Automated Medication Platform with Video Observation and Facial Recognition to Improve Adherence to Antiretroviral Therapy in Patients with HIV/AIDS

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Sponsor: HiDO Technologies

Funded by: HiDO Technologies

Version Number: 2.2

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute of Mental Health Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

1 PROTOCOL SUMMARY

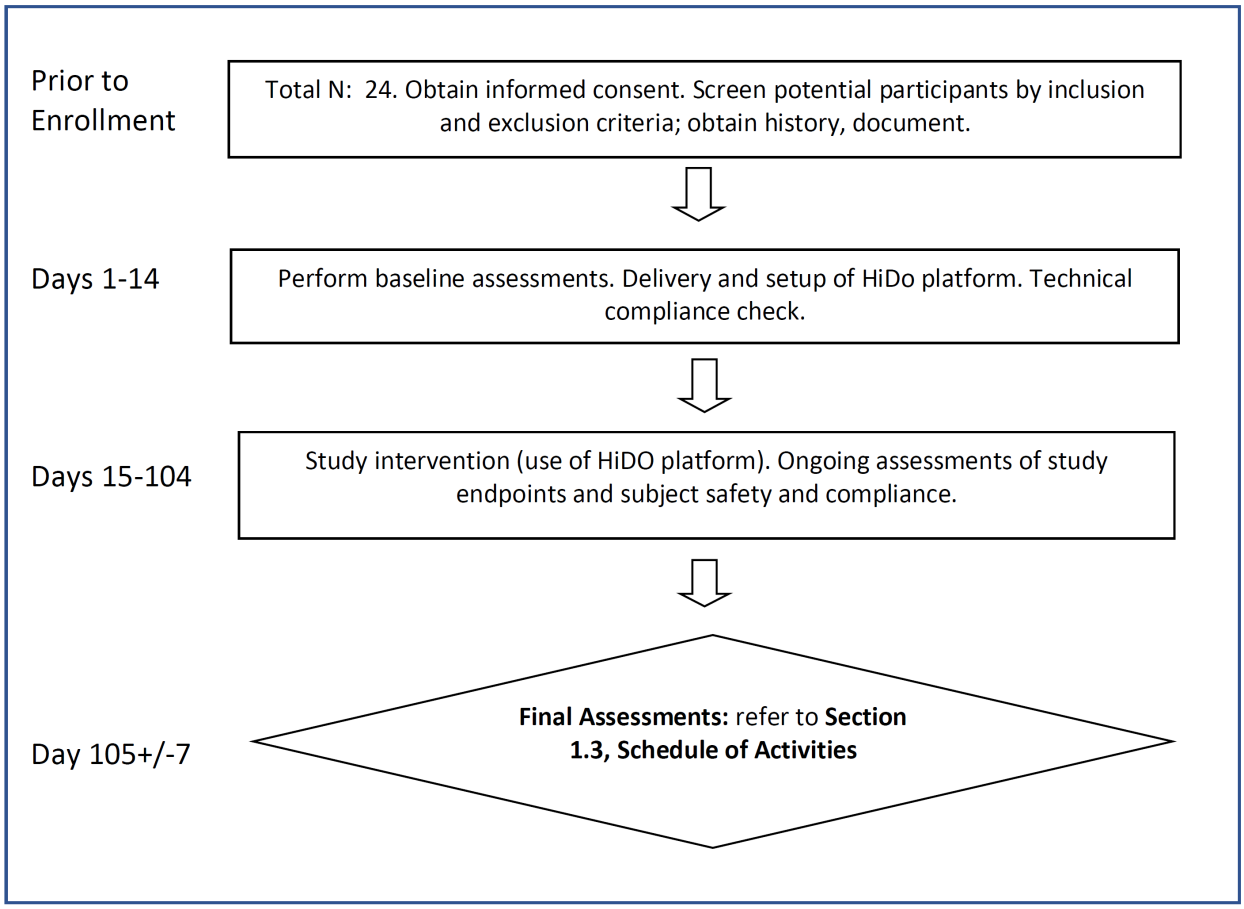
1.1 SYNOPSIS

Title:	Automated Medication Platform with Video Observation and Facial Recognition to Improve Adherence to Antiretroviral Therapy in Patients with HIV/AIDS
Study Description:	This is an unblinded study of the HiDO automated medication adherence platform in patients ages 18 to 55 who are currently taking ART. From this population, 24 participants will be recruited to use the HiDO medication adherence platform for a 90-day intervention period. Medication adherence and device usability will be measured by various means. It is hypothesized that: a) use of HiDO will result in ≥95% medication adherence over 90 days; b) usability scores for the HiDO platform (as measured by Time on Task values and error rates) will be equal to or better than published benchmark rates for similar platforms; c) System Usability Scale (SUS) value will be >68; d) greater than 80% of participants will indicate that they are Likely or Strongly Likely to recommend the HiDO device to a friend or colleague.
Objectives:	Primary Objective: Determine the effect of automated medication adherence platform (HiDO) on medication compliance. Secondary Objective: Determine usability of automated medication adherence platform (HiDO), as indicated by user ease of adoption (Time on Task, error rates), standardized user experience metric (SUS), and user endorsement (Net Promoter Score).

