The Ethics of Electronically Monitoring Adherence to Antiretroviral Therapy: Theoretical Considerations and Empiric Findings

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Contributions and Acknowledgements

The research presented here represents the collaboration of many individuals, in both the US and Uganda. Angella Musiimenta, our study’s principal investigator in Mbarara, provided an immense amount of support, particularly in navigating the Ugandan research system and providing key cultural insights. Sylvia Natukunda, our research assistant in Uganda, conducted, translated and transcribed a huge number of interviews (including all UARTO participant interviews), was a key cultural coach, and helped me conduct the day-to-day operations of the study in Mbarara. Bridget Burns, our American research assistant, not only helped with qualitative data analysis, but also instructed me on the gritty details of qualitative data analysis and provided hugely helpful anthropologic insights into our data. Nicholas Musinguzi helped with data analysis (including running most of the quantitative data analysis) and was also a patient teacher as he led me through the logic of the statistics we employed. Norma Ware and David Bangsberg provided essential consultation on qualitative research methods (including careful review of our interview documents) and EAM-based research in Uganda. Dan Wikler and Henry Richardson provided important insights and discussion on many of the normative ethical considerations we describe. The staff of Mbarara University of Science and Technology, the MGH Center for Global Health, and the Global Health Collaborative in Mbarara, Uganda, made me feel at home and supported me while I carried out this research; in particular, the staff of the UARTO study graciously offered me advice and kept our study on track. I owe a special thanks to all of the participants in our interviews and focused group discussion.

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To reflect this extensive collaboration, I use “we” and “our” throughout this thesis. However, for purposes of this thesis, which unfortunately does not allow co-authorship, I will note that I led study development, day-to-day conduct, data analysis, and writing of the papers and presentations upon which this thesis is based. All arguments and conclusions are ultimately my own.
Abstract

Research Problem: Many electronic adherence monitors (EAMs) exist to track medication adherence, but despite attention in the popular press and expanding use of these devices, the ethics of using EAMs are largely unexplored.

Methods: We began by identifying and describing key philosophical considerations that may be relevant to EAM use. We then empirically assessed these considerations among EAM users in rural Uganda. The Uganda AIDS Rural Treatment Outcomes (UARTO) study was an observational cohort study involving standard and real-time EAMs for HIV antiretroviral therapy. We conducted qualitative interviews with 72 individuals (UARTO participants and staff, and local ethical board members). Interviews focused on pre-identified normative domains, but were open-ended to allow novel considerations to emerge. Directed content analysis was used to analyze relevance of hypothesized ethical considerations.

Findings: In philosophical analysis, we identified privacy, confidentiality, trust, dependence, and ancillary care obligations as potential considerations for EAM use. UARTO participants were most concerned about confidentiality (revelation of HIV status via EAM use) and trust (researchers believing the EAM rather than the participant’s self-reported adherence). Participants also reported concerns about privacy (feeling judged if providers learned about their non-adherence) and dependence (needing the device to remain adherent). Concerns about EAMs’ impact on autonomy were seldom mentioned.

Conclusions: Among rural Ugandans participating in a study of HIV antiretroviral adherence, privacy, confidentiality, trust, and dependence were identified as key ethical considerations for EAM use, while autonomy was less important. These findings should inform EAM-based study design, clinical use of EAMs, and health technology deployment in resource-limited settings.

1 A version of this abstract and the empiric findings discussed here are currently under review for presentation at the 2016 International Association of Bioethics conference (Edinburgh, 14-17 June, 2016), submitted as: Campbell JI, Burns B, Natukunda S, Eyal N, Musiimenta A, Haberer JE. Key Ethical Considerations for Electronically Monitoring Antiretroviral Adherence – Qualitative Evidence from Uganda.
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Glossary

API – Autonomy Preferences Index
ARV – Antiretroviral
CAB – Community Advisory Board
CPAP – Continuous Positive Airway Pressure
DOT – Directly Observed Therapy
EAM – Electronic Adherence Monitor
HIPAA – Health Insurance Portability and Accountability Act
I: – Interviewer
IQR – Interquartile Range
IRB – Institutional Review Board
MEMS – Medication Event Monitoring System
MRRH – Mbarara Regional Referral Hospital
MUST – Mbarara University of Science and Technology
NIH – National Institutes of Health
NNRTI – non-nucleoside reverse-transcriptase inhibitor
R: – Respondent
RA – Research Assistant
REC – Research Ethics Committee
REDCap – Research Electronic Data Capture
SD – Standard Deviation
SMS – Short Messaging System
TB – Tuberculosis
UARTO – Uganda AIDS Rural Treatment Outcomes
USD – United States Dollar
Introduction²

A wide array of electronic adherence monitors (EAMs) is now available to remotely record and characterize adherence to medical recommendations, particularly with regard to medication adherence (Table 1). For example, medication bottles can be fitted with electronic caps that record a time and date stamp whenever the bottle cap is removed and replaced, providing downloadable data that function as surrogate indicators for pill-taking behavior. Newer technologies transmit this adherence data in real time, typically over cellular networks (1). The most recent advances in adherence monitoring technology include pills that record actual ingestion (2), as well as drug metabolite detectors (3). These technologies enhance our ability to understand adherence behaviors, but their use also raises important, unexplored ethical questions. This thesis develops a range of ethical considerations for EAM use, and uses empiric data to explore these considerations among HIV-infected individuals in Uganda, a prototypical setting for EAM-based research. Although empiric data may not fully answer normative ethical questions about EAM use, a robust understanding of attitudes towards using these devices will help to identify concerns that are relevant in this setting, elucidate cultural nuances that shape EAM users’ experiences, and describe the practical meanings and implications of normative concerns surrounding EAM use.

Our goal is to use this normative framework and empiric evidence to provide guidance for researchers conducting EAM-based adherence studies, ethics community charged with ensuring that these studies meet the highest ethical standards, and clinicians who may in the near future use EAMs in clinical care. To this end, we conclude with a series of questions, built upon both normative and empiric analysis, that address the range of ethical considerations for EAM use and that could be used to guide relevant parties when designing or evaluating EAM-based studies or clinical interventions. The research presented here aims to fill a vacuum of theory, data

and guidance that is all the more necessary because of recent trends in surveillance technology and growing societal concerns about monitoring (4).

Background and State of the Literature

Ethical Considerations in Health Monitoring and Promotion: Lessons from Telemedicine and Directly Observed Therapy

Although the technology and behaviors associated with EAM use generate unique and previously largely unexplored ethical considerations, general measurement of adherence has garnered some prior ethical analysis. This analysis has revealed the potential for adherence monitoring—in any manner—to jeopardize an individual’s privacy, autonomy, and best interests (5). Others have suggested that monitoring adherence may also create a sense of paternalism in that it implies submissiveness or obedience to providers (6). Focused studies on the ethics of medical monitoring have been concentrated in two fields: telemedicine for monitoring of the elderly and directly observed therapy (DOT) for tuberculosis (TB) treatment. Both of these fields yield important insights into the ethics of EAM monitoring for HIV.

Prior literature on telemedicine monitoring of the elderly, in which devices such as cameras and fall detectors can detect dangerous actions (like a fall) as well as more benign daily activities (like walking through a living room), reiterates general ethical considerations for the use of adherence monitors, including threats to privacy and autonomy (7, 8). Mittlestadt, in a review of telemedicine ethics, notes several considerations that are relevant to EAM use, including autonomy, obtrusiveness/visibility of the monitoring system, and stigmatization (9). Autonomy has been a notable focus in this discussion, and prior work has described how different facets of autonomy may compete: in particular while monitoring may decrease freedom due to observation of home activities, this may be compensated by increased freedom of movement due to perceived improvements in safety (10-12). For instance, although monitoring may limit what individuals may do at home (e.g. they may not feel comfortable walking through their living rooms in their underwear if a monitoring camera is present), improved safety arising from monitoring may give them freedom to live at home in the first place, instead of in a healthcare facility. Monitoring, therefore, may limit autonomy in some areas while enhancing it in others.
Studies on the ethics of anti-TB DOT add considerations of public health to this discussion. TB therapy inherently balances individual rights with concerns for public health. Hurtig and colleagues note that while DOT may be a reasonable method of TB control from a biomedical perspective, it frequently ignores social, economic and cultural contexts of therapy; typical justifications of DOT, they argue, unreasonably minimize considerations of stigma, disclosure, and economic burden on individuals (13). Empiric evidence for the relevance of these concerns was found in a cross-cultural study of ethics of DOT in Norway and Ethiopia, where DOT was found in some instances to threaten autonomy and patient dignity while overly burdening socially disadvantaged patients, without providing fair reciprocation for the time and effort they allocate for treatment (14). These researchers found that in the extreme, DOT-based tuberculosis therapy was perceived to be humiliating and disempowering (15). Nevertheless, DOT’s success at preventing TB transmission (16) has been used to justify perceived harms, and in the US, several states’ legal systems allow for compulsory DOT to protect public health (17). The case may be different for HIV. Pointing to lack of evidence that DOT prevents development of viral resistance or HIV transmission, Liechty and Bangsberg argue that concerns about stigma and limitations on individual rights are not sufficiently counterbalanced by public health gains from DOT of ARVs (18).

In sum, general discussions of adherence monitoring have identified privacy and autonomy, against a backdrop of paternalism, as key considerations in the ethics of adherence monitoring. Telemedicine highlights the tradeoffs in liberties at an individual level that monitoring may demand. DOT raises the necessity to weigh individual rights against public health when monitoring adherence, particularly in treatment of communicable disease. These cases all have monitoring of health behaviors at their heart. What is different about EAMs?

**Benefits of EAM Use**

EAM devices provide a number of benefits compared to traditional methods of adherence measurement. By automatically and objectively recording adherence events, EAMs avoid recall and social desirability biases that often complicate self-reported data and result in misclassification of adherence (19). Although these devices are imperfect (e.g., opening a pill bottle does not always correspond with ingestion of a pill) and not always used in the intended way, EAMs nevertheless provide objective information that may reduce uncertainty about individuals’ adherence behavior (20), and can identify daily adherence patterns (21, 22). EAMs
may also improve quantification of adherence when self-reporting adherence is challenging, such as in pediatric populations (23). Furthermore, EAMs may be integrated into routine practices (e.g., opening a pill storage container) and thereby collect data passively, without the frequent visits required by DOT that may be disruptive and stigmatizing (13, 18). Unlike most other forms of adherence measurement, real-time EAMs also present the opportunity to learn about incomplete adherence as it happens (24).

EAM interventions developed to date show promise as tools for clinical care and public health. For instance, EAMs are being used to facilitate feedback to non-adherent HIV patients in order to improve adherence (25, 26). This type of intervention may be especially critical for conditions like HIV, in which viral suppression can be lost after missing just a few doses of antiretroviral therapy, leading to drug resistance (27, 28) and increased risk of transmission (29). Recent trials have shown that EAM-triggered reminder systems, such as “beeps” when a dose was not taken at a specified time (30), or even home visits (31), may increase adherence. Because of the prevalence of cell phones in many of the settings where EAMs have been studied, recent research on using EAMs to promote adherence to ARVs in resource limited settings has focused on linking real-time adherence monitoring to short messaging system (SMS) text message reminders, although these trials have not been powered to investigate virologic responses to interventions (1, 32, 33). The physical presence of an EAM, the knowledge that one’s adherence is being monitored, and/or the possibility of rapid intervention after an adherence lapse is detected may serve as additional reminders to take medications (i.e., a mechanism for the Hawthorne effect) (34, 35).

**Ethical Challenges in EAM Use: General Considerations and Existing Literature**

EAMs also raise potential ethical concerns. In particular, the continuous presence of EAMs in individuals’ private life and the devices’ relative ability to integrate into individuals’ daily routines and environments enable EAMs and those collecting EAM data an unprecedented view of day-to-day activities. Furthermore, EAMs are designed to monitor prescribed behaviors (as opposed to routine daily activities monitored by other types of devices, such as fall detectors and other telemedicine devices), introducing further concerns about power dynamics between observers and observed.

The first writing on the ethics of EAMs arose in response to two studies that employed EAMs to investigate respiratory disease. In the first study, description of the nature of
monitoring was vague (36), while the second study used a deliberately covert electronic monitor (37). In response, Levine stressed the fraught nature of covert monitoring, both in terms of requirements for consent and the potential for covert monitoring to lead to “inflicting insights” upon participants—in other words, creating negative feelings when they learn that their non-adherence or intended deception was known by researchers all along (38). Stringent consenting requirements for covertly monitoring adherence have been subsequently reinforced (23). Rand (notably, the first author on one of the respiratory disease monitoring studies) and Sevick outlined broader ethical considerations for the use of EAMs. They point out potentially devastating results of monitored adherence, such as denial of insurance coverage or medical therapy in response to low adherence rates. More generally, they echo discussions of telemedicine and DOT, raising concerns about privacy and autonomy and suggesting that “[w]e are on the threshold of having an armamentarium of ‘big brother’ strategies to determine who is noncompliant” (5). The specter of “Big Brother” through adherence monitoring, in which patients cannot undertake desired actions because of providers’ intrusive observation of their adherence (and potentially other) behaviors, has appeared in subsequent writing about EAMs (39), including in the popular press (40).

Ethical Challenges in EAM Use

While authors have highlighted concerns in covert monitoring and raised the threat of “Big Brother” as ethical considerations in EAM use, these considerations do not cover the full spectrum of questions that these devices raise. The remainder of this introduction will extend this range of potential ethical concerns. Specifically, we identify privacy and confidentiality, autonomy, trust, dependence, and ancillary care obligations as key ethical considerations in EAM use, with particular focus on EAMs used in HIV research. We devote separate sections to each of these concerns. Within each section, we outline the underpinnings of the concern and then provide a counterpoint or ways to potentially alleviate the concern. Key empiric questions pertaining to each section that inform empiric data gathering are summarized in Table 2.

