unanticipated problems or unexpected serious adverse events that may be related to the study protocol (within 48-72 hours)
b. IRB-approved revisions to the study protocol that indicate a change in risk for participants
c. A summary of recommendations made by the DSMB or other monitoring entity and the action plan for response
d. Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions

The DSMB will be comprised of a small group of experts from the Columbia University School of Nursing and Case Western School of Nursing (at least 2 members who are independent of the protocol) who will review data from this study. The DSMB will be comprised of Drs. Larson (Associate Dean for Research), Arcia (Columbia University School of Nursing faculty) and Webel (Case Western University School of Nursing faculty) who will review the data every six months and meet once a year since the study procedures are of minimal risk to study participants. During their yearly monitoring, the DSMB will assess participant recruitment, intervention effects, and potential adverse events. The Board will create an action plan if concerns arise. All adverse events will be reported per the CUMC IRB, the NIH and the AHRQ. In addition, an external advisory board for the project will meet in person annually at CUMC and will review progress on enrollment, the study outcomes, and progress on the project.

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