Endpoints:	Primary Endpoint: Medication adherence as assessed by remote observation through the HiDO device at 90 days. Secondary Endpoints: Time on Task for initial registration, "first click" testing, facial recognition setup, medication administration, number and type of critical and non-critical errors and error-free rate, System Usability Scale (SUS), Net Promoter Score.
Study Population:	Sample of 24 participants from U.S. population of individuals ages 18 and older who are currently taking antiretroviral therapy (ART).
Phase:	1
Description of Sites/Facilities Enrolling Participants:	HiDO Technologies 2191 Frascati Dr. El Dorado Hills, CA 95762-3970
Description of Study Intervention:	HiDO is an automated Artificial Intelligence driven direct observation medication adherence platform. The platform is a 510K exempt Class I medical device (890.5050) that integrates medication dispensing, dose administration time, pill count and front facing video cameras to validate the right medications, at the right time to the right patient. The device dispenses up to 7 different types of medications simultaneously. The camera logs every dose using facial recognition and provides real time consumption logs. Investigators have access to video observation logs, patient dose time, adherence trends, and study level adherence measures. For this study, the HiDO medication adherence platform will be delivered to the residence of each participant by the researcher, who will provide instructions for performing device setup that includes linking the HiDO device to the participant's smartphone and filling the device with ART. The participant receives a smartphone alert when it is time to take a medication, and then pushes the button on the device to receive the correct medicine at the given time. If the patient does not respond, additional reminders are sent via phone and SMS. Medication adherence will be measured over 90 days using the HiDO device. Additionally, participants will participate in a semi-structured interview following the 90-day period to assess system usability.
Study Duration:	12 months
Participant Duration:	104 days

1.2 SCHEMA

Figure 1. Study Schema for, "Automated Medication Platform with Video Observation and Facial Recognition to Improve Adherence to Antiretroviral Therapy in Patients with HIV/AIDS



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening / baseline measurement Day -14 to -1	Week 1, Day 1 (Completion of platform setup)	Week 2, Day 14 +/-1 day	Week 4, Day 28 +/-1 day	Week 6, Day 42 +/-1 day	Week 8, Day 56 +/-1 day	Week 10, Day 70 +/-1 day	Week 12, Day 84 +/-1 day	Week 13, Day 90 +/-1 day	Week 14, Day 97 +/-7 days
Informed consent	X									
Demographics	X									
Medication adherence self-report	X									
Delivery of HiDO platform	X									
Assisted platform setup	X									
Time on Task	X	X	X						X	
Error rate	X	X	X						X	
Automated medication adherence		X----------	----------	----------	----------	----------	----------	----------	----------	X
Device log audit				X		X		X		X
Usability assessment (semi-structured interview)										X
Adverse event review and evaluation		X----------	----------	----------	----------	----------	----------	----------	----------	X
Complete Case Report Forms (CRFs)	X----------	----------	----------	----------	----------	----------	----------	----------	----------	X

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

HIV drug treatment saves lives. Antiretroviral therapy (ART) has directly and irrefutably reduced the death rate of people with HIV/AIDS. Because of public health measures including the administration of ART, AIDS-related deaths declined by 38% from 2000 to 2017—saving more than 11 million lives worldwide. [1] A high degree of adherence to ART is an essential part of this success. People living with HIV (PLWH) who strictly follow their ART regimens can control the disease. For example, 102 patients with acute or early HIV-1 infection were prospectively followed; 97% of those who strictly followed ART had undetectable viral levels at a median of 11 weeks and 92% had continued viral suppression at 18 months.[2] When HIV is suppressed in this way, the risk-of developing an AIDS-defining condition is greatly reduced.[3] In fact, the immune system can even reconstitute itself.[4] Moreover, patients who achieve viral suppression do not transmit HIV to others.[5-7] Likewise, people at high risk who consistently take daily pre-exposure prophylaxis (PrEP) can substantially reduce their risk of acquiring HIV infection.[7] The same protective effect has been observed for post-exposure prophylaxis (PEP); however, the key to the success of ART, PrEP and PEP is strict adherence.

Nonadherence in clinical trials has profound economic and societal costs. Medication adherence is critically important during clinical trials. Investigators insist on (or assume) adherence rates of ≥95%, however, substantial evidence exists that actual adherence in trials is far less than that.[8,9] Gossec et al. performed a meta-analysis of 192 publications of RCTs in six chronic conditions and observes a median compliance of 93% through pill count adherence measures.[10] However, when bodily fluid measurements

were used to assess adherence in this same population, the values were substantially lower, 54% to 68%.[9] This means that pill count is an inaccurate measure of adherence and true medication adherence rates are below 70%.[9] High levels of medication adherence are perhaps no more important than they are in HIV clinical trials. Considering that patients with adherence rates of <95% are 3.5 times as likely to have treatment failure as defined as HIV-1 RNA >50 copies/ml than those with 95% adherence or greater.[11] While recent work using real world data has suggested that HIV viral suppression may be possible with adherence rates as low as 80%, this appears to be ART regimen-dependent.[12] Since we know that viral suppression is now possible with ART and interrupting transmission is possible with PrEP and PEP, the FDA will almost assuredly require viral suppression as an endpoint in anti-HIV medication trials. Compliance of less than 68% will cause IMPs to fail. If participants in a placebo-controlled trial are taking less than 70% of their study medication doses, the effect in active arm will be underestimated. Poor actual adherence during clinical trials skews data, confounds statistical analyses, increases participant discontinuation rates, lengthens recruitment periods and extends the total duration of clinical trials.[13] Non-adherence is directly responsible for longer and more costly clinical trials.[13] These costs are estimated to be in excess of $1.5 billion capitalized over the time required to develop a single new investigational medicinal product (IMP).[9] This not only costs clinical trial sponsors substantial sums of money, but it slows the development of new therapies and decreases the pool of eligible study participants in future trials (e.g. most trials exclude potential participants who recently participated in a clinical trial). Timeline expansion translates to $600,000 per day in lost revenue opportunity for products with focused indications and up to $8 Million per day for broadly used medications.[13]

Efforts to improve adherence are only modestly successful. Multiple factors contribute to nonadherence.[14] These factors include the complexity of taking medications, time burden on the patient, the patient's perception of benefits and risks. Several measures have been proposed and deployed to improve adherence. These include behavioral skills training, medication adherence training, phone reminders, text reminders, smart pill caps, and various combinations thereof. Kanters and colleagues systematically reviewed 85 medication adherence trials comprising 16,271 participants and after conducting a network meta-analysis concluded, “Several interventions can improve adherence and viral suppression; generally, their estimated effects were modest and waned over time.” [15] The usual methods for monitoring adherence in clinical trials are self-reported medication adherence, pharmacy refill data, Medication Event Monitoring Systems, and therapeutic drug monitoring. Each of these methods has its strengths and weaknesses; but none can be considered a gold standard because of their inherent limitations. Direct observation could be the gold standard, but it is prohibitively expensive and impractical.