Autonomy

Adherence monitoring may limit an individual’s autonomy in two ways: her ability to be non-adherent (5), and her ability to undertake wanted behaviors due to a fear of monitoring.
To what extent would EAMs limit the ability to be non-adherent? Underlying this question is the assertion that fully competent adults generally retain the right to refuse treatment, an assertion that is generally upheld in our legal system. Thus, individuals generally face a choice of taking medication or not. Use of EAMs, and any resulting perceived threat of rebuke due to non-adherence, may compel individuals to take their drugs, even when they do not want to. This may be particularly problematic with use of devices that continuously report behavior to providers and researchers, which could enable frequent or highly-specific feedback from people in positions of power (e.g., researchers or physicians). Although individuals can deceive clinicians or researchers with some EAMs (e.g., an individual may open the lid of an electronically-equipped pill box without removing any pills), other EAMs, like positive airway pressure (CPAP) monitors (37) and recently-approved pill monitors that document ingestion (2), may preclude this option and thereby eliminate a potential autonomy-sparing escape valve.

Adherence monitoring may also limit autonomy more generally, because the researchers’ or the practitioners’ (perceived) omnipresent gaze may undermine individuals’ autonomy to behave in ways construed as non-normative, embarrassing, or simply private. This may partly explain why users of some telemedicine devices describe a need to hide themselves from the device and thereby avoid observation (41). Whether warranted or not, such perceptions of close monitoring are precisely what leads to the suggestion, by researchers and the popular press, that some forms of EAM verge on “Big Brother” (5, 39, 40).

Concerns about autonomy may also have practical implications. For instance, autonomy concerns may matter in that they can affect future adherence. EAMs may constrict the ways in which an individual takes control of or personalizes her or his own health care. For example, EAM-based studies require an individual to use a particular device that may not be convenient or easy to use, often instead of a more convenient pill box or other container (23, 42, 43). This tradeoff may both constrain the user’s ability to take medications in the way she chooses (limiting autonomy) and, in so doing, hurt the acceptability of the device. This requirement may actually result in decreased adherence if the individual is unable or disinclined to use the EAM (43).

There are several potential responses to these concerns. First, an EAM-user’s loss of the freedom to be non-adherent is arguably a “freedom” that is of relatively little worth to her (44). Second, ideal informed consent would ensure that if study participation involves loss of
autonomy through EAM use, participants will have made a voluntary decision to forfeit that autonomy (45). Any further purported threats to autonomy would hence be seen as exercises in self-binding (i.e. so-called “Ulyssian contracts” (46)). Third, the moral urgency of employing an EAM to improve adherence or the understanding of adherence may override concerns about minor losses of autonomy generated by EAMs. Practically, if EAMs become standard of clinical care, allowing participants to opt into EAM use (instead of lacking choice or having to opt out) could mitigate concerns about loss of autonomy.

**Privacy and Confidentiality**

Here, we define concerns about privacy as those focusing on researcher or clinician access to personal information about the EAM user other than the behavior being monitored. In contrast, confidentiality pertains to outsiders’ access to personal health information obtained, transmitted, or implied by EAMs.

Because EAMs frequently or continuously assess individuals’ behavior, these devices may necessitate greater sacrifice of privacy than would non-electronic methods of measuring adherence. EAMs may give researchers grounds to form assumptions about users’ personal habits, including those outside the realm of specific behaviors that the devices were intended to measure. For example, in one study of electronic scoliosis brace monitoring in a pediatric population, researchers speculated that one user’s brace removal that occurred regularly in the morning reflected times that she was bathing, and data patterns suggested to these researchers that other users stayed in bed longer on the weekends (47). As this study exemplifies, EAM users and even researchers may not be aware of what behaviors are being monitored until the devices’ records are analyzed, raising potential complications with informed consent procedures. Even when such detail-revealing monitoring is not possible, individuals may fear that it is: in a study assessing acceptability of an EAM to measure anti-malarial bed net use in Uganda, one respondent described concern about researchers observing her while asleep, although the device had no capacity to do so (48). Practically, privacy concerns have been cited as barriers to participant retention in one EAM-based study of HIV in the US (49).

Although some breaches of privacy may occur with EAM use, the characteristics of each device may substantially affect the extent of possible breaches (e.g., an electronic pill bottle that measures openings and closings may not be capable of revealing as many personal details as an electronic scoliosis brace). Additionally, while any in-person medical checkup and intervention
may require patients to forfeit some degree of privacy (e.g., a provider may ask what time a patient wears a scoliosis brace or why she removes it), in striving to objectively monitor individuals, EAMs may impede users’ putative right to withhold information from researchers or providers.

Turning to confidentiality, one of the primary risks that EAMs pose to users is the potential for unintended disease status disclosure, information that is ideally revealed only by choice. Risks to confidentiality are of particular concern in HIV, given the frequent use of EAMs in HIV research and the stigma associated with this diagnosis (50–52). For instance, if a neighbor sees an individual using an EAM, questions may lead to unintended disclosure of that individual’s HIV status, as has occurred in an EAM-based study in Uganda (JEH; unpublished). Similar concerns about HIV status arose in a South African study of EAM (53). One root cause of this scenario is that EAMs are used primarily for HIV research in some parts of the world, and therefore may imply that users have HIV.

Given the potentially personal nature of the information that EAMs collect, and their definitional reliance upon electronic data storage and potentially wireless transmission, discussion of confidentiality must also include consideration of data security. Some safeguards already exist as blanket protections against dissemination of private electronic health information. In the U.S., privacy and security rules in the Health Insurance Portability and Accountability Act (HIPAA) govern the security of electronic personal health information in clinical practice (54), including electronic information collected by EAMs for clinical care. But as recent, prominent security breaches have shown, electronic data is at risk even in settings with strictly enforced protections (55), and EAMs are frequently used in parts of the world where electronic health data are not stringently regulated (56).

Ethical concerns about privacy and confidentiality also involve individuals' perceptions of such concerns, and the psychological impact of these perceptions. The criteria for determining how much an individual will tolerate loss of privacy and/or confidentiality is culturally relative and likely condition specific (57). For instance, HIV patients in India and Malawi expressed concerns that electronic pill bottles could raise suspicions from family and neighbors, representing a threat to confidentiality (58), a concern that has been mirrored in the United States (49). Similar concerns were raised with regard to SMS adherence reminders in an adherence intervention study in Cameroon (59). However, these concerns have not been mirrored in
experiences among HIV patients in Uganda (24), Tanzania (60) or South Africa (53). Regional differences may reflect variations in how people from different cultures conceive of privacy and confidentiality, geographic and cultural differences in the level of HIV-associated stigma, or exposure to technology. Protective measures may remain necessary, even—and perhaps particularly—when risk for harm exists but target populations are not highly concerned about privacy and confidentiality.

Many of the issues raised above are ideally already addressed in research contexts by informed consent, which may ensure that any loss of privacy or confidentiality is authorized. However, the case is less clear when EAMs are used in clinical settings. Although there is a precedent for written informed consent in clinical scenarios involving chemotherapy (61) and surgery (62, 63), patients are typically not required to sign informed consent before receiving prescription medications, which would be housed in an EAM. There is also a risk that requiring explicit, written informed consent for prescriptions could present logistical barriers and/or intimidate individuals, and would require careful implementation. Finally, informed consent may not fully alleviate privacy and confidentiality concerns when patients are covertly monitored (36, 37, 64), and consent is obtained only at the end of a study. For example, researchers may learn details about all patients who are monitored, only to find that some refuse consent—after their behaviors have already been revealed to researchers.

Apart from informed consent, several practical responses may help alleviate these concerns. For instance, a blinded monitoring approach, in which a third-party researcher or clinical aide with no personal contact with research subjects or patients reviews adherence data could alleviate some concerns, much in the same way that security x-ray readers are physically separated from passengers during airport security checks. Additionally, deliberately using particular EAM devices not only for stigmatized disease but also for non-stigmatized diseases (like hypertension) could help disguise who has the stigmatized disease. Concerns about confidentiality might further be mitigated by modified device design (e.g. devices that resemble everyday technology, to conceal that they carry HIV medications) and widespread use of EAMs for both stigmatized and non-stigmatized diseases.

Trust and Relationships

Trust is vital in patient-provider and participant-researcher relationships, and may itself increase adherence (65). Constant monitoring for perceived adherence lapses may suggest that
the individual has something to hide (66), or that an individual’s report of adherence cannot be fully trusted. This implication may be perceived as belittling or insulting. In a study of an EAM to monitor health care providers’ use of hand sanitizers, one participant (a health care provider) remarked, “Why do we need to be treated like kindergartners? I’m a professional” (67). Furthermore, reported results from an EAM may contradict users’ reports; though fallible, EAMs provide objective measures of adherence that are typically more accurate than self-reported information (68). Calling attention to discrepant reports may imply that the EAM user cannot remember their adherence or is intentionally being deceptive, an implication that may, in turn, damage the patient-provider or participant-researcher relationship.

There are several theoretical and practical answers to these concerns. In the event that mistrust is a concern, a small degree of mistrust may be seen as an acceptable cost of optimizing adherence. After all, physicians routinely seek objective verification of data that patients could self-report, without implying significant distrust (e.g. asking a patient to step on a scale to verify self-reported weight loss). Additionally, devices that facilitate patient self-monitoring (e.g., pill bottles that display the number of cap openings to patients (69)) may convert the device from a mechanism solely designed for data gathering to a tool that empowers users to monitor their own choices better. Some consumer products that could be considered to be EAMs, such as commercially available activity monitors, complete this transition by making the user both the monitor and the monitored.

Dependence

When individuals use EAMs for extended periods of time, they may become accustomed to the devices and to any associated interventions. For instance, in a small study where an EAM was used to measure adherence following kidney transplantation, transplant patients reported feeling “a sense of dependency” on the device as early as three weeks after starting to use it (70). Discussing home monitoring of the elderly, some have suggested that dependence upon monitoring system may decrease users’ self-reliance (8, 9, 71). Although this may not be intrinsically harmful as long as the individual has access to the device (and any attendant interventions), harm may occur if, at the end of a study or when insurance coverage changes, monitoring is taken away from individuals who have become reliant upon them. Potential dependence on new technology is not unique to EAMs. But EAM-based studies often involve long-term, frequent use, creating high likelihood for dependence upon the device itself.
Moreover, currently, EAMs and the infrastructure supporting their use are rarely available outside research studies, limiting post-trial use of the devices. Additionally, technology, and particularly novel devices, always has the potential to fail (24, 72). Taken together, development of dependence upon EAMs may ultimately prove harmful, particularly to research participants. In response, adoption of EAMs in routine clinical care could potentially alleviate some of these concerns. If the device or monitoring were always available to individuals, there would be no negative consequences to developing dependence upon them. Additionally, to alleviate negative consequences of dependence, studies could be instructed to assist patients in identifying sustainable adherence strategies that could be used beyond the conclusion of the study.

**Ancillary Care Obligations in Research**

Non-adherence, particularly to drugs like ARVs, can be dangerous to individuals, in the case of HIV leading to development of viral resistance. When an EAM detects non-adherence in a research study, this information becomes available to researchers, sometimes in real time (73), but rarely to the participant’s direct care providers. Richardson has argued that researchers assume some degree of responsibility for research participants’ health while participants are enrolled in a trial (74). Because participants provide consent for researchers to observe adherence behaviors, EAMs may create an obligation for researchers to help participants improve their adherence.

But EAMs pose a unique strain on demands for ancillary care obligations. Various methods have been devised to respond rapidly to recognized instances of non-adherence, such as home visits and text messages (which have been shown to increase adherence in diabetic (75), epileptic (76), and HIV patients (77, 78)). But because of resource limitations and the large amount of data that EAMs collect, researchers will almost certainly lack the capacity to act immediately on all instances of detected, potentially dangerous non-adherence. Furthermore, demanding that researchers act on detected instances of non-adherence could disrupt the scientific aims of studies.

In response, although research participants may tacitly entrust components of their healthcare to researchers, who, Richardson argues, thereby acquire some duties to provide related ancillary care, Richardson adds that the “scope of entrustment” depends on the study aim or design (79). Therefore, researchers may not always be obliged to intervene in cases of identified non-adherence. It remains unclear the extent to which EAM users entrust their care to
researchers. Practically, development of low-intensity adherence interventions (e.g. text messages) as part of EAM-based research studies could address the challenges associated with frequent intervention without imposing onerous demands on investigators, although the efficacy of these interventions needs further examination.

Summary

The development and increasing use of EAMs has raised general ethical concerns in academic writing, and accusations of “Big Brother” in the popular press. However, no focused analysis of the ethics of EAM use has been conducted. As researchers, clinicians and policy-makers decide when and how to use EAMs, philosophical responses and practical solutions to the ethical challenges that these technologies raise will become necessary. Building upon prior theoretical and empiric work on use of DOT and telemedicine, we identify ethical challenges to EAM use surrounding autonomy, privacy, confidentiality, trust, dependence and ancillary care obligations. Understanding the basic ethical challenges surrounding EAM use, as well as potential solutions, will help improve the experience of using these devices and preempt later dilemmas or harms. These theoretical underpinnings inform the main questions and hypotheses to be tested in the empiric research described in this thesis.
Methods

This study used semi-structured qualitative interviews and formal surveys to assess attitudes surrounding the ethics of EAM use in rural Uganda. We assessed attitudes towards use of Wisepill (Wisepill Technologies, South Africa), an electronically-enabled pill bottle that holds 30-60 pills and sends a short message service (SMS) signal to researchers whenever the device is opened (a marker of pill removal and ingestion) (Figure 1). The device was used as part of the Uganda AIDS Rural Treatment Outcomes (UARTO) study (24), an observational study of individuals initiating HIV antiretroviral therapy in southwestern Uganda (conducted 2005-2015). A primary goal of the UARTO study was to investigate adherence patterns and behavior. From 2005-2011, Medication Event Monitoring System (MEMS) caps were used to monitor adherence. From 2011 to 2015, most participants transitioned to Wisepill use, although lack of cellular signal at home, long distance from clinic, or refusal to use the device were reasons for device non-use according UARTO’s protocol (participants could remain in UARTO even if they did not use Wisepill). Interruptions in Wisepill signals were investigated as they occurred to understand behavioral determinants of ARV adherence, as well as biological consequences of incomplete adherence (e.g., loss of viral suppression). Data from this study were used to validate Wisepill signals as a measure of adherence. When no Wisepill signals were detected for at least 48 hours, a research assistant would follow up with the participant to determine the cause of the lapse. Blood was also requested from the participant to assess for virologic changes in response to non-adherence.

Study Setting

We conducted our study in southwestern Uganda (Mbarara, population ~80,000) (Figure 2). HIV prevalence was estimated to be 11.8% in 2010 (80). Participants in UARTO were all recruited from the Mbarara Regional Referral Hospital’s (MRRH) Immune Suppression Syndrome Clinic, where patients receive CD4 and viral load testing, as well as ARVs, for free. Mbarara is home to Mbarara University of Science and Technology (MUST). MUST hosts a research ethics committee (REC), comprised of faculty members, that approves all studies that take place at MRRH, as well as a community advisory board (CAB) made up of faculty and community members, which advises the REC.
Population

We recruited participants from four distinct groups to obtain varied perspectives on EAM use in Mbarara: 1) UARTO participants who used Wisepill (n = 40); 2) UARTO participants who did not use Wisepill (n = 20); 3) UARTO research assistants (RAs) who interfaced with participants (n = 6); and 4) members of the MUST research ethics community (REC or CAB members) (n = 6). Research assistants identified key informants, who were purposefully sampled. Consent was provided in Runyankole or English, according to each participant’s preference.

Hypotheses

Based on initial theoretical work (81), we hypothesized that privacy and confidentiality, autonomy, trust, dependence, and ancillary care obligations would be key ethical considerations for use of EAMs in this setting. We left open the possibility that other considerations would emerge from interviews and surveys, and that some of the hypothesized considerations would not be relevant in this setting. We also hypothesized that ethical considerations may have factored into UARTO participants’ choice to use Wisepill.

Data Collection

Qualitative Data

Open-ended, guided interviews were conducted from August 2014 to June 2015. Data collection was performed in four phases. Interviews were conducted using a semi-structured interview guide that was tailored to each phase. All interviews were conducted in a private research office or the participant’s home, per the participant’s preference.

First, we conducted exploratory interviews with UARTO participants who used the EAM (n = 20), in order to understand general impressions of EAM use. Interview domains covered likes and dislikes of the device and likes and dislikes of UARTO participation. Results from these exploratory interviews were analyzed after all 20 participants had been interviewed, and results informed subsequent data collection.

Second, we conducted focused interviews with three groups: UARTO participants who used the EAM (n = 20), who did not use the EAM (n=20), and UARTO research assistants. Interview domains were derived from initial hypotheses, and also covered the role of social support in longitudinal study participation, a key theme that emerged during exploratory interviews. A single (non-UARTO) RA conducted UARTO participant interviews (including
exploratory interviews) in Runyankole, and subsequently translated interviews into English at time of transcription. A second researcher conducted all UARTO interviews, in English.

Third, we conducted a focused group discussion with members of MUST’s research ethics community (REC and CAB members) (n = 6). In addition to covering hypothesized ethical considerations related to EAM use in Mbarara, the discussion also contained questions related to the utility of proposed guidelines for review of EAM-based studies.

A schematic outlining hypothesis generation in relation to different participant groups is presented in Figure 3.

Quantitative Data

All participants completed standardized questionnaires. UARTO participants completed a basic assessment of socioeconomic status, including questions on salary, non-salary income, and household expenditures. UARTO RAs and REC members completed basic demographic surveys. All participants completed an HIV stigma scale: UARTO participants were given the updated Internalized AIDS-Related Stigma Scale (82); responses were summed and a score out of 7 was computed, with 0 indicating no internalized stigma and 7 indicating maximum internalized stigma. UARTO RAs and ethics community members completed a standardized, four-question scale of acceptance attitudes towards those living with HIV (83); a non-supportive response to any question indicated an overall non-supportive attitude. All participants completed a modified, semi-qualitative cross-cultural privacy assessment (84), the shared decision making and information seeking subscales from the Autonomy Preference Index (API) (85), the Trust in Physicians Scale (86), and the short-version trust in medical researchers scale (87). Responses to the privacy scale were reported as percent reporting each answer for each question. The autonomy subscales were computed by coding responses from 0 to 4, with 4 indicating greatest preference for autonomy; scores from each question were summed, and the total was scaled from 0 to 100, with 0 indicating no preference for autonomy, 50 indicating ambivalence, and 100 indicating greatest preference for autonomy. The same approach was used to compute scores for both trust scales, with 0 indicating complete distrust, 50 indicating ambivalence, and 100 indicating complete trust. Surveys were translated into Runyankole. It is important to note that surveys on privacy, autonomy, and patient trust have not been validated in this setting. Surveys were used to provide a global picture of these issues, rather than provide definitive, quantitative assessments.
After data collection, all data was entered into a secured electronic database using Research Electronic Data Capture (REDCap) version 6 (88).

**Data Analysis**

Questionnaire data were summarized and compared between Wisepill users and non-users using Fisher’s exact test (for contingency tables) and Wilcoxon rank sum test (for continuously distributed variables), with \( p<0.05 \) representing statistical significance. Statistical tests were conducted using STATA version 13.

Qualitative data analysis aimed to identify and characterize ethical considerations for EAM use among HIV patients in southwestern Uganda. We assessed the relevance of hypothesized ethical considerations, using a directed content analysis approach (81). We also employed an inductive content analysis approach (89) to identify additional considerations that had not been previously hypothesized. Initial analysis began with review and discussion of 20% of interviews by two researchers (Jeffrey Campbell and Bridget Burns), with substantial input from two additional researchers (Jessica Haberer and Angella Musiimenta), to identify relevant content. Content was then organized as codes in a codebook. Codebook development was iterative and involved defining codes and identifying representative quotes from transcripts to illustrate these codes. Summary definitions of codes were developed to facilitate coding. The final codebook was then imported into NVivo version 11, and two researchers (Jeffrey Campbell and Bridget Burns) used this software to code all interviews, with 26% overlap in coding. Although categories were developed using data from all participants, our use of different participant subgroups (e.g. EAM users and non-users) allowed us to compare what these groups thought about identified ethical considerations.

**Ethical Review**

This study was reviewed and approved by the institutional review board (IRB) at Partners Healthcare (through Massachusetts General Hospital), the REC at MUST, and the Uganda National Council of Science and Technology. After reviewing the study design, the IRB at Harvard Medical School ceded full review to the IRB at Partners Healthcare.

**Role of the Funding Source**

This study was funded by a US National Institutes of Health (NIH) grant (1R21AI108329). The funder had no role in study objectives, design or decisions to publish.
Results

Participant Demographics and Socioeconomics

A total of 72 participants were enrolled; 40 were EAM users in the UARTO study (20 participated in exploratory interviews and 20 participated in focused interviews), 20 were EAM non-users in the UARTO study, six were research staff for the UARTO study, and six were members of the local ethics community. Table 3 shows basic demographic and socioeconomic characteristics of the study population. EAM users were significantly younger than EAM non-users (median 40 vs. 45 years, p = 0.03). The majority of UARTO participants (both EAM users and non-users) were female, reflective of the sex breakdown of individuals receiving ARVs at Mbarara Regional Referral Hospital. The majority of UARTO participants were literate, had attended at least primary school, and lived in rural areas. Indicators of socio-economic status were similar among all participant groups with the exception that monthly non-salary income was higher among EAM non-users (median $63 vs. $12 per month, p = 0.04). Within the six ethics community members recruited for participation in the focused group discussion, four were members of the local research ethics committee (REC) and two were members of the committee’s community advisory board (CAB). We present results in two sections: first, we address the relevance of hypothesized ethical considerations (using deductive qualitative analysis), and second, we address emergent considerations that were not hypothesized (using inductive qualitative analysis). Within pertinent deductive sections, we begin by presenting quantitative results from surveys to help contextualize qualitative findings (e.g. we present quantitative results from the Autonomy Preferences Index prior to describing qualitative data on autonomy). Quantitative results are summarized in Table 4. In quotations below, “I:” refers to the interviewer, while “R:” refers to the respondent. Key qualitative findings are summarized in Table 5.

Deductive Qualitative and Contextualizing Quantitative Results

Autonomy Transgression is Not Perceived as a Major Consideration for EAM Use in Southwestern Uganda

Overall, according to the shared decision making subscale of the Autonomy Preferences Index (API), we found slight preference among UARTO participants that their providers take
greater control in medical decision-making, as opposed to giving patients detailed control over medical decisions. There was no significant difference in preference for shared medical decision-making between EAM users and non-users ($p = 0.58$). In contrast, on average, participants expressed a general preference towards seeking more information in the information-seeking subscale of the API. There was no significant difference in scores between EAM users and non-users. Summary statistics for survey responses are presented in Table 4. In qualitative data, we sought to understand the impact that the EAM had on individuals’ perceptions of autonomy, as well as specific actions or omissions of actions that could be construed as limiting autonomy. Specifically, we queried participants about a sense of obligation to take ARVs due to monitoring, as well as ways in which EAM use and monitoring affected behavior.

*Monitoring May Create a Positively-Perceived Sense of Obligation to be Adherent*

Does monitoring create a sense of obligation to take medications, even when the participant would rather not take medications? Occasionally. Most participants described how reporting from the device created no sense of obligation to take medications, and no EAM non-users described autonomy-limiting factors as reasons to not use the device. Nevertheless, some participants reported feelings of obligation to adhere due to the EAM and monitoring, even when they did not want to take medications. For instance, one EAM user reported:

R: Yes, the truth is yes my mind is now stuck on Wisepill and my time for taking my medication. When I look at it I get this feeling like it’s there to monitor me so I should take my medication and I think if I did not have it things would be different. I: How [would it be] different? R: I take [ARVs] only when I want. (Male EAM user, age 38)

This sense of obligation was often mediated through a sense of being “forced” to take medications, or out of a desire not to let researchers down. (As a routine study procedure, participants would be visited at home following adherence lapses of >48 hours, and blood would be collected.) Another EAM user noted:

R: Because it forces you to take your drugs, because you know that it can report you. So you end up taking [ARVs] anyway even if you never wanted to take them. (Female EAM user, age 45)

The feeling of being forced to take medications frequently arose from a desire to avoid “punishment” or “abuse” from researchers, typically in the form of a blood draw prompted by detected non-adherence:
I: What does the device do? R: It helped me to remember to take my drugs because [I] was worried that if I do not take my drugs they will come and draw my blood so I made sure that I take my drugs. (Male EAM user, age 40)

The “obligation” to take medications due to reporting from the EAM could also be perceived positively. In these cases, even though participants felt compelled to take their medications, this arose because monitoring was perceived as a source of “encouragement” to help them achieve their goal of being adherent. One EAM user noted:

[I]t motivates me not to miss [taking ARVs]. I try to not miss because if I miss they call me to find out why, so this encourages me not to miss. (Male EAM user, age 38)

For these participants, encouragement or motivation to adhere that arose from monitoring was often a way to counter personal flaws, such as “laziness” or “negligence” that would result in non-adherence. One participant relayed that “fear” could be a positive tool:

[The EAM] also motivates us to take our drugs well. Just like when you have like a child who fears to be reported for doing wrong, the same applies to us the HIV patients who are using the device because we always fear that the device will report us. So we end up taking the drugs, even if we would have maybe not taken them due to either laziness or negligence. (Female EAM user, age 45)

In addition to creating a sense of obligation to be adherent, another way in which monitoring could affect autonomy was by creating a need to undertake particular unwanted behaviors because the participant used the device, or by limiting other behaviors unrelated to adherence. A few participants noted that they would undertake specific behaviors to ensure that the device sent a signal, behaviors that they would not have undertaken otherwise:

This device had failed to grab network in my house. I had to first go to a hilly place because my house was like on a valley and I used to first go to a hilly place for the device to be able to send a message…I: So how did this network issue make you feel? R: I felt bad of course because it used to disturb me going to this hilly place to look for network. (Male EAM user, age 64)

However, such instances were rare, as were positive responses to the question “have you ever had a change of plans due to Wisepill”.

In sum, EAMs induced a sense of obligation to take medications in some participants; in these cases, obligation to adhere was often mediated by fear of repercussions or negative feelings when researchers detected non-adherence. But more often, when monitoring prompted
adherence, this was perceived positively, as a way to counterbalance individual flaws that would lead to non-adherence.