Directly observed therapy could be a solution. Directly observed therapy is a means of encouraging strict medication adherence in which a health-care worker or other competent individual physically watches a patient consume their medication. Given the importance of strict medication adherence in HIV/AIDS, there have been efforts to institute directly observed therapy adherence measures.[16,17] A systematic review and meta-analysis showed that directly-observed therapy of ART “had a significant effect on virologic, immunologic, and adherence outcomes.”[18] In-person, directly observed therapy has its critics, however. They suggest it is coercive, dehumanizing, and hinders autonomy.[19-21]

2.2 RATIONALE

Directly observed therapy could be the gold standard for HIV, but the process must eliminate the burden of travel, the loss of autonomy and the high cost of direct observation. Poor medication adherence is an ongoing problem in clinical trials, especially in medications to treat HIV/AIDS. Even high potency, low genetic resistance ART regimens require adherence above 80% (and recommended adherence is greater than 95% regardless of agents). This means they fail to achieve viral suppression, are a source of drug-resistance strains of HIV, are more difficult to treat, can advance to AIDS, and acquire opportunistic infections and develop AIDS-related cancers. In clinical trials, poor adherence skews data, making the active arm seem less potent than control. Drug development programs may be scuttled due to poor and unrealized poor adherence.

The purpose of the current study is to test the effectiveness of HiDO, an automated medication adherence platform, in both improving medication adherence among HIV/AIDS patients and providing a better user experience compared to existing medication adherence devices.

> ***Hypothesis 1:*** *Use of the HiDO automated medication adherence platform will result in ≥95% medication adherence over 90 days.*
> ***Hypothesis 2:*** *Usability scores for the HiDO platform (as measured by Time on Task for initial registration, "first click" testing, facial recognition setup, and medication administration, number and type of critical and non-critical errors, and error-free rate) will be equal to or better than published benchmark rates for similar platforms.*
> ***Hypothesis 3:*** *The System Usability Scale (SUS) value for the HiDo platform will be equal to or better than published benchmark rates for similar platforms (>68).*
> ***Hypothesis 4:*** *Greater than 80% of participants will indicate that they are Likely or Strongly Likely to recommend the HiDo device to a friend or colleague.*

HiDO is an automated AI (Artificial Intelligence)-driven, direct observation medication adherence platform. The platform is a 510K exempt Class I medical device that integrates medication dispensing, dose administration time, pill count and a front-facing video and infrared cameras to validate the right medications, the right time go to the right patient. The camera logs every dose using facial recognition and provides real-time consumption logs. Investigators have access to video observation logs, patient dose time, adherence trends, and study-level adherence through the platform's dashboard. Study participant can set up the device in minutes using their smartphone. Data is stored securely in the cloud and accessible in real-time. The technology has been awarded a provisional patent.

Medications may be filled by a pharmacist or clinical trial site. The device is not locked, which allows patients to retrieve or refill medications manually if needed, but notifies the researcher whenever the closing mechanism on the back of the unit is opened. A cap is selected that indicates the pill size and type, which is then placed on the pill bottle. The 40-dram (5 oz.) bin for each medication is inserted into the HiDO unit; up to 7 different medications can be housed at one time in separate bins. The HiDO unit senses the medication(s) and dispenses the medication(s) at the specified time and dosage level. Patients are alerted by the desktop HiDO unit and via smartphone when it is time to take their medication. Facial recognition software detects the patient through front-facing video cameras and identifies that it is, indeed, the person who is supposed to take the medication. The camera records and confirms that the patient consumes the medication, recording the exact time and medication(s) taken. The patient, caregivers, health care team (and clinic trial investigators) can track medication adherence in real time using a dashboard. The HiDO device enables remote monitoring and can also collect patient-reported outcomes, adverse events, disease symptoms, treatment satisfaction, and other data.

HiDO is the first device of its kind to integrate medication reminders, patient reported outcomes, drug dispensing, and remote/recorded observed therapy is a single platform (see Figure 2). The device collects real-time data for medication adherence, dose administration time, 14-day adherence trend analysis and video recording of medication consumption. These capabilities help satisfy the new FDA remote-monitoring guidance issued August 2020. Both pharmaceutical and clinical trial organizations have expressed interest in leveraging the HiDO device across the HIV and other drug development pipelines. While clinical trialists do use body fluid sampling to assess adherence, the advent of COVID-19 has dramatically reduced in-person clinical trial visits. Sponsors are aggressively pursuing ways to meet FDA requirements with fewer in-person visits.

Figure 2. Comparison of HiDO with available medication adherence platforms.

Product	Description	Pros	Cons
HiDO	Automated video-observed therapy and medication dispenser	• Sorts and dispenses pills • Observes and records therapy • Facial recognition biometrics • Tracks drug administration • Medication reminders • Holds up to 7 drugs x 40 doses • Can be used with standard pill bottle	• Some patients may not like video recording
Proteus	Ingestible sensor	• Completely assures drug is swallowed	• Patients don't like swallowing a device • Patients must track their own medications and regimen • No integrated reminders • FDA approval required for each molecule (very costly)
AiCure	Video-observed therapy via smartphone	• Observes and records therapy • Facial recognition biometrics	• Patients must be able to hold the phone properly to engage the device • Cumbersome and tedious • Some patients may not like video recording
Livi	Medication dispenser	• Sorts and dispenses pills • Tracks drug administration	• Does not observe therapy • Uncontrolled ejection of pills or pills get stuck • Large, bulky unit • Does not detect pills • Not a "smart" unit • High user burden
Pillo	Medication dispenser with biometrics	• Facial recognition • Medication reminders • Anthropomorphized "face" on dispenser	• Does not record drug administration or confirm drug consumption • Only holds 28 doses • Each pill needs to be loaded individually
Pillsy	Smart pill cap, MEMS	• Medication reminders on app and phone • Can be used with standard pill bottle	• Patients can open the cap to stop alert but not take the drug • Does not record drug administration or confirm drug consumption
URSure	Urine ART testing	• Confirms drug was taken	• Creates a negative user experience; people are drug tested like criminals • Limited scope of accuracy; valid only 4-7 days; requires frequent testing