Privacy: The EAM did not Reveal Excessive Information to Providers, but Participants were Concerned about Providers Knowing about Non-Adherence

Baseline attitudes surrounding privacy are presented in Table 2. The majority of UARITO participants who we interviewed (both EAM users and non-users) stated that they required privacy when experiencing a negative mood (e.g. angry or anxious). They identified physical conditions of their environments (e.g. noise) as most likely to induce a need for privacy, and infrequently included others when wanting privacy. They required occasional experiences of privacy, lasting a short-medium amount of time. In interviews, participants had few concerns about disclosing personal health information (aside from adherence information (see below), and occasionally information about their sex lives) to providers or researchers, and many saw forfeiture of privacy as a contingency of study participation:

I: Do you have any health-related information that you feel doctors or other health professionals or researchers should not know about? R: No. I know that if I need to be treated by the doctor and I was allowed to join the study I should not hide them anything. (Female EAM non-user, age 39)

We investigated two primary considerations surrounding privacy: 1) Does EAM use reveal private, adherence-unrelated details of individuals’ lives to researchers, and 2) Does EAM use reveal excess information about participants’ adherence to researchers, to the extent that participants are unable to hide their adherence? 3

EAMs Do Not Reveal Details of Users’ Personal Lives to Providers

In the focused group discussion, research ethics community members brought up the potential for the device to monitor more than it was intended to:

I would only be uncomfortable in the sense that technology can be abused in that people go ahead and do more than they had intended to. (Focused group discussion participant)

However, EAM users did not share this concern. Lack of concern was often founded on patients’ trust for researchers. For example, one EAM user stated:

3 Questions about the intrinsic problems with examining private information were investigated as aspects of trust (i.e. does it indicate lack of trust to ask someone to account for prescribed behaviors), rather than as issues of intrinsic privacy violations.
I: Are you concerned that more private information may be revealed by Wisepill, other than how you take your medication? R: I know that they want to know only how I take my drugs. I have never thought about anything else other than that because that is what they told me and I trust them. I: Please tell me more about trust. R: At the beginning of the study they told us that they will keep our private information confidential and we have never heard any one complaining about being disclosed so that is why I trust them and I know that my private information is kept confidential. (Female EAM user, age 45)

In fact, as this participant mentioned, participants were much more concerned about issues of confidentiality, and were primarily concerned with privacy in terms of the potential for researchers or providers to reveal information to third parties. Although there were some aspects of personal health that individuals stated they would like to keep private from providers (e.g. their sex lives), they did not connect revelation of these details to EAMs. Accordingly, focused group discussion participants emphasized that openness about the capabilities of the device would be essential to maintaining the device’s acceptability:

I think if the patient understands what the device is going to observe there is going to be no problem. But if he gets a mixed feeling that this may observe other things like alcohol or smoking, if there is failure to understand some information, it may cause discomfort to [EAM users] a bit so he may change a few of his behaviors. (Focused group discussion participant)

**EAMs May Reveal Excess Information about Adherence to Providers**

Participants noted that EAMs accurately reported their adherence, and could prevent “lying” about adherence. But for this objective measure of individuals’ adherence to be considered “excessive”, there needed to be an aspect of harm or resentment associated with reporting of adherence. Participants were split on this issue. Some noted that no harm was done when researchers obtained detailed knowledge about their adherence:

I: Are you concerned about the opinions that researchers form based on the information sent by the Wiseill? R: I cannot get concerned because I know that what the device reports about me is correct so I know that the opinions they make are based on that. So I do not mind. (Female EAM user, age 47)

In fact, many participants noted that they would be willing to tell their researchers (and providers) about instances of non-adherence as a way to solicit advice:

I: What if you miss, can you tell your RA about it? R: Yes I can tell her because I know that she can help me. I: How? R: She can advise me on what I should do in order not to forget again. (Female EAM non-user, age 33)
However, several participants offered a contrasting perspective, describing their reluctance to tell researchers about non-adherence, typically out of fear that the researchers would form a negative impression of the participants:

I: What about your RA, can you tell her in case you miss your medication? R: I cannot tell her surely. I: Why? R: I just cannot tell her because I do not want her to have a bad impression on me. I: What would be the harm about telling her in case you missed? R: She can think that you are a careless person and she can lose morale in helping you. (Male EAM user, age 64)

Concerns about negative impressions arising from detected non-adherence prompted one participant to refuse the device:

I: Can you tell your RA if you missed your dose of your medicine? R: To tell you the truth I cannot tell [my RA] because I know that if I tell her she will think that that is the reason why I refused Wisepill. I: But is it true, is it the reason why you refused Wisepill? R: [She laughs] Yes surely that is why I refused Wisepill because I told you I was moving up and down and I knew that I would be busy and I delay to open the device and she found out about this she would feel bad about me. (Female EAM non-user, age 46)

While participants were divided about whether or not to divulge adherence information to researchers, most expressed reluctance to divulge non-adherence to providers. Reluctance was based on fear that providers would form negative impressions of participants, or that knowledge of non-adherence would disrupt relationships with providers, damage trust, or result in “abuse” or being sent to an adherence counselor.

I: Why can’t you tell your doctor about [missing ARVs]? R: It’s because they rebuke us and they send you to the counselor. And yet we come when we are in a rush to go back and do our daily chores. (Female EAM non-user, age 42)

I: Assuming that you miss can you tell your doctor about it? R: I cannot tell him because I fear that he can abuse me because he gives me drugs and I fail to take them. (Female EAM non-user, age 45)

**EAMs both threaten and protect confidentiality**

*Contextualizing Disclosure*

Before describing the effects of EAMs on disclosure, it is important to understand the nuanced role that disclosure played for participants outside the context of monitoring. Of the 60 UARTO participants interviewed, 58 (97%) reported that they had told someone about their HIV status. Nevertheless, in interviews, participants frequently described unwillingness to disclose
their HIV status to others. Participants’ reluctance to disclose HIV status was primarily driven out of a sense of stigma associated with HIV. They described fears that after learning about their HIV status, others would think that they were “dying”, “immoral”, “bad people”, “useless people”, and “taking drugs so as to keep spreading the disease”. Some participants reported potentially serious consequences of disclosure, such as spouses leaving them. For these participants, withholding disease status information served as protection against these perceived insults and effects.

Disclosure also served a positive role for several participants, perhaps explaining the high proportion of individuals who reported having disclosed to others. Participants were motivated to disclose because of four main factors. First, participants noted that they simply were no longer “ashamed” about their HIV status, and therefore saw no reason to keep it secret:

Why don’t you hide your HIV status? R: I have lived with HIV for a long time that am now used I no longer get ashamed. (Female EAM user, age 47)

Second, disclosing served a general function of combating stigma, which participants did in part for the benefit of others:

I: Why do you want many people to see you? R: I mean make for us the HIV positive people a party, then I want many people to see me and know that I also [have] HIV and I do not hide behind. Am encouraged and I believe that I encourage others. I: Encourage others about what? R: Encouraging others who may still be stigmatized by the fact that they have HIV. (Female EAM user, age 46)

Like this participant, several others described ways in which they attempt to broadcast their HIV status as widely as possible:

Do you like to keep [your HIV status] a secret? R: For me I do not keep it a secret. Even I can go to a church and I declare my status. I even used to go on radios to disclose my status. (Female EAM user, age 43)

Disclosing to help others combat stigma was founded upon an understanding that there exists a community of individuals living with HIV, which forms the basis of the third reason why participants were willing to disclose: knowing that they were not alone in living with HIV:

How would you feel if someone saw it? R: It has no problem because I do not hide my HIV status. I: Why don’t you hide your status? R: The fact that [I] am not the only one, I don’t mind. (Female EAM user, age 45)
Finally, participants use disclosure as a way to make sure there would be others available to care for them in case they became sick. In this way, disclosure facilitated development of a social support network:

R: My neighbors know, I told them about my status because I know that in case I get a problem they can help me better if they know that I have HIV. (Male EAM user, age 36)

Participants Disclose Most Frequently to those People Closest to Them

Although there were variations (for example, disclosing to other HIV patients but not to one’s wife), in general, participants noted being most likely to disclose to their immediate families. They were somewhat less likely to disclose to others with HIV, to whom they would reveal their status because of common understanding of what it was like to live with HIV:

How do you feel about sharing your HIV medication information? R: Sharing it with an HIV positive person is okay but sharing with a negative person is not okay because such a person does understand what we go through.” (Female EAM non-user, age 42)

They were least likely to disclose to members of the general public. All participants had disclosed to researchers (both to UARTO researchers and to the interviewer in our study team) as a prerequisite of study participation.

EAMs Protects Confidentiality

We sought to understand concerns about EAMs or monitoring revealing information that would typically be privileged to the patient-provider or participant-researcher relationship.

The EAM protected HIV status primarily by concealing that it contained ARVs. One of the primary threats to confidentiality that this population endorsed was that others could notice ARV pills or pill bottles, and participants also described risk of disclosure from the characteristic sound of pills rattling in the manufacturer’s bottle (provided to all patients receiving ARVs from the local HIV clinic), and from general community knowledge that bottles contained ARVs. Participants noted that the EAM does not look like a pill bottle, but instead like other devices, such as a phone or “computer”:

So I see it has no problem even if you are going somewhere you go with it. It’s not heavy and even if people see it they can think it’s a phone other than the other ones, which are written on ARV and any one can know them. (Male EAM user, age 39)
One participant also described how she would tell inquisitive friends that the EAM was a phone if asked about it, in order to avoid disclosing to them. (The device was not always mistaken for a benign object like a phone—two participants recalled instances in which the device had been mistaken for a bomb.) Participants felt that the device’s ability to conceal HIV status, and thereby help avert the consequences of stigma, was one of the primary benefits of EAM use:

I: According to you, who should use Wisepill? R: It should be used by everyone who lives with HIV. I: Why? R: Because it keeps drugs well and it helps those who have a lot of stigma. When one has it no one can know that it contains HIV drugs. (Female EAM user, age 43)

Disclosure May Mitigate Benefits of Monitoring Technologies – Focused Group Discussion Perspectives

Participants in the focused group discussion (comprised of ethics review board and its community advisory board members) emphasized issues of disclosure. One member noted that the burgeoning use of technology in everyday life, including for adherence monitoring, held great potential, but the risk of disclosure due to this technology was something that could mandate certain protections. Highlighting the positives and negatives of using the device, she said:

So it’s a good thing to go electronic. I believe it comes with benefits. But on the community perspective I think there are certain bad things that we may need to guard against. It’s a good thing to be in constant communication with your clinical care provider, but it’s also not going to be good if the device that you are using is going to cause you discomfort at home like having unintended disclosure. (Focused group discussion participant)

One participant raised the possibility of electronic transmission from the device being used by third parties to identify people with HIV, a viewpoint that was rarely expressed by UARTO participants or researchers:

We may not have anticipated them but they come across but I may tend to think that whatever company one is working with somebody might have the ability to look at the data and locate that in village ABC there is a device here and there. Could there be a possibility that one may be able to tell that the person living in this particular village has the device and is HIV positive? And that could be a bad thing if at all it can be done. (Focused group discussion participant)

Disclosure Concerns are a Driver of EAM Non-Use

The device also had the potential to threaten disclosure. This was mediated by three related factors, which often negated the key ways in which the device protected HIV status
described above. First, participants were concerned that others would notice them opening the EAM to take pills out:

The only problem it has is that it can easily disclose you to the public, because when you start opening it everybody can see it and know. (Male EAM user, age 38)

Second, some participants were concerned that others would know that the device contained ARVs even without seeing the device opened.

I: Does seeing the device necessarily mean that you have HIV? R: You never know. Someone may see it and know that it’s a device used by HIV patients. I: How would you feel if someone saw it? R: I would feel very bad if it’s seen by some who is not an HIV patient like I said before these people like to mock us. But am sure nobody can see it because I like keeping it a secret. (Female EAM user, age 39)

And third, participants were concerned that features of the device, such as a blinking light that activates when the device sends a cellular signal, or the unusual (for rural Uganda) appearance of the device, would lead to questions about its function from curious observers.

R: I refused to use it because the way they explained it knew that it would draw attention from people especially when it lights when opened. (Female EAM non-user, age 52)

**EAMs may Facilitate Wanted Disclosure**

Although most participants conveyed either an ambivalent or negative attitude about disclosure resulting from EAM use, a few participants described using the EAM to facilitate wanted disclosure. This could come about in two ways: using the device to publicly disclose in order to enable HIV education, and using the device to catalyze conversations with family members or friends:

My other plan is that when I start my medication again I get the device back and I put it in the wardrobe with my drugs and when [my husband] comes and looks at it then I tell him that I tested for HIV recently and they gave me drugs and that is a device for keeping my drugs. I will tell him to even open it and I explain to him everything about it. Just like that. (Female EAM non-user, age 33)

One research assistant noted a positive outcome from an unintended disclosure due to the device by a similar mechanism:

There is a participant of mine who had not disclosed to the wife. However [disclosure] was a good thing for him. He went and left the device on the bed and went away so the wife came and saw the device on the bed. She even opened it
and saw the drugs. So when he came she asked him what it is and he explained everything. (RA, age 40)

UARTO Participation May Lead to Status Disclosure

Finally, several participants noted that aspects of study participation could lead to HIV status disclosure, irrespective of EAM use. Most commonly, this would arise from study visits to participants’ homes:

R: I told my RA to stop coming because I realized that this would threaten my disclosure in my family and in the village. When I married the new wife I did not want her to know that I am in the study…I don’t want everyone to know. Especially if they keep seeing cars coming to my home they might be inquisitive and I do not want that. (Male EAM user, age 64)

Linkages Between Monitoring, Trust, and Relationships

Both EAM users and non-users expressed generally trusting attitudes towards researchers and medical providers alike, according to the Medical Researchers Trust Scale and the Trust in Physicians Scale. There were no significant differences in trust between EAM users and non-users. In qualitative analysis, we investigated the relationship between monitoring and trust, as well as broader themes surrounding adherence and trust and their implications for expanded EAM use.

Trust is Often Founded upon Adherence

Participants noted that non-adherence would decrease trust from both researchers and providers. In fact, participants described how their adherence was foundational to trust between them and researchers/providers. Several participants described how providers trusted patients less when the patient appears clinically ill:

In most cases the reason why doctors fail to trust patients is because they keep wondering why the person is not responding to medication. This can cause the doctor to doubt the patient. Like for example at times we can be there at the clinic and they bring in someone who is really badly off, whose hair has all fallen off, the toes are all out and the person really looks bad. So when the doctor sees such a person they know that this person must have not been taking their medication. (Female EAM user, age 46)

Adherence Monitoring Enhances Trust
Although participants noted that the EAM would “prevent lying” about adherence, there was not a general perception that they were asked to use the device because researchers did not trust them. Instead, monitoring could enhance trust:

I think [researchers] can trust us more if they know that we take our drugs well and even I think that is why they gave out Wisepill: to be able to know the truth. Without monitoring of course they trust you less. (Female EAM non-user, age 53)

**Negative Feelings Resulting from Conflicting EAM- and Self-Reported Adherence**

In cases of possible device failure (e.g., cellular network outages), participants felt researchers would not believe them if they reported being adherent while the device reported otherwise. In these cases, participants felt that they were unfairly distrusted, and from a physical standpoint, unfairly subjugated to a blood draw.

I: Are you concerned about the opinions that researchers form based on the information sent by the wise pill? R: It happened last year they came and drew my blood about three times thinking that I was not taking my drugs and yet I was taking them. I told them but they did not believe me. This totally disturbed me. You know, I told them the truth but they did not believe me, and they went ahead and drew my blood three times. I complained a lot that they were drawing my blood for nothing so finally they went and checked and found out that actually it was the network problem. (Female EAM user, age 45)

Meanwhile, research assistants were faced with reconciling the conflicting reports. One research assistant described how this could lead to feelings of guilt on the part of researchers:

R: Obviously I felt bad. Here you are to draw blood because the device does not show [that the participant took ARVs] but the participant says he was taking the medication. But you have to draw the blood well knowing that it’s a technical problem of the device. So you feel so bad inside yourself thinking what if it backfills [data transmits after a delay]. After working on it, what would you tell the participant? (RA, age 32)

Research assistants noted that this could ultimately decrease participants’ trust in researchers:

[1]If you tell someone you have missed and she says no then you take blood and next time another person you say has missed and then you take blood they will meet and share. They can meet somewhere even at the clinic and share and they will lose trust in you. (RA, age 40)

**Perceived Trust Affects Participants’ Relationships with Researchers and Providers**

Participants described maintenance of trust as a motivating factor to conceal instances of non-adherence. This was typically mediated by a perception that mistrust would damage the participant-researcher relationship. One participant noted:
I: Do you think UARTO researchers would trust you more, or less, if they knew how you take your medication? R: They can trust you less if they see that you are not taking your drugs well. If you take your drugs well, I think your relationship with UARTO researchers can be good, but if you miss then your relationship with them can be bad. (Female EAM non-user, age 38)

Participants reported consternation that researchers’ and providers’ incorrect impressions about the EAM user when learning about adherence:

I: Do you think UARTO researchers would trust you more, or less if they knew how you take your medication. R: Trust can change because they can think that you are careless and yet one may just forget because forgetting is normal. (Female EAM non-user, age 45)

Some EAM Users Describe Becoming Dependent upon the Device to Adhere

In order to learn about potential dependence upon the device, we queried participants of their need to use the EAM to be adherent, as well as the effects of removing the EAM.

Removing EAMs May Lead to Non-Adherence

Several EAM users noted fears about changes to adherence if the device were removed. This concern typically arose out of a feeling that the device helped adherence:

R: Yes it will disturb me [to have the device removed] because I have been used to it and I think I might even miss my doses if I do not have it. I: Why? R: Because it has been reminding me. (Male EAM user, age 38)

UARTO research assistants noted that participants had eloped with the device when threatened with device removal:

Now they have begun to just run away with [the EAMs] because they don’t want us to remove these devices from them. There’s one participant from one of the RAs recently, she stays in Entebbe [260Km away from the study site], and she was here and they wanted to dis-enroll, and they told her that simply because she is far we will not be able to follow you up, we will need to take this device from you. Now after telling her, she escaped before we even did the interview. So you can see how these people are really attached to their device. (RA, age 36)

Even when EAM users stated that their adherence wouId not be affected if the device were removed, most requested to keep the device at the close of the study, even in the absence of adherence monitoring. This desire was primarily driven by the EAM’s uses as a protective case for pills and as an adherence reminder:

Maybe finally I want to say that they should leave us with the device when the study closes so that we can keep in our drugs. (Female EAM user, age 45)
Many EAM users concluded their interviews with spontaneous requests to keep the device at the close of the UARTO study.

**Ingrained Adherence Behaviors Limit Dependence**

Several EAM users denied feeling dependent upon the device to adhere, particularly when asked how their adherence would be affected if the device were taken away. They typically referred to a deep-seated motivation to be adherent, sometimes created by long-term EAM use:

> If they take it I can cope with the situation of not having it. I have been with it long enough to not forget to take my medicine in time because my mind is now fixed on it. (Female EAM user, age 47)

Additionally, many participants noted that they had been taking their medications before using the device, and had not become dependent upon it since starting to use it:

> As for me I may not be disturbed but something can change about me. It’s like when you are used to a phone, you can miss it if it gets lost. But it cannot affect how I take my drugs because I was taking them even before I got the device. (Female EAM user, age 43)

**Addressing Dependence when Studies Conclude – Focused Group Discussion Perspectives**

Most participants in the focused group discussion thought that participants should be given ample warning before the study ended, due to concern that they had become dependent upon the device to be adherent:

> It’s important because abrupt withdraw of something you have liked has consequences on your behavior and my behavior. If it has been motivating me and you abruptly withdraw it, I may need to be prepared for this change. (Focused group discussion participant)

There were mixed opinions about whether the device should be made available to participants at the conclusion of the study. Some members advocated for accounting for usefulness to participants and participants’ preferences when determining whether or not to make the device available:

> To add on that it may be good to withdraw the device, but if at the point of withdrawal the participant clearly mentions that they would prefer to remain with the device because of the attachment they have with it and they can demonstrate how they will use it, then you can leave them with the devices. We draw guidelines but in following them we break someone’s heart so we should be open minded so that we can explain about it and not to forcefully take the device against their will. (Focused group discussion participant)
However, others noted that the devices were designed primarily for research, using the devices incurred substantial cost, and that this could prevent the device from being used widely in clinical care in this setting:

For me I feel that the purpose of the research is important but I won’t go away from the fact that there is a cost associated with this and the fact that these devices came purposely for the research. So it’s important to prepare these participants early so that they know that they are research gadgets. Yes it’s beneficial, but given the cost and what you had planned even they are not enough to serve all the participants in the clinic. I think if the participant is well prepared [the devices] can be withdrawn and used for other important aspects, be it research or clinic. (Focused group discussion participant)

Ancillary Care Obligations: Participants and Research Assistants Believe that Adherence Support is a Key Component of Study Participation

Ancillary care obligations refer to medical support owed to research participants that falls outside the scope of the study’s activities. While empiric data does not neatly answer whether or not specific ancillary care obligations exist in monitoring studies, it can shed light on participants’ expectations and the ways in which study procedures are already perceived to provide care that could be considered “ancillary”. We asked participants broadly about what clinical support they thought they were entitled to due to study participation, and specifically if researchers had an obligation to help them adhere.

The majority of participants stated that researchers had a role in helping them adhere to ARVs:

As a research person she follows me up to ensure that I take my drugs well as the doctor prescribes it to me. (Male EAM non-user, age 48)

RAs were often viewed as “intermediaries” between doctors and patients, both in their responsibility to help participants take medications and in their ability to help with adherence-unrelated activities:

R: As a research person she follows me up to ensure that I take my drugs well as the doctor prescribes it to me. She checks my medical documents to make sure that there is no mistake and to make sure that I follow my return dates. (Male EAM non-user, age 48)
Altogether, participants felt that researchers wanted them to “live long”, and that monitoring arose out of a feeling of “caring”. This was felt to motivate researchers’ obligations to follow up with participants to ensure adherence and facilitate clinical follow up on their adherence.

Research assistants also felt that it was part of their job to help participants adhere. One research assistant described:

I have a passion for these participants so I feel they should take their drugs rightly and when I come across one with a challenge I take them to their counselors. I tell them to make sure they take their drugs well because if they don’t they would be in danger.

Knowledge of participants’ adherence behaviors and ability to learn when participants were non-adherent augmented this perceived responsibility to help them adhere:

I: As a researcher do you feel like you have a role in supporting people taking their medicines? R: Yes I do. I: Tell more about that. R: I monitor them, I visit them, I ask them questions and am always informed what’s happening with their medication. (RA, age 39)

Guideline Acceptability

We asked focused group discussion members whether or not guidelines outlining ethical challenges to EAM-based research and responses to these challenges would be useful for the local ethics community, which is charged with reviewing EAM-based studies at MUST.

Members agreed that such guidelines would be valuable:

It’s good to have guidelines but on both sides it would also be a duty of the research ethics committee that there may be a specific guide about the introduction of the newer devices because there are people out in the world who want to study the device but they do not know how to do it. So if we had a guide from the research committee to guide them that would be acceptable. (Focused group discussion participant)

However, they noted that guidelines should be “acceptable to the [local] community” in order to “not confuse the ethical body”.

Participant-Generated Content

When and How to Use EAMs

EAM Use Should be Opt-In

We sought to understand participants’ attitudes towards how EAM use should be presented to patients if the device were used in a clinical setting. Most participants thought that
the choice to use the device should be presented to potential users, who would then have the option to agree to use or not use the device according to their own preferences. For example, one participant stated in response to our questioning about EAM use in clinical care:

Let them teach the people how it works and they give it to only those who ask for it. (EAM user, age 38)

Participants noted several reasons why individuals may not want to use the device (see below), which motivated their opinion that use of the device should be opt-in. These included issues of stigma and disclosure, the fact that individuals may not use the device if they did not like it, and the opinion that the device may not be useful to everyone.

A few participants advocated for a hard paternalistic approach to device deployment. For example, one EAM non-user stated:

I: Should people ask for it or should the doctor give it as part of the regular clinical care? R: I think doctors should give Wisepill according to their judgment because the doctor can know whether one can manage to use it or not depending on how he has accessed this person. (Female EAM non-user, age 53)

Likewise, one research assistant suggested that all clinics distributing ARVs adopt EAMs due to adherence benefits that the devices brought about.

The mandatory use of EAMs in relation to public health benefit was a topic of lively debate in the focused group discussion. Members endorsed the idea that the device would lead to improved adherence, which could in turn have both individual and public health benefits. Nevertheless, there was consensus that EAM use should be fully voluntary, even in cases when non-adherent individuals with high viral loads could potentially infect others. Members agreed that individuals must make an “informed decision” before using the device.

Reasons To and To Not Use the EAM

We queried EAM users about what they liked about the device and why they used it. Similarly, we asked EAM non-users why they refused the device. Together, these perspectives provide a range of reasons to and to not use EAMs in this setting, which are summarized in Table 6.

Both EAM users and non-users reported a number of reasons to use the device. The most common reasons were: the device protected drugs from the environment and from other people, the device helped to organize drugs and/or remind users to take medications, the device did not
look like a pill bottle and prevents disease status disclosure, and the device served as a status symbol.

EAM non-users reported a number of explanations for not using the device, and also mentioned hypothetical reasons or reasons that did not directly pertain to their own decision to use the device. Of note, several participants reported factors relating to the logistics of using the device, such as lack of cellular signal at their homes or being told to not use the device (although the UARTO study protocol did not dictate such directions) as reasons for not using the device. We term as “external factors” these reasons for not using the device that were not related to the participants’ preferences.
Discussion

To our knowledge, this study is the first to theoretically and empirically analyze ethical considerations of using EAMs. We developed a preliminary set of ethical considerations that we hypothesized may be relevant for EAM use generally, namely privacy and confidentiality, autonomy, trust, dependence, and ancillary care obligations. We then assessed the relevance and nuances of these considerations for HIV-infected individuals using real-time EAMs in rural Uganda, which provided cross-cultural insight into these considerations. Better understanding the ethical challenges surrounding use of these devices has implications for device design, deployment, and oversight.

What Ethical Considerations are Relevant to EAM use Among HIV-Infected Individuals in Rural Southwestern Uganda?

Privacy

Charles Fried has argued that privacy is vital for “love and friendship” because it creates an environment in which an individual can selectively reveal personal information to others, and thereby privilege particular relationships (90). We sought to understand if EAM use caused privacy infringements that would threaten what Fried considers to be the core benefits of privacy. Based on our theoretical analysis, we assessed privacy among HIV-infected individuals using EAMs with two key questions in mind: does monitoring reveal personal details to those doing the monitoring, and does researchers’ detailed knowledge of adherence cause harm?

Participants had few concerns that EAM would reveal personal information to researchers or providers. Specifically, no concerns were raised about EAM monitoring revealing details of users’ behaviors or personal lives outside the realm of adherence. This finding may reflect the generally limited capabilities of the device to monitor activities other than pill-taking behavior. Another potential explanation is that participants simply had not thought about the device in relation to monitoring of private behaviors. Generally, there was little concern about authority figures (researchers and providers) learning details about individuals’ personal lives per se. Concern only arose when loss of privacy resulted in direct negative consequences, i.e. when providers would learn about non-adherence.

Although relatively rare, some participants had concerns about the EAM revealing adherence information to researchers. This concern was consequence-driven: participants felt that researchers would form a negative impression of participants if the device revealed
imperfect adherence. These participants feared that the EAM would limit their ability to selectively report adherence in a way that would avoid negative impressions or feelings on the part of researchers. For these patients, the device could have infringed upon a putative right to withhold adherence information from researchers. However, for the majority of participants, the ability to withhold adherence information from researchers was not a major consideration. In contrast, several participants were concerned about clinical providers learning about non-adherence. An often-repeated concern was that providers who learned about non-adherence would “abuse” participants or send them to a disliked adherence counselor. We did not specifically ask about attitudes towards providers learning about adherence using EAMs. But these concerns could be exacerbated by routine use of the device in clinical care in the future, particularly objective monitoring conflicts with EAM-users’ desires to please their providers or avoid negative adherence interventions.

In sum, privacy concerns mattered to participants in relation to providers learning about non-adherence, but participants were generally accepting of researchers learning about missed doses. When concerns did arise, they related to consequences of revealed non-adherence, either in terms of damaged relationships or of direct unwanted clinical interactions, but not to the fact of monitoring in itself. This result argues for a “carrots” rather than a “sticks” approach to using EAM-based interventions if EAMs are used for adherence promotion in this setting. Participants had few concerns related to the device revealing adherence-unrelated information to providers or researchers. Researchers or clinical providers wishing to use EAMs as interventions to improve adherence should consider the balance between rewards for adherence versus punishments for non-adherence, and how this may affect the acceptability of the device.

Confidentiality

As described in the introduction, whereas privacy pertains to researcher or clinician access to information about the EAM user other than the behavior being monitored, confidentiality relates to third-party access to personal health information obtained, transmitted, or implied by EAM. Disclosure of HIV status was the primary threat to confidentiality arising from EAM use. While researchers would not be directly responsible for most breaches of confidentiality—specifically disclosure—arising from EAM use, such as when an inquisitive neighbor sees and asks about the device, confidentiality is nonetheless important to consider in that it affects willingness to use the device and may cause harms to study participants. We
therefore sought to understand participants’ concerns regarding EAM use and disclosure of HIV status.