Demonstrating the feasibility of the technology proposed in this application is a critical step in device development. The data collected during this study will allow HiDO to refine and finalize the platform. It will also demonstrate preliminary impact, which will be important for determining whether the technology should be further developed and will likely be one of the factors that attracts financial

investors. Additional funding of a successful medication adherence device will allow expansion and commercialization of this platform, which can lower the costs of and disruptions to clinical trials, improve medication adherence in vulnerable patient populations, and ultimately change the trajectory of HIV/AIDS morbidity and mortality on a population level.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

A potential risk to participants is breach of confidentiality, which exists both as an immediate and long-term risk. There is also an immediate risk that the platform hardware or software may malfunction in some way, which may affect data capture, data transmission, or medication dispensing. These errors may affect the reliability of the device in providing timely dosage reminders, accurate remote monitoring, and accurate dispensing of medication.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may directly benefit from better and more consistent medication adherence resulting from use of the HiDO platform, which would increase the chance of achieving and maintaining viral suppression. Participants, as well as the population at large, may experience indirect long-term benefit from the development of automated medication adherence platforms that improve treatment outcomes and lower the cost of new drug development (as described previously in Section 2.2, Rationale).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risk of breach of confidentiality risk is mitigated through use of stringent data security procedures. Data collected through the HiDO device is stored on Amazon Web Services (AWS), a HIPAA-compliant cloud computing platform. Other electronic data not stored on the AWS cloud platform are stored locally on encrypted and password-protected computers accessible only to the research staff. Any paper records generated are stored in locked cabinets accessible only to the researcher staff. Data accessed from clinical records are de-identified prior to being recorded into the research database.

Regarding the risk of device malfunction, these risks are unavoidable to some degree, given that the purpose of the study is to assess device functioning. To mitigate the risk to participants posed by platform malfunctions, participants are advised of these risks and reminded to adhere to their prescribed ART treatment protocol in the event that the device malfunctions, both during the consent process and with written instructions included in HiDO device packaging (see Appendix A: HiDO Product Brochure). Additionally, participants are able to manually access medications loaded into the device, should the device fail to dispense them automatically.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the effect of automated medication adherence platform (HiDO) on medication compliance.	Mean adherence rate to ART in all patients across 90 days (quantified as (n. of doses provided — n. of doses taken) / n. of doses provided x 100)	Adherence data are automatically and continuously recorded by HiDO device, and directly confirmable through manual audit of video recordings.
Secondary		
Determine usability of automated medication adherence platform (HiDO), as indicated by user ease of adoption (Time on Task, error rates), standardized user experience metric (SUS), and user endorsement (Net Promoter Score).	Measured at Week 2: • Time on Task for initial registration • Time on Task for "first click" testing • Time on Task for facial recognition setup • Time on Task for medication administration • Number and type of critical and non-critical errors • Error-free rate Measured after 90 days use of platform: • Score on System Usability Scale (SUS) • Net Promoter Score	Time on Task and error rates may be compared to published benchmarks for similar platforms. According to usability.gov published by the U.S. Department of Health & Human Services, the SUS is regarded as a reliable tool to assess usability and has become the industry standard.[24] Results from the SUS have been published in over 1,300 publications. [24] It can be used on small sample sizes with reliable results and can effectively discriminate between usable and unusable systems. The Net Promoter Score is based on the response to the question, "How likely is it that you would recommend our device to a friend or colleague?" on a 5-point Likert scale.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study description: This is an unblinded, Phase 1 study of the HiDO automated medication adherence platform in patients ages 18 and older with HIV/AIDS who are currently taking ART. For this single-site device study, clinical collaborators will recruit 24 participants into a single study group. After a screening period of up to 14 days, participants will receive the 90-day intervention that consists of using of an automated medication adherence platform. Medication adherence will be assessed through observed therapy using front-facing cameras on the device.

Study device: HiDO is an automated Artificial Intelligence driven direct observation medication adherence platform. The platform is a 510K exempt Class I medical device that integrates medication dispensing, dose administration time, pill count and a front facing video camera to validate the right medications, at right time to the right patient. The camera logs every dose using facial recognition and provides real time consumption logs. The device dispenses up to 7 different types of medications simultaneously. Investigators have access to video observation logs, patient dose time, adherence trends, and study level adherence through a cloud-based electronic dashboard. Data is stored securely in the cloud and accessible real-time.

Study Procedures: As part of screening procedures, participants complete a 10-minute medication adherence self-assessment via phone. The researcher will schedule a visit to the participant's home, expected to last approximately 45 minutes, to conduct consent process and set up the device. After conducting consent procedures and collecting participant demographic information, the researcher will deliver the HiDO device to each participant's home and assist each participant with platform setup, which includes loading ART medications into the dispenser (up to 7 different types), calibrating facial-recognition, and setting up the participant's smartphone to interact with the device. Following platform setup, participants use the HiDO platform for 90 days, which will provide notifications for, dispense, and monitor each participant's ART dosing. At the end of the 90-day intervention period, participants complete a semi-structured interview, administered via phone and lasting approximately 30 minutes, to assess device usability and complete post-intervention medication adherence self-assessment. Excluding screening, total study duration is 104 days +/- 7 days.

Data are collected for medication adherence and usability from the following sources:

1. Medication adherence:
    a. Automated dosage logs generated by HiDO device
    b. Manual audit of automated dosage logs
    c. Pre- and post-study medication adherence self-assessment questionnaire

2. Usability:
    a. Automated user logs generated by HiDO device
    b. Post-study semi-structured interview
    c. System Usability Scale
    d. Net Promoter Score

Hypotheses:

Hypothesis 1: Use of the HiDO automated medication adherence platform will result in ≥95% medication adherence over 90 days.

Hypothesis 2: Usability scores for the HiDO platform (as measured by Time on Task for initial registration, "first click" testing, facial recognition setup, and medication administration, number and type of critical and non-critical errors, and error-free rate) will be equal to or better than published benchmark rates for similar platforms.