In this setting, participants considered disclosure through lenses of stigma and social support. Prior research from this setting has shown that individuals with more internalized stigma are less likely to disclose HIV seropositivity to others, and that “social distance” modifies likelihood to disclose, with closer social relationships attenuating the stigma-induced barrier to disclose (91). Our results are congruent with these prior findings: participants generally felt less reluctant to disclose to close social contacts, such as partners or family, compared to coworkers or strangers. Participants in our study were generally reluctant to disclose because of fear of insults and social isolation. Additional research from this setting has shown that individuals often fear disclosure because they feel that disclosure will undermine social relationships (92), and there was evidence that this fear played into our participants’ reluctance to disclose, particularly to employers and co-workers. However, disclosure also played a positive role for some participants, in particular as a way to build or mobilize social networks to assist them in times of need. For example, disclosure enabled them to feel secure that they would have close social contacts—family, friends, and neighbors—available to take care of them in case they fell sick. While we did not specifically correlate measures of HIV stigma with perceptions of social support, others have done so in this context, finding that increasing stigma is negatively correlated with level of social support (93). Accordingly, for our participants, the balance between perceived stigma and need for social support may have affected relative willingness to disclose.

Prior studies have found mixed evidence of concern about HIV serostatus disclosure arising from EAM use, with participants in acceptability studies expressing both concern (49, 58, 94) and lack of concern (24, 53, 60) that EAMs would lead to disclosure. We found evidence for three predominant attitudes related to disclosure that corroborate and modify these prior findings. First, a substantial subset of participants did not consider disclosure in relation to EAM use. These participants had typically disclosed to a wide group of people, and the device did not pose a specific threat to confidentiality.

Second, for some individuals, the EAM did threaten disclosure. Among concerned participants, there was worry that the device would draw attention from curious others, either because others saw them taking pills out of the device or because the device looked unusual.
Fear that the EAM would be noticed led some EAM users to conceal their devices. This finding supports results from an earlier acceptability study of a wireless EAM in China, in which some participants expressed concerns about use of the device resulting in disclosure (94). This has potential implications for adherence, since reluctance to take medications in front of others has been linked to skipping doses (95). A more worrying finding is that fear of disclosure from the device arose as a common reason to not use the device, corroborating findings from the aforementioned wireless EAM study in China (94). Among our participants, EAM non-users generally expressed more concerns about the device leading to disclosure than did EAM users. This concern could pose a significant barrier to device use if the device is rolled out for clinical care, despite lack of evidence that the device frequently leads to actual disclosure (24, 94). Widespread use of the device may be particularly problematic among individuals or in contexts where there is a large degree of internalized stigma.

Third, the EAM prevented and even facilitated disclosure. For most EAM users, the device protected secrecy of HIV seropositivity, precisely because it did not look like a standard pill bottle. In a setting with relatively low levels of technology exposure, its physical similarity to a cellphone often confused would-be inquisitive strangers, hiding the pills that would have revealed HIV status. Few participants expressed concern that others would know what the device was (an ARV container) without seeing pills emerging from the device, a fact that could change if EAMs becomes more widely used within the community. In addition, in a few cases, the EAM enabled desired disclosure, corroborating prior work by Pisarski and colleagues, who have described how EAMs may be used intentionally as a tool to facilitate wanted disclosure (96). While this work has shown that wanted disclosure occurred with close social contacts, we also found evidence that individuals used the EAM to disclose HIV status to broader groups of people, including strangers and the public at large. In one instance, a participant purposefully opened the device in public to reveal her status, an action that could unfortunately have unintended consequences for individuals who like the device because it conceals their ARVs.

Apart from EAM use, some participants were concerned that study visits could lead to disclosure. While this was a known risk for enrollment in the study, and efforts were made to mitigate the risk (using unmarked cars for home visits, meeting participants away from home, etc.), this concern has implications for proposed responses to non-adherence if EAMs are used in intervention studies or for clinical care. In particular, this result suggests that less obvious
adherence interventions, such as text messages, may be more acceptable than more publicly obvious interventions, like home visits. This position has been argued with regard to directly observed ARV therapy as well (18).

In sum, participants expressed a range of attitudes regarding EAM use and confidentiality, focusing on HIV status disclosure. Although no predominant attitude emerged, internalized stigma, social distance and the extent to which the EAM was specifically associated (or not associated) with HIV in participants’ communities modulated the extent to which individuals were concerned about the device threatening disclosure. Fear of disclosure was a key factor associated with device non-use.

**Trust and Relationships**

In his classic essay on trust, egalitarianism and respect, Jonathan Wolff has argued that when someone does not fully trust another, this necessarily implies a lack of respect (66). Calling someone to account for their behaviors instead of trusting their word, for example by monitoring them, could imply lack of trust and, therefore, lack of respect. While our data cannot confirm or refute Wolff’s theoretically-based argument, they can illuminate the practical nuances of how trust is understood, and how the interaction of trust and monitoring affect those being monitored. We sought to understand the relationship between adherence monitoring and trust in two ways: first, did adherence monitoring imply mistrust to those being monitored? And second, if mistrust entered the equation, did this have tangible effects on individuals’ relationships with researchers or providers? We sought to understand these questions from the participants’ perspective, both with relation to their trust in providers/researchers and with relation to providers’/researchers’ perceived mistrust of participants.

Did participants understand monitoring to be a way to hold them accountable, or imply that their word could not be trusted? This occurred in instances when researchers were perceived to believe the device’s adherence report over the participants’ self-report (despite research assistants assuring participants that they indeed believed the participants). In these cases, participants were distressed for two principal reasons, both of which could affect their relationships with researchers. First, participants were disturbed because researchers’ perceived disbelief of the participant’s word. However, a second, more palpable cause for disturbance was the blood draw that resulted from detected non-adherence in the UARTO study. In cases of discrepant reporting, participants stated that researchers unfairly inflicted the blood draw upon
them. At the extreme, discrepant reporting could result in participants losing faith in the study, and, according to research assistants, being lost to follow up.

However, outside the context of discrepant reporting, participants did not feel that the EAM indicated mistrust. Instead, there was a general impression that the EAM actually increased trust. For most participants, trust was primarily understood as researchers’ knowledge or confidence that participants were taking drugs as prescribed, rather than in relation to the veracity of the participants’ word. Stated another way, what participants found most important about trust was that researchers knew they were taking their therapy on time—researchers “trusted” them to be adherent; participants placed less value in researchers believing what they said, even for participants who noted that the device prevented lying. Therefore, the device, by accurately reporting adherence, increased researchers’ confidence (or “trust”) in participants. Using this second definition of trust—i.e. based on confidence that individuals were adherent—participants noted that lack of trust could be deleterious to their interactions and relationships with both providers and researchers, leading to perceptions of judgment and, potentially, to concealment of non-adherence.

One could argue that what matters most regarding trust in relation to monitoring is creating a system in which mistrust is does not dissuade individuals from using the EAM, not preservation of trust for its own sake. Eyal has argued that some medical practices and research procedures may diminish trust but are nonetheless valuable and warranted (Eyal highlights the case of informed consent, but the argument may also apply to other practices, such as electronic monitoring) (97). Our results suggest that distrust could affect individuals’ motivation to continue using the device when device and participant report discrepant adherence. But the EAM is, in part, designed to accomplish just this: be a more reliable monitor of adherence than users themselves. Perceived minor loss of trust, such as in the instances that our participants brought up, may well be a necessary cost in exchange for a better understanding of adherence. However, continuing to optimize the device’s sensitivity and specificity, and its ability to accurately report adherence, could limit instances in which individuals feel that they are being unfairly accused of non-adherence. Furthermore, framing the device as a tool to enhance trust between users with researchers, a perception that many of our participants held, could improve the acceptability of monitoring in a community.
It is also important to note that maintenance of trust could provide a positive motivation to adhere. Others have found that trust in providers is a predictor of adherence (98-100), and trust in physicians and HIV medications has been demonstrated to be positively associated with acceptance of ARVs (99). While a trusting relationship between patients and providers is one in which patients would likely feel supported to adhere to medications, as these studies have suggested, our results provide another potential mechanism linking trust to adherence, particularly within the context of adherence monitoring. For our participants, trust was a hallmark of a close relationship with providers and researchers, and maintenance of trust depended upon adherence. Maintenance of trust therefore acted as a mechanism for the Hawthorne effect (101), in which observation of adherence increased adherence.

In sum, in this setting, the interaction of monitoring and trust mattered to participants in two principal ways. First, in some instances, trust in individuals’ word mattered when the EAM and the individual reported different adherence rates. In these instances, perceptions of mistrust could result in harm to participant-researcher relationships. Second, participants saw trust as a valuable characteristic of their relationship with researchers and providers that arose from adhering to ARVs. EAMs, by reporting adherence, could therefore foster trust. Perceptions of mistrust were deleterious to the participant-researcher and patient-provider relationship, but this served as a strong motivation to adhere.

*Dependence*

Becoming dependent upon a medical device, particularly one that monitors and prompts interventions to change behavior, may result in decreased self-reliance (8, 9, 71). In terms of EAMs, this translates into developing reliance upon the device or interventions based upon it to adhere. Dependence is not necessarily harmful to individuals as long as they have access to the device, in the same way that becoming dependent upon a standard pill organizer is not intrinsically harmful. Dependence becomes problematic, however, when the tools upon which the individuals are dependent are removed. In UARTO, participants were monitored using EAMs for several years. In 2015 UARTO closed, shortly after our interviews concluded. Participants were allowed to keep the EAM devices to use as pill containers, a decision that was a response to theoretical and anecdotal concerns about dependence upon the device. However, the monitoring aspect of the study was removed. Removal of monitoring raised the possibility that participants’ adherence could be affected if they had become reliant upon the device or monitoring to take
their medications, despite the fact that prior to study closure, participants indicated (by signing a contract) that they understood that monitoring would no longer be provided. We sought to understand the extent to which participants felt dependent upon the study and on the device, with a particular emphasis on dependence to be adherent to ARVs, in anticipation of loss of monitoring (interviews were conducted before UARTO closed).

Did EAM users rely upon the device or monitoring to be adherent? Participants were split on this question, typically relating to their perceived intrinsic ability to adhere. Some participants reported that ingrained behaviors were responsible for their adherence, and device use had no impact on pill-taking behaviors. Others described feeling reliant upon the device to take their medications. One of the principle positive features of the device that participants referenced was that it served as an adherence reminder, whether through its physical presence or because it reminded participants that they were being monitored. Notably, both participants who claimed self-reliance and those who stated that they were reliant upon the device described these benefits; the chief difference between these two groups was the importance of these benefits in their ability to take medication as directed.

In cases when participants took medications out of a sense of obligation or order to please researchers, the shift in motivation from participant-driven factors to external incentives could represent a crowding out of intrinsic motivation to adhere, as some have argued with regard to financial incentives for adherence (102). In their influential discussion of intrinsic and extrinsic motivation, Ryan and Deci suggest that a mix of extrinsic and intrinsic factors motivates most actions (103), and this seemed to be the case with regard to adherence among this study’s participants. Development of dependence and loss of intrinsic motivation have largely been tied to loss of autonomy to act according to one’s own (intrinsic) values (71, 103). However, even though some participants expressed a sense of obligation to take medication, this was typically perceived as a benefit, and not a limitation on their ability to act as they chose. Thus, while dependence upon external pressure to adhere may represent some loss of intrinsic motivation, the negative practical effects of this once again only become relevant when this external pressure (i.e. monitoring) is taken away.

Do researchers have a responsibility to address dependence upon EAMs, particularly when studies close? On one hand, dependence arose as a side-effect of using the device—it was not researchers’ intention to motivate adherence with monitoring, or for the device to provide
benefits aside from simply recording users’ pill-taking behaviors. This may place some onus on researchers to address negative health effects of removing the device, as they would address other side effects resulting from the study (although this is a complex issue—see the discussion of ancillary care obligations, below).

On the other hand, a number of factors may mitigate researchers’ responsibilities to fully address dependence upon the device or monitoring. First, it is unclear if loss of extrinsic motivation upon which a participant is dependent actually translates into decreased adherence after the study concludes. Although this question is ripe for empiric study, it would be unreasonable to charge researchers with maintaining (now ex-) participants’ adherence ad infinitum without a clear sense of what loss of adherence the researchers are actually addressing. Second, building (or rebuilding) intrinsic motivation to be adherent when a source of extrinsic motivation is lost may be challenging. A number of studies aimed at building intrinsic motivation to adhere to ARVs in resource-limited settings, typically using text messages, have been carried out (32, 33, 104-106), but there remains equipoise as to the best ways to motivate adherence. Given the lack of a clear way to build intrinsic motivation, participants may simply become dependent upon any intervention meant to replace monitoring, leaving them to wait until this new source of motivation disappears as well. Third, although EAM users may become dependent upon the device to address internal (e.g. forgetfulness) or structural (e.g. lack of clean drug storage) barriers to adherence, this in effect represents an unintended benefit of study participation, rather than a true problem of dependence. Studies often impart small, unforeseen benefits to research subjects (for instance, relying upon an RA to schedule follow-up appointments with a clinician), which are not carried forward once the study ends or the participant graduates. Instead, it is typically the clinical and public health system’s responsibility to sustainably provide these benefits to all relevant individuals, rather than the researchers’ responsibility to provide them specifically for study participants. Finally, do researchers have a responsibility to ensure post-trial access to the device and monitoring in the same way that research participants receive post-trial access to ARVs? In the case of UARTO and most other observational EAM-based studies, this question is moot because the device and monitoring have not been shown to enhance participants’ adherence, nor were they evaluated to show this effect.

In sum, EAM users may become dependent upon the device to adhere and to bypass some barriers to adherence. While this may affect the balance of participants’ intrinsic versus
extrinsic motivation to adhere, dependence may be most problematic when EAMs are removed at the end of a study, because at that point it could have a negative effect on their adherence. A number of factors, ranging from resource-constraints to equipoise about the efficacy of potential interventions, mitigate researchers’ responsibility to address dependence. But sources of dependence noted in observational EAM studies like UARTO may provide fruitful ground for subsequent intervention-based studies and clinical and public health adherence interventions.

**Ancillary Care Obligations**

Richardson and Belsky have argued that researchers have a special obligation to provide ancillary care to research participants when researchers discover a need for care through research activities (74, 107). Two theories have evolved to determine the scope of this obligation. Richardson for the validity of a “partial entrustment model,” in which participants’ waiver of privacy rights when they sign informed consent translates into entrusting aspects of their care to researchers (74). In contrast, Dickert and Wendler argue that the complex and variable nature of participant-researcher relationships prevents use of systematic rules to determine ancillary care obligations (108). Both arguments hold that researchers have some responsibility to participants when health concerns are detected due to study procedures, and that the depth of researchers’ relationships with participants partly guides the scope of obligation to address these concerns.

Non-adherence was the principal potential health hazard that UARTO researchers would detect through the EAM, and we sought to understand participants’ expectations that researchers would address non-adherence (despite the explanation to participants, during the consenting process, that the study was observational in nature). Broadly, there was consensus among our study participants that researchers should and did provide adherence support to participants, even though this was not a deliberate objective of the study. Most participants viewed this as a core component of their RAs’ roles. This included both interventions when participants were non-adherent and general support to keep participants adherent. However, these findings do not necessarily equate to a justification that adherence support, in cases of EAM-detected low adherence, is an ancillary obligation of researchers.

One could argue that using EAMs to measure non-adherence results in some obligation to address dangerous levels of non-adherence. This obligation would arise because revelation of dangerous non-adherence occurs specifically in the context of a study procedure (i.e. EAM use). Most of our participants used an non-nucleoside reverse-transcriptase (NNRTI)-based ARV
regimen, according to World Health Organization and Uganda national HIV guidelines (109, 110), and recent research has shown that adherence rates of approximately 80% may be sufficient to achieve viral suppression (111, 112). Therefore, an obligation to intercede could arise when EAMs detect that an individual’s adherence dropped below this threshold.

However, as was the case for addressing dependence, a number of factors may limit researchers’ obligations and ability to intercede. First, by providing ancillary care whenever an EAM detects non-adherence, observational EAM-based studies designed to measure adherence would effectively be converted into intervention studies; intervening to improve a main study outcome (adherence rate) would disrupt the objectivity of the study. Second, as both Belsky/Richardson and Dickert/Wendler suggest, cost of providing ancillary care may be prohibitive, which limits obligations. Devoting precious study funds to provision of ancillary care, at least in the case of EAM-based research, may greatly impede researchers’ abilities to investigate their study aims. Sponsor-mandated requirements for provision of expensive ancillary care would likely reduce the overall number of studies that could be funded, and hence slow scientific advancement. Third, while original arguments for providing ancillary care rested upon the existence of an obvious, effective intervention to rectify a health hazard (e.g. providing ARVs to research participants found to have HIV in the course of study participation), no clear equivalent exists to address non-adherence. Although SMS messages in response to EAM-detected non-adherence show promise (32, 33, 104), are acceptable in many settings (1), and may be marginally inexpensive (113, 114), further research is needed to determine their clinical utility. Other interventions, such as home visits, are not only resource-intensive but may also be stigmatizing, intrusive, and threaten disclosure (18). Finally, providing adherence interventions to study participants but not to those who are not in the study raises a question of equity. Others have argued, in the context of post-trial access to ARVs, that considerations of justice and reciprocity provide some justification for prioritizing participants over non-participants in providing beneficial interventions (115). However, actual provision of these interventions is the responsibility of the health system, not of individual research studies. Otherwise, providing a focused public health intervention to improve ARV adherence only to study participants could provide undue inducement to participate in the study, particularly because such an intervention is not, to date, standard of care in any setting.
In sum, participants expressed an expectation that researchers would help them adhere to ARVs despite the fact that this support was not a stated goal of the study. However, while this suggests that participants may be receptive to adherence interventions, it does not translate into an obligation to provide such interventions. The obligation to responding to EAM-based non-adherence is tempered by a number of practical and theoretical challenges. Further research on EAM-based adherence interventions may improve the ability to address detected non-adherence, and may make provision of ancillary care more feasible, but not necessarily more obligatory, in EAM-based HIV adherence studies. Additionally, the expectation of adherence support argues for careful discussion about ancillary care obligations when enrolling participants into studies.

Emergent Ethical Considerations

Two main areas of consideration emerged from interviews that we had not specifically set out to investigate. First, participants reported a number of motivations to participate in the UARTO study (data not shown). Among these, hoping for a cure to HIV and receipt of social support from study participation stood out as key ethical considerations. We have described development of social support elsewhere (116), and limit discussion of these issues here because they relate more to the ethics of conducting observational trials generally, and less on particular implications of EAM use. Second, participants noted a number of reasons both to use and to not use EAMs, and described ways in which they preferred that the device be presented to them. We describe these considerations here.

Reasons for and against Use of EAMs, and for Opt-In versus Opt-Out

EAM-users described a range of what we term physical and relational reasons to use the device (Table 6). These reasons were unanticipated, and may be hard for researchers to predict prior to enrolling participants in studies using EAMs. Some of these reasons also underscore social benefits that may arise from the deployment of novel technology in resource-limited settings. In particular, the perception that the device could serve as a status symbol because it looked unique represents a benefit that may vary by study location, and also an unintended inducement to use the device. Participant-described reasons to use the devices raise two key ethical points. First, they highlight the potential for unintended benefits to sway individuals’ motivation for participating in an EAM-based study. Second, they highlight why EAM users may become dependent on the device or study. While specific responses to these reasons for
device use will vary by individual and setting, the emergence of unanticipated benefits argues for vigilance on the part of researchers.

Conversely, EAM non-users also described a range of physical and relational reasons to avoid use of the device, which suggest ways in which the device could be improved. While some of these reasons were specific to individuals (e.g. no longer taking ARVs), others provide generalizable lessons. For instance, several participants described how attention-grabbing features of the device, such as its blinking lights or unusual shape, could pique others’ curiosity and lead to tampering with the device or HIV status disclosure. Eliminating eye-catching features of the device, such as its light, could alleviate this concern, as would making the device resemble a common personal item, like a cell phone, even more than it already does.

In addition to asking participants why they chose to use or not to use the EAM, we asked about the way in which they thought the device should be deployed in clinical care, if at all. Specifically, we wanted to understand their attitudes towards opt-in versus opt-out use of the device and monitoring. Sunstein and Thaler, in advocating for “libertarian paternalism” to help individuals make the optimal choices, have argued that an “opt-out” approach to enrolling individuals in an intervention preserves their autonomy while simultaneously shaping choice architecture such that they will be “nudged” towards making the best choice (117). If EAM-based monitoring or intervention strategies are shown to be beneficial to adherence and are rolled out in clinical care, providers will face the question of how best to enroll patients in these intervention strategies. In our interviews, there was overwhelming support for an opt-in approach to EAM use. Participants and RAs strongly advocated for a process in which patients would be presented with information about their options and then would be asked to select to use or not use the device. These responses may have been biased by participants’ and researchers’ experience in a study, in which the study mandated that would-be participants undergo an informed consent process and then “opt-into” trial participation. Nevertheless, participants’ responses to the Autonomy Preferences Index (API), in which they expressed a preference for information seeking, are concordant with this general approach to opt-in device use following an information-obtaining process.
What ethical considerations are less relevant to EAM use according to HIV patients in rural Uganda?

Autonomy

Autonomy, broadly defined, is the ability “to live one's life according to reasons and motives that are taken as one's own and not the product of manipulative or distorting external forces” (118). We sought to understand the way EAMs affected individuals’ ability to pursue desired behavior or created a sense of obligation to be adherent to medication.

In general, participants expressed a preference for being well informed about medical decisions, but were willing to cede control over medical decisions to their providers, according to the API. Other studies have found similar results (strong preference for information, but limited preference for decision-making) using this scale in the developed world (85, 119, 120), although evidence from the developing world is lacking. These results provide corroborating evidence that participants were accepting of quasi-paternalistic provision of healthcare, likely augmented by the perceived status of physicians in rural Uganda, as well as the trust that participants felt towards both providers and researchers (according to the Trust in Physicians Scale).

Against this backdrop, we found that participants did feel a sense of obligation to take their medications because of monitoring, but this was rarely perceived negatively or as a sacrifice of freedom. Instead, even when monitoring induced adherence via mechanisms that were perceived as negative (e.g. avoiding a feared blood draw), the overall effect was seen as a benefit to the participant. Furthermore, most participants described the value of adherence, and saw monitoring as a way to overcome personal barriers to adherence (such as forgetfulness). Conly, in her descriptively-titled book Against Autonomy, argues that sacrificing some autonomy and accepting a degree paternalism may be beneficial to attaining one’s goals (121), and there was evidence that participants essentially endorsed this argument. For these participants, the freedom to be non-adherent was not perceived to be a freedom worth preserving in order to maintain autonomy; it was instead a “freedom” that participants were more than willing to sacrifice in order to be more adherent. Viewed another way, on the balance, monitoring can be seen as a way to improve autonomy—participants lost freedom to be non-adherent but gained freedom to achieve their goal of taking their medications as prescribed.

Even though threat to autonomy, in the ways that we examined it, did not emerge as an important concern for EAM use in this setting, this does not necessarily mean that it would not
be important in other contexts. Understanding local attitudes towards concepts like autonomy will be key for determining how best to deploy these devices in other settings.

**The Role of Empiric Data to Address Normative Ethical Issues**

Many of the ethical issues raised in the theoretical groundwork of this thesis are normative, but our methods were largely empiric. Philosophers have debated the role of empiric data to address normative questions (122, 123). Two so-called “meta-ethical fallacies” (124)—problems of using empiric results to define, support or refute normative theory—are particularly relevant to our study. First, the *is-ought* problem is typically understood to posit that an *ought* statement cannot arise from any number of purely *is* statements. In other words, statements about what *should be* done cannot arise solely from statements of what *is* done. Second, the “fact-value distinction” is most relevantly understood to imply that “science is value-free”, and that normative ethical discourse by definition lacks key features of scientific discourse (such as objectivity) that makes the two incompatible (124). Therefore, like the *is-ought* problem, the fact-value distinction implies that objectively-obtained scientific findings are fundamentally unable to define the contours of normative concepts.

We offer several responses that preserve the validity of our study. The *is-ought* problem poses a challenge for studies that are, on the face of it, purely descriptive, but that then attempt to convert these pure descriptions into normative conclusions. Although our results are descriptive, they seek to clarify—but not confirm or refute—hypotheses that are founded upon normative analysis. Our results suggest how and in what ways normative considerations may be practically taken into account when deploying EAMs, but they do not touch the underlying validity of these normative principles. For instance, whether or not autonomy is important in research studies is a normative question that we do not attempt to answer; in contrast, how individuals’ perceptions of autonomy interact with monitoring, and the resulting ways in which a researcher should approach autonomy questions when designing an EAM-based study, are questions that our results shed light upon. Similarly, in examining the ways in which normative considerations are practically relevant among our participants, we do not seek to fundamentally redefine the meaning of these normative considerations; attempting to redefine them would violate the fact-value distinction.

A central premise of this study was that our initial normative hypotheses might not have fully characterized the range of ethical considerations relevant to EAM use in the minds of HIV
patients in rural Uganda. Our research was therefore predicated upon the idea that cultural relativism is vital to understanding the ethics of technology use, and that empiric data can best inform an understanding of how cultural attitudes affect core ethical considerations. Some authors have argued against the merit of cultural relativism in determining guiding moral principles. Schafer-Landau, for instance, argues that cultural relativism opens the door for “all moral codes...[to be] morally equivalent”, therefore leaving no room “fundamental moral progress” (125). Our approach nevertheless remains valid for the same reasons that it holds up to the fact-value distinction: we do not seek to redefine ethical concepts using a culturally-based framework, or cast judgment upon rural Ugandans’ rights to autonomy, privacy, etc. Instead, our results identify what our participants find important about these concepts with regard to a specific health technology. Much of the extant writing about the ethics of EAM use has approached the topic from a decidedly Western vantage point. For example, this literature frequently hones in on the concept of “Big Brother”, a concept familiar to Americans but foreign to most rural Ugandans who have never read 1984 or experienced news-cycles dominated by discussion of government surveillance (this has lead others to advocate for a distinctive “African bioethics” that emphasizes the role of community and places less emphasis on concepts like individual autonomy (126)). Our results highlight the importance of understanding local attitudes towards considerations like privacy and autonomy when EAMs are used. While ideally local ethics review boards are able to provide site-specific insights during pre-approval study review, local review is not always possible and experience with the relevant issues may be limited. When local review is unavailable, it becomes incumbent upon researchers to determine what local attitudes may be problematic prior to device deployment.

Limitations

In addition to general limitations of qualitative study design and content analysis (89, 127), our study has several specific limitations. First, we did not interview participants who refused participation in UARTO, and we therefore missed interviewing participants with potentially unique attitudes surrounding EAM use and trial participation more generally. Second, participants were all drawn from a single site in Uganda, used (or had refused) a single type of device that was being used to study a single disease (HIV). Third, although efforts were made to make participants feel at ease during interviews and to convince them that their responses would have no impact on their medical care, there is a possibility that their responses were biased by
social desirability. Fourth, none of the quantitative scales we used to contextualize ethical considerations (e.g. the Autonomy Preferences Index) have been validated in this population, limiting our ability to draw discrete, quantitatively supported conclusions from participants’ scores.

**Implications and Recommendations for Further Research**

Our results, in combination with our initial normative analysis, outline key points that researchers, ethics committees and clinicians should consider when evaluating EAM-based studies or interventions. We present these as a series of practical questions to guide review and planning of future work (Table 7). We expect that future research into the ethical considerations surrounding EAM use in other settings will add to and modify these questions.