Hypothesis 3: The System Usability Scale (SUS) value for the HiDO platform will be equal to or better than published benchmark rates for similar platforms (>68).

Hypothesis 4: Greater than 80% of participants will indicate that they are Likely or Strongly Likely to recommend the HiDO device to a friend or colleague.

Selection bias: Every effort will be made to draw a sample that represents the patient population in terms of race, ethnicity, and gender.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Our main goal is to demonstrate ≥95% adherence to ART in all patients across 90 days. Admittedly, this is a very high bar. However, we are confident that we will achieve it, even for patients who have problematic use. Our informal user testing to date has shown remarkable adherence rates with the HiDO device, and these have improved as we have moved into the current version (Version 3).

For participants who completely withdraw from the study before 90 days, adherence percentage will only be calculated for the time that they participated. While we will likely glean important information from those who do drop out early, these dropouts will not affect our primary endpoint calculation. We may also fail to recruit a pool of participants that reflects the diversity of the national HIV patient population. We expect, however, to be close, and will be able to recruit a sample sufficient to intelligently plan for larger scale future testing in diverse populations. If successful, we will have demonstrated that our automated medication adherence platform is highly usable, preliminarily enables strict adherence to ART, and is ready for larger scale testing in Phase II.

4.3 JUSTIFICATION FOR DOSE

Not applicable.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, ages 18 and older
4. Prescribed at least one existing ART
5. Self-reported as taking less than 100% of ART does in past 30 days
6. Access to a personal smartphone and Wi-Fi connection

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Changes to ART regimen within the previous 2 months
2. Anticipated changes to ART regiment during the study period
3. Illicit drug use within the past 6 months, excluding marijuana
4. Diagnosis of dementia of any type
5. Participation in a clinical study within the previous 3 months

Participants will be recruited without bias to gender/gender identity, race, ethnicity, religion, or sexual orientation from existing patient populations using anti-retroviral therapy.

Children have been excluded from the current study; while they stand to benefit from such a device and may be included in future study phases, the proposed sample size is not large enough to account for the possible influence of parents upon children's medication adherence. As both illicit drug use and dementia may also interfere with medication adherence in unanticipated ways, the current trial phase will exclude individuals self-reporting recent illicit drug use and/or a diagnosis of dementia; future trial phases may expand selection criteria to include these individuals. To maintain consistency in study conditions, individuals with recent or imminent changes to their ART regimen are also excluded.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details,

eligibility criteria, and any serious adverse event (SAE). Data from screen failures are retained as for other participant data (see Section 10.1.9.2).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of access to a personal smartphone and Wi-Fi connection may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The target sample will approximate the distribution of HIV/AIDS patients by race and ethnicity, and will equally enroll men and women, as seen in Figure 3.

Figure 3. Target sample by gender, race, and ethnicity.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	5	0	0	10
White	4	4	3	3	14
More than One Race	0	0	0	0	0
Total	9	9	3	3	24

Participants will be recruited from the outpatient population of HIV/AIDS patients in the San Francisco Bay region of California; the study will not enroll participants outside of the United States. Potential participants will be recruited using a 1-page flyer that will be posted in one or more medical practices in the Bay Area that specialize in the prevention and treatment of HIV/AIDS; providers and staff of these practices are not otherwise affiliated with the study.

It is expected that approximately 75% of screened patients will be determined eligible for study enrollment, so approximately 32 individuals will be screened to reach the target sample size (n=24), which we expect to occur at a rate of approximately 2 participants per week.

To aid retention efforts, medication adherence for each participant is monitored through the HiDO platform. The HiDO unit is first and foremost a medication adherence device. The device will transmit real time data about adherence and trial participation. To maintain study integrity, we cannot intervene to promote adherence beyond the reminders and prompts provided by the medication adherence system. That said, having the device in the home is a powerful, indirect participant retention tool.

To compensate participants for their time, participants will receive $100 gift card, which is disbursed upon return of the HiDO device. Participants who do not complete study receive $5 for each full week

from device setup to date of notification by either party of study withdrawal, delivered by Visa gift card at device pickup.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

HiDO (Health Information Data Outcomes) core product is an encrypted highly secure, Web-based system on AWS used to collect, track, and report patient medication consumption for the purpose of improving the data integrity of clinical research, patient care, and public health. The platform is a 510K exempt Class I medical device that integrates medication dispensing, dose administration time, pill count and a front facing video camera to validate the right medications, at right time to the right patient. The camera logs every dose using facial recognition and provides real time consumption logs. The device dispenses up to 7 different types of medications simultaneously from 40-dram bins.

See Appendix A (HiDO Product Brochure) for hardware specifications.

Core (AMCS) features and functions include: [1]

- *Patient-compliance (Real-time)*: Dynamic clinical dashboards, mobile consent, adherence screen, push notifications, large font and buttons (single, multi, date, number, free-text, visual pain, VAS, etc.), multiple language capability, robust survey parameters
    - Flexible patient dashboards – Clinical Studies and Public Health populations are customized by individual principal investigators and public health departments: Validated compliance methodology and video observation therapy.
    - Conditional patient surveys – Surveys are dynamically built for an individual patient based on two levels of conditional parameters: Conditional survey assignments and questioning (branching logic within a survey takes the patient to new questions within the survey or to new surveys).
- *Patient embedded surveys*:
    - Easy-to-use patient surveys – Form-based patient surveys quickly capture adverse events and treatment side effects, easy-to-use user interface, and reporting.
    - Multiple episodes of care – Clinical dashboards that show multiple consumptions, viewed, and recorded for clinician analysis; this allows for more accurate assessment of a patient's longitudinal progress of care and better understand variability in aggregate data analysis.
    - Dynamic clinical protocols – On completion of a clinician survey, additional questions may be asked based on the protocols set up for that clinical area and a combination of clinician and patient survey responses; these protocols can be used to educate patients and track compliance with standard processes of care defined by the study protocols;

[1] Please note that the current study does not employ or test the mobile consent, patient survey, or patient education features.

such care processes could include evidence-based protocols, quality measures, red flag considerations, or study-based protocols.

- *Patient education*: tailored to patient responses, drug information and disease guidance, web links to patient education (e.g., Healthwise, CDC)
- *Reporting*: HiDO includes five types of reporting:
    - Clinician summary report – displays summary of individual patient-reported data, longitudinal adherence timeline, highlighted color coded (Green/Yellow/Red)
    - Patient-viewable mobile dashboards – tailored to patient adherence records, trend analysis of consumption, pills missed/taken, and links to websites
    - Standard aggregate data reports – aggregate survey responses, aggregate outcomes, individual summary scores (parameter-driven, save templates)
    - Standard operational reports – pending surveys, survey compliance, patient contact, etc. (parameter-driven, save templates)
    - Custom reporting via separate database – HL-7 outbound interface to client local database for client reporting
- *Workflow*: Auto-queuing of surveys (based on logic), push notifications to mobile, role-based worklists, contact log
- *Site setup configuration*: patient group, appointment types, queuing logic, site preferences, users, clinicians
- *Data transfer*: System interfaces (Scheduling system, patient portal, EMR, data warehouse); Data extracts (tab-delimited, SAS)
- *Security*: functionality security by role, standard or advanced data security by clinical area; HIPAA audit logs; HTTPS / 128-bit SSL; VPN; FTP over SSL; password security; server protection via multiple firewalls, intrusion detection system.
    - Patient Profile describes key components of a patient in an easy-to-use structure in four categories delineated by tab structures including: General, Insurance, Personal, and Clinical information for that patient; the goal is to minimize the information stored on this profile to be only the patient information needed to assign surveys (e.g., demographic, disease or condition, insurance type), assist the clinician in the clinician survey process, and provide a database suitable to support research and clinical studies; ideally, the information that is contained on the clinicians electronic medical record (EMR) is downloaded from that system and not re-entered

Video/Audio recording of the medication consumption is about 10 seconds in duration. The recording does not start until the patient unlocks the device with facial recognition and verifies the appropriate medication dispensing. The research team is HIPPA certified, and recordings are encrypted via AWS secured HIPPA storage.

6.1.2 DOSING AND ADMINISTRATION

The Principal Investigator will deliver the device to the participant's home and will assist each participant with initial device setup that includes filling the device with ART (the device holds and can dispense up to 7 different medications), installing the device app on the participant's smartphone, and configuring the device and app. The participant receives a smartphone alert when it is time to take a medication. The participant then pushes the button on the device and receives the correct medicine at the given time. In addition to tracking time, frequency, and other medication administration data, the

device video records the interaction to verify that the medication was consumed. If the patient does not $respond, additional reminders are sent via SMS and read as: "It's time to take your morning medication" (for late doses scheduled for 12pm Pacific Time or earlier) of "It's time to take your evening medication" (for late doses scheduled after 12pm Pacific Time).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

At the beginning of the study, the HiDO medication adherence platform will be delivered in person to the home of record of each participant. At the end of the 90-day intervention period, the device will be picked up from the participant's home by the PI.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

See Appendix A (HiDO Product Brochure)

6.2.3 PRODUCT STORAGE AND STABILITY

The HiDO device should be kept away from damp or wet areas and out of reach of pets and children.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Study compliance will be assessed through manual audits of HiDO dosage logs, which verify interaction with participant through video recording, and completion of post-intervention interview and questionnaire.

6.5 CONCOMITANT THERAPY

Not applicable.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from HiDO platform use does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. Although not expected to occur, if a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Incarceration

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant Case Report Form (CRF). Participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced as needed to ensure a sample size of at least 15 participants.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she does not complete the post-intervention interview and questionnaire and is unable to be contacted by the study site staff.

The following actions must be taken if an enrolled participant does not complete the post-intervention interview and questionnaire:

- The site will attempt to contact the participant to determine the cause of the missed interview, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Study data will be gathered through the following procedures:

- **Interaction with HiDO platform**. Dosage logs, video recording of participant during dosing
- **Questionnaires and interviews.** Self-reported medication adherence, usability metrics, open-ended consumer feedback.

8.2 SAFETY AND OTHER ASSESSMENTS

Automated medication logs from the HiDO device, and manual audits thereof, will be used to assess safety – for instance, in the unlikely event that the HiDO device contributes to substantially lower medication adherence as compared to baseline. Logs will be audited monthly beginning in Week 4 of the earliest participant enrollment.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The CTCAE V. 4.03 will be used in this study. Each adverse event must be assigned a Grade, which refers to the severity of the adverse event. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event on this general guideline:

Grade 1 – Mild AE
Grade 2 – Moderate AE
Grade 3 – Severe AE
Grade 4 – Life-threatening or disabling AE
Grade 5 – Death related to AE

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other

concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Serious adverse events will be collected throughout the study period. All serious adverse events must be reported to HiDO Technologies within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and submitted to HiDO Technologies. The Principal Investigator will notify the IRB of serious adverse events within seven days or as otherwise specified by local policies.

Disease-related events (DREs) can be expected to occur among the study population, which may include HIV/AIDS patients. These events are recorded by research staff, but are not reported as for AEs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the reviewing IRB and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Not applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-

approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within seven days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 30 days of the investigator becoming aware of the problem.

An investigator shall submit to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be verbally notified about UPs as required to disclosure known risks and maintain informed consent.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint (1): Determine the effect of automated medication adherence platform (HiDO) on medication compliance.

H_0: Use of the HiDO automated medication adherence platform will result in <94% medication adherence over 90 days.
H_a: Use of the HiDO automated medication adherence platform will result in ≥95% medication adherence over 90 days.

Primary endpoint (1) will be analyzed once study intervention for all participants is completed.

Secondary Efficacy Endpoint (2): Determine usability of automated medication adherence platform (HiDO), as indicated by user ease of adoption (Time on Task, error rates).

H_0: Usability scores for the HiDO platform (as measured by Time on Task for initial registration, "first click" testing, facial recognition setup, and medication administration, number and type of critical and non-critical errors, and error-free rate) will be lower than published benchmark rates for similar platforms.
H_a: Usability scores for the HiDO platform (as measured by Time on Task for initial registration, "first click" testing, facial recognition setup, and medication administration, number and type of critical and non-critical errors, and error-free rate) will be equal to or better than published benchmark rates for similar platforms.

Secondary endpoint (2) will be analyzed once all participants have completed 14 days of study intervention.

Secondary Efficacy Endpoint (3): Determine usability of automated medication adherence platform (HiDO), as indicated by standardized user experience metric (SUS).

H_0: The System Usability Scale (SUS) value for the HiDo platform will be lower than published benchmark rates for similar platforms (≤68).
H_a: The System Usability Scale (SUS) value for the HiDo platform will be better than published benchmark rates for similar platforms (>68).

Secondary endpoint (3) will be analyzed once all participants have completed the post-intervention interview.

Secondary Efficacy Endpoint (4): Determine usability of automated medication adherence platform (HiDO), as indicated by user endorsement (Net Promoter Score).

H_0: 80% or fewer participants will indicate that they are Likely or Strongly Likely to recommend the HiDo device to a friend or colleague.

H_a: Greater than 80% of participants will indicate that they are Likely or Strongly Likely to recommend the HiDo device to a friend or colleague.

Secondary endpoint (4) will be analyzed once all participants have completed the post-intervention interview.

9.2 SAMPLE SIZE DETERMINATION

TARGET SAMPLE SIZE: 24

The current study is a pilot study, the intent of which is to gather preliminary data on device usage to determine whether further study with a larger sample is both possible and merited based on early findings of the device's efficacy and usability. For this study, the expected effect of the device upon medication adherence is expected to be moderate to large, based on an expected 95% adherence rate post-study in relation to reported adherence rates in clinical trials of 54% to 68%, which is used to estimate baseline adherence.[9] Based on the expectation of moderate treatment effect, a sample size of between 10-15 is indicated as sufficient. [26,27] A target sample size of 24 should be sufficient to ensure at least 15 participants will complete the study at an estimated 60% completion rate of recruited participants.

9.3 POPULATIONS FOR ANALYSES

- Modified Intention-to-Treat Analysis Dataset: participants who are enrolled for at least 7 days of the 90-day intervention period
- Per-Protocol Analysis Dataset: participants who complete the 90-day intervention period and post-study interview and questionnaire.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Categorical and continuous data will be presented as percentages, means with standard deviations, median, range.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Given the small sample size and specification of secondary endpoints, descriptive statistics are sufficient to either accept or reject the null hypothesis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Given the small sample size and specification of all secondary endpoints, descriptive statistics are sufficient to either accept or reject the null hypotheses.

9.4.4 SAFETY ANALYSES

Not applicable.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

For each part of the study, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and pre-intervention medication adherence variables.

Demographic variables of screen failure participants and reasons for screen failures will be summarized overall for participants who are screened, but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

The sample size is not sufficient to conduct formal sub-group analyses, and the study was not designed for this purpose.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be tabulated by measure and time point.

9.4.9 EXPLORATORY ANALYSES

Qualitative data produced by answers to open-ended interview questions will be reviewed to determine any relevant aspects of the participant's experience with the device that were not captured by the System Usability Scale or the Net Promoter Scale.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- Recruitment flyer
- Device flyer
- Consent form
- Informed consent SOP[2]

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific interventions. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agencies, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

[2] This document describes the steps of the consent process; it is not provided to participants.

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator. The study site will permit access to such records.

The study participant's contact information will be securely stored at the research site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at HiDO Technologies. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by HiDO Technologies research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at HiDO Technologies.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Charles Gellman, MSHI, MBA (Principal Investigator). Mr. Gellman's has a strong background in statistics, clinical informatics, and data analysis in which he has accelerated the understanding of health data to improve health outcomes. His thesis research focused on performance metrics of hospital

mortality, readmissions and health care associated infections across the country using the Centers for Medicare & Medicaid Services (CMS) aggregated hospital database. He will oversee all aspects of the trial including device manufacturing, deployment, recapture, data acquisition, analysis, and reporting.

10.1.6 SAFETY OVERSIGHT

Not applicable.

10.1.7 CLINICAL MONITORING

Not applicable.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be flagged for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Study data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) are stored on AWS, a 21 CFR Part 11-compliant cloud computing platform. The data system includes password protection; internal quality checks are conducted manually to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents may be retained indefinitely, and for a minimum of 3 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 3 years from the date of the Federal Financial Report (FFR) submission. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation or scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the reviewing Institutional Review Board (IRB) per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Data from this study will not be shared. Findings of this study may be published.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed in a way that is appropriate to the individual's participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
HER	Electronic Health Records
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.1	7/1/21	See separated sheet "2021-07-01 Responses to review"	Address pre-review comments
2.2	7/20/21	Fixed a typo per reviewer's request; clarified data retention policy	Address reviewer conditions

11 REFERENCES

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12 APPENDIX A: HIDO PRODUCT BROCHURE

<attach product brochure here>

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The rights below are set out by the California legislature as the rights of every person asked to be in a research study.

As an Experimental subject, you have the following rights:

1. To be told what the study is trying to find out.
2. To be told what will happen to you and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen for research purposes.
4. To be told if you can expect any benefit from participating and, if so, what the benefit might be.
5. To be told the other choices you have and how they compare to being in the study.
6. To be allowed to ask any questions concerning the study, both before agreeing to be involved and any time during the course of the study.
7. To be told what sort of medical treatment is available if complications arise.
8. To refuse to participate at all or to change your mind about participation after the study is started. The decision will not affect your right to receive the care you would receive if you were not in the study.
9. To receive a copy of the signed and dated consent form.
10. To be free of pressure when considering whether you want to agree to be in the study.

If you have other questions, ask the researcher or the research assistant. In addition, you may contact Ethical & Independent Review Services (E&I) Institutional Review Board, which is concerned with protection of volunteers in this research project. You may reach the E&I office by calling (800) 472-3241 from 9:00 AM to 4:30 PM (Pacific Time) Monday to Friday or by writing them at subject@eandireview.com.

I have been given a copy of this form to keep and to refer to as needed.

Signature _____ Date _____

CONSENT FORM
for a Research Study titled:
"Automated Medication Platform with Video Observation and Facial Recognition to Improve Adherence to Antiretroviral Therapy in Patients with HIV/AIDS"

You are being asked to participate in a research study: This study looks at whether a new "smart" medication dispenser will help HIV/AIDS patients have fewer late or missed doses of their antiretroviral therapy (ART) medications. You will use the smart medication dispenser for 90 days, and then complete a 30-minute interview about your experience with the smart medication dispenser.

What will be involved if you participate? Before you start your participation in this study, you will provide some information about your background and recent medical history to determine if you are eligible to enroll in this study. If you are enrolled, a Wi-Fi enabled automated medication dispenser will be delivered to your home address. This device dispenses up to seven different medications at the time that you are scheduled to take them. The device also confirms your doses using facial recognition, video records you taking your medication, sends reminders and alerts to your smartphone, and sends information about your dosage to the researcher; if you do not want to be video recorded, you cannot take part in this study. The researcher will visit your home to deliver the device, help you set it up, and link it to your smartphone. This visit is expected to last about 45 minutes.

After you use the device for 90 days, you will complete an interview that asks about your experience with the device. This interview may take place either remotely (by phone or through a videoconference platform such as Zoom), or in your home when the medication dispenser is picked up. The interview will take about 30 minutes.

At the end of the study, the medication dispenser will be picked up from your house by the researcher.

Are there any risks, discomforts, or costs? There is a risk that your private information may be seen by someone other than the researcher. To protect you against this risk, the researchers will remove your name and contact information from the other information that you provide and store it separately. All of your information will be stored either in a locked file cabinet that only the researchers can access, on a computer that is encrypted and protected by a password known only to the researchers, or in secure cloud-based storage. Information that is transmitted over the internet is encrypted (scrambled) so that it cannot be viewed by others.

There is a risk that the device may malfunction, which may include not dispensing the correct dose at the correct time or not reminding you when to take your dose. This is an unavoidable risk because the purpose of this study is to evaluate the device. Since the device can malfunction, it is your responsibility to take your prescribed medications as directed by your doctor. If your device fails to automatically dispense your medications, you will be able to open the device to access your medications manually. This medication dispenser has a childproof lid, but as with any other medication container, you should keep this device out of the reach of children and pets.

If you are injured by participating in this study please seek medical care. Report any research-related injury or if you think you may have been harmed by participating in this study to the study Principal Investigator Charles Gellman at charles@hidohealth.com or <add phone number>.

Are there any benefits to yourself or others? By using the device, you may have fewer late or missed ART doses, which may decrease your viral load. In the future, other people may benefit from the availability of a "smart" medication dispenser.

Are there any costs or payment if you decide to participate? At the end of the study, you will receive a $100 VISA gift card to compensate you for your participation when the researcher picks up the medication dispenser from your home. If you are unable to complete the study, you will receive partial compensation of $5 per week, which you will receive as a Visa gift card when the researcher picks up the medication dispenser from your home.

Because the medication dispenser transmits data using Wifi, internet access, mobile text and minutes, and data usage costs may apply.

You will not be compensated for any products, services, or intellectual property developed as a result of this study.

Your participation is voluntary. This study does not involve any medical treatment. You may refuse to participate without any penalty or loss of benefits to which you are otherwise entitled. If you agree to participate, you can change your mind about participating, and can leave the study at any time without any penalty or loss of benefits to which you are otherwise entitled.

Your confidentiality and privacy will be protected. Your identity will be kept as confidential as possible, meaning that it will not be shared with anyone other than this study's research team. To further protect your confidentiality, the information you provide – which includes your medication logs and video recordings recorded by the medication dispenser, your interview responses, and any other information you provide to us – will be stored on an encrypted and password-protected computer or cloud-based storage that is only accessible by the research team. The data collected in this research study may also be used for future product development and/or applications to the FDA or other regulatory agencies. The study data may be kept indefinitely.

Except for video recordings, your information will be de-identified, meaning that any information that could be used to identify you (such as your name or address) will be removed from the rest of your information and replaced with an identification number. Your de-identified data may be used in future research without asking for your consent.

The device will take video recordings of your face. These recordings are used only to test a security feature of the device that confirms the medication dispensed by the device is taken by you and not another person. These video recordings will not be de-identified, will not be used for future research, and will not be shared with other researchers.

There are some people that will have access to the research data such as the study sponsor HiDO Technologies, the Institutional Review Board (IRB) that reviewed this study, the Food and Drug Administration (FDA), and other regulatory agencies for monitoring and auditing purposes.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Procedures for Termination of Study Participation. You can be removed from the study at any time and for any reason without your consent. Some of the reasons you can be removed are listed below.

- You do not follow the instructions, rules, and restrictions given by the study staff.
- You do not continue to meet the requirements for the study.
- The study staff decides it is in your best interest.
- The Sponsor stops the study or asks that you be removed from the study.

If you have questions about this study, to offer input or if you are injured or harmed by participating in this study, please contact Charles Gellman at charles@hidohealth.com or <800-phone number TBD>.

An Institutional Review Board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact Ethical & Independent Review Services IRB, at 1-800-472-3241 or by email at subject@eandireview.com. Reference E&I study number 21110.

HAVING READ THE INFORMATION PROVIDED, YOU MUST DECIDE WHETHER OR NOT YOU WISH TO PARTICIPATE IN THIS RESEARCH STUDY. YOUR SIGNATURE INDICATES YOUR WILLINGNESS TO PARTICIPATE.

I have read this consent form. I have been given enough time to consider participation, ask questions, and my questions have been answered. I am giving voluntary and informed consent to participate in this study. I agree to be video recorded. I will be given a signed copy of this consent form and the Experimental Subject's Bill of Rights.

_____ _____

Signature of participant Date

_____

Printed name of participant

I have reviewed this study consent form with this person and answered all questions. In my opinion this person is giving voluntary and informed consent.

_____ _____

Signature of investigator obtaining consent Date

_____

Printed name investigator obtaining consent