The following key categories may help to conceptually organize the different practical aspects of the ethics of EAM use:

1. **Device and monitoring characteristics** – What behaviors can the device reveal? What diseases is it used to study? To what extent does monitoring create an inducement to adhere?

2. **Population and setting characteristics** – How are different ethical considerations understood in individual settings/target populations, and how do they impact individuals’ day-to-day lives? What motivates these individuals to be monitored or participate in monitoring studies? How are healthcare providers and researchers perceived in these settings, to what extent are they trusted, and what relationships exist between EAM-users and researchers/providers?

3. **Study characteristics (may also pertain to clinical care)** – What types of support do monitoring studies provide to participants, whether intended or not? What plans are in place to address development of dependence upon the EAM/study procedures, and what resources are available to address health hazards revealed through monitoring or other study procedures?

Although our results are specific to EAM use among a certain Ugandan population, they nevertheless suggest broader lessons for use of technology in health research in resource-limited settings. First, they highlight the importance of understanding local cultural variation in reception of technologies. Siedner and colleagues have described the need for further research into predictors of technology acceptability in resource-limited settings (128). Although our study did
not specifically assess the acceptability of EAMs in Uganda, our results complement prior acceptability studies of this device by identifying factors that potentially contribute to acceptability, such as background attitudes about relationships with providers. Our results also indicate that research participants place substantial value in health technology given to them for research purposes, and that this technology can provide both instrumental (e.g. by improving adherence) and social (e.g. by serving as a status symbol) benefit. Participants’ lack of resources and the resource-limited milieu in which they live likely accentuate these attributed benefits. This in turn has practical implications in settings where expensive-looking or unusual technologies are likely to draw others’ curiosity, which we found to be one of participants’ principle concerns related to HIV status disclosure. It also suggests that allowing participants to keep devices at the conclusion of studies whenever possible may go a long way in engendering good will in these settings.

Second, our study raises issues of cost-effectiveness, sustainability, and resource-allocation when relatively expensive devices (Wisepill costs ~$175/device, and monitoring and interventions add to this price tag) are used in resource-limited settings. As described above, cost considerations are particularly relevant when considering dependence and ancillary care obligations, in that cost of interventions may directly influence the extent of researchers’ responsibilities to address these concerns. While we do not address issues of cost or cost effectiveness specifically, our results call for increased attention to cost-effectiveness and sustainability when technology is used in research in resource-limited settings (and resource-rich settings as well).

Several questions about the ethics of EAM use remain. A key premise of our study was that cultural factors and local attitudes matters when considering the ethics of using EAMs, and so additional research like ours is needed in other settings. Additionally, we only assessed EAM use in HIV research; although similar factors may be pertinent for EAM use for other conditions and in clinical care, these contexts deserve dedicated empiric study. Further empiric work could also shed light on the harms caused by some of the concerns that we described, such as the relationship between dependence upon an EAM/monitoring and long-term, post-trial adherence. A number of normative questions also deserve further study. We highlight the most important remaining normative questions here: What minimum privacy and confidentiality standards remain necessary, even—and perhaps particularly—when target populations are not highly
concerned about privacy and confidentiality? Does monitoring necessarily imply mistrust, even when those being monitored do not perceive mistrust? Should access to EAM-based interventions that improve adherence be considered a right, just like access to medications themselves? To what extent can and should pressure to be adherent due to monitoring be used as a clinical intervention? Rigorously assessing these questions will have implications for EAM use, and for monitoring in healthcare more broadly.
Summary

This study was the first, to our knowledge, to empirically analyze attitudes surrounding the ethics of EAM use. This empiric work built upon and was informed by a foundation of philosophical exploration. Putting the philosophic and empiric work together, we found privacy, confidentiality, trust, dependence, ancillary care obligations and reasons to participate in research studies to be key ethical considerations for EAM use among individuals taking ARVs in southwestern Uganda, while autonomy was not a major consideration. We believe these considerations and the associated nuances that we describe will help inform researchers, ethics review boards, and clinicians who plan to use and evaluate EAMs in research and in clinical care. To this end, we have summarized essential questions for consideration when designing or evaluating such research or clinical tools (Table 7). Answering these questions in the specific locations where EAMs are to be used would provide ideal guidance for individual settings. Our hope is that proactive consideration of these questions will avert potential downstream harms that EAMs could cause.
References


Tables and Figures

Table 1. Examples of EAM devices and the illnesses for which they have been used to study or treat.

<table>
<thead>
<tr>
<th>Electronic Adherence Monitor</th>
<th>Illnesses Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic medication containers</td>
<td>HIV (129), diabetes (26), cancer (130), hypertension (131), lupus (132)</td>
</tr>
<tr>
<td>Real-time electronic medication containers</td>
<td>HIV (24), tuberculosis (133)</td>
</tr>
<tr>
<td>Electronic blister packs</td>
<td>Post-transplant immunosuppression (70), hypertension (134)</td>
</tr>
<tr>
<td>Electronic braces</td>
<td>Scoliosis (135)</td>
</tr>
<tr>
<td>Electronic nebulizers</td>
<td>Smoking-related pulmonary disease (136), cystic fibrosis (137)</td>
</tr>
<tr>
<td>Electronic inhalers</td>
<td>Asthma (138)</td>
</tr>
<tr>
<td>Electronic continuous positive airway masks</td>
<td>Sleep apnea (139)</td>
</tr>
<tr>
<td>Electronic auto-injectors</td>
<td>Multiple sclerosis (140)</td>
</tr>
<tr>
<td>Monitoring-enabled vibration platforms</td>
<td>Osteoporosis (141)</td>
</tr>
<tr>
<td>Global positioning systems</td>
<td>Physical activity (142)</td>
</tr>
</tbody>
</table>
Table 2. Empiric questions related to EAM use.

<table>
<thead>
<tr>
<th>Ethics Domain</th>
<th>Empiric Questions</th>
</tr>
</thead>
</table>
| **Autonomy**          | • How do individuals express their preferences for autonomy?  
                        • Do EAMs or monitoring affect perceptions of autonomy?  
                        • Does monitoring create a sense of obligation to be adherent?  
                        • Does monitoring affect behaviors unrelated to adherence?  
                        • Does monitoring affect EAM users’ ability to pursue activities that they want to pursue, or cause them to undertake activities that otherwise they would not have?  
                        • How do key groups view opt-in versus opt-out use of EAMs in clinical care? |
| **Privacy and Confidentiality** | • How do local cultural attitudes affect perceptions of threats to privacy and confidentiality caused by EAMs?  
                        • Does EAM use reveal private, adherence-unrelated details of individuals’ lives to researchers?  
                        • Does EAM use reveal excess information about participants’ adherence to researchers, to the extent that participants are unable to hide their adherence?  
                        • Do EAMs threaten disease status disclosure?  
                        • Does electronic data collection or transfer threaten confidentiality? |
| **Trust**             | • Do EAMs imply mistrust of a patient’s word?  
                        • How does monitoring affect trust between participants and researchers?  
                        • To what extent is trust founded upon adherence?  
                        • How do perceptions of trust affect individuals’ relationships with researchers or providers? |
| **Dependence**        | • Do EAM users become dependent upon their device or monitoring to be adherent?  
                        • What effect would removing the device have on participants’ adherence and health?  
                        • What should be done with EAMs when research studies close? |
| **Ancillary Care Obligations** | • What needs for ancillary care arise in an EAM-based observational adherence monitoring study?  
                        • What expectations do study participants have for researchers to provide clinical care or respond to instances of non-adherence?  
                        • What capacity do researchers have to respond to EAM-detected non-adherence? |
Table 3. Demographic characteristics

<table>
<thead>
<tr>
<th>UARTO Participants</th>
<th>EAM Users (n = 40)</th>
<th>EAM Non-Users (n = 20)</th>
<th>p-value (difference between EAM users and non-users)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, [IQR])</td>
<td>41 [35-46]</td>
<td>45 [42-50]</td>
<td>0.03</td>
</tr>
<tr>
<td>Female (%)</td>
<td>70</td>
<td>65</td>
<td>0.77</td>
</tr>
<tr>
<td>Literate (%)</td>
<td>90</td>
<td>85</td>
<td>0.68</td>
</tr>
<tr>
<td>Education Level (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never attended school</td>
<td>4 [10]</td>
<td>2 [10]</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>23 [57.5]</td>
<td>11 [55]</td>
<td></td>
</tr>
<tr>
<td>O-Level*</td>
<td>9 [22.5]</td>
<td>3 [15]</td>
<td></td>
</tr>
<tr>
<td>A-Level*</td>
<td>1 [2.5]</td>
<td>3 [15]</td>
<td></td>
</tr>
<tr>
<td>Location of household (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large city</td>
<td>0 [0]</td>
<td>0 [0]</td>
<td></td>
</tr>
<tr>
<td>Town/Village</td>
<td>15 [37.5]</td>
<td>3 [15]</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>25 [62.5]</td>
<td>17 [85]</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earns a salary? (n [%])</td>
<td>8 [20%]</td>
<td>5 [25%]</td>
<td>0.74</td>
</tr>
<tr>
<td>Monthly salary (median [IQR]) (USD)†</td>
<td>$65 [$44 - $130]</td>
<td>$116 [$87 - $116]</td>
<td>0.42</td>
</tr>
<tr>
<td>Monthly non-salary income (median [IQR]) (USD)†</td>
<td>$12 [$4 - $36]</td>
<td>$63 [$24 - $81]</td>
<td>0.04</td>
</tr>
<tr>
<td>Monthly household expenditures (median [IQR]) (USD)†</td>
<td>$75 [$39 - $148]</td>
<td>$87 [$22 - $171]</td>
<td>0.67</td>
</tr>
</tbody>
</table>

UARTO RA’s

<table>
<thead>
<tr>
<th>n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, [IQR])</td>
</tr>
<tr>
<td>Female (n [%])</td>
</tr>
</tbody>
</table>

Ethics Community Members

<table>
<thead>
<tr>
<th>n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, [IQR])</td>
</tr>
<tr>
<td>Female (n [%])</td>
</tr>
</tbody>
</table>

Role (n [%])

- Data manager | 1 [16.7] |
- Administrator | 1 [16.7] |
- Clinician | 2 [33] |
- CAB Member | 2 [33] |

Member of an institutional review board? | 4 [66] |

* In the Uganda education system, A-Level is approximately equivalent to American high school. O-Level is two-year, post-secondary, pre-university schooling.
† Monetary conversion calculated at 1 US Dollar = 3445 Ugandan Shillings (as of January 12, 2015)
### Table 4. Quantitative survey results.

<table>
<thead>
<tr>
<th></th>
<th><strong>UARTO Participants</strong></th>
<th></th>
<th></th>
<th><strong>Research Community</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall (n = 60)</td>
<td>EAM Users (n = 40)</td>
<td>EAM Non-Users (n = 20)</td>
<td>p-value (EAM users vs. non-users)</td>
<td>Overall (n = 6)</td>
<td>UARTO RA’s (n = 6)</td>
<td>Ethics Community Members (n = 6)</td>
</tr>
<tr>
<td><strong>Autonomy (mean [SD])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trust (mean [SD])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stigma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalized Stigma (modified IARSS) (mean [SD])</td>
<td>1.22 [1.38]</td>
<td>1.15 [1.46]</td>
<td>1.35 [1.23]</td>
<td>0.40</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Externalized stigma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Told others about status (n [%])</td>
<td>58 [97%]</td>
<td>39 [98%]</td>
<td>19 [95%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Number told (mean [SD])</td>
<td>5.2 [2.0]</td>
<td>5.5 [1.8]</td>
<td>4.8 [2.3]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Qualitative number told? (n [%])</td>
<td>2 [4%]</td>
<td>1 [3%]</td>
<td>1 [5%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>No one</td>
<td>A few people</td>
<td>18 [30%]</td>
<td>12 [30%]</td>
<td>6 [30%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Half of the people</td>
<td>8 [13%]</td>
<td>4 [10%]</td>
<td>4 [20%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Most of the people</td>
<td>8 [13%]</td>
<td>6 [15%]</td>
<td>2 [10%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Everyone</td>
<td>24 [40%]</td>
<td>17 [42%]</td>
<td>7 [35%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Accepting attitudes scale (% with accepting attitudes)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Privacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Set</td>
<td>15 [25%]</td>
<td>13 [33%]</td>
<td>2 [10%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Positive</td>
<td>45 [75%]</td>
<td>27 [67%]</td>
<td>18 [90%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Antecedents to privacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>19 [32%]</td>
<td>10 [25%]</td>
<td>9 [45%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Motivational</td>
<td>0 [0%]</td>
<td>0 [0%]</td>
<td>0 [0%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Physical</td>
<td>35 [58%]</td>
<td>24 [60%]</td>
<td>11 [55%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Organismic</td>
<td>6 [10%]</td>
<td>6 [15%]</td>
<td>0 [0%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Other people in privacy experience</td>
<td>40 [66%]</td>
<td>25 [62%]</td>
<td>15 [75%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Never</td>
<td>18 [30%]</td>
<td>13 [32%]</td>
<td>5 [25%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rarely</td>
<td>1 [2%]</td>
<td>1 [3%]</td>
<td>0 [0%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>25-50% of the time</td>
<td>1 [2%]</td>
<td>1 [3%]</td>
<td>0 [0%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>More than 50% of the time</td>
<td>1 [2%]</td>
<td>1 [3%]</td>
<td>0 [0%]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Ability to achieve privacy when required?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Usually</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>1 [2%]</td>
<td>28 [47%]</td>
<td>21 [35%]</td>
<td>10 [16%]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 [33%]</td>
<td>15 [25%]</td>
<td>7 [11%]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 [10%]</td>
<td>3 [5%]</td>
</tr>
</tbody>
</table>

### Privacy after-effects

<table>
<thead>
<tr>
<th></th>
<th>More relaxed</th>
<th>Less emotional</th>
<th>Refreshed</th>
<th>Back to normal</th>
<th>Less relaxed</th>
<th>More emotional</th>
<th>More tired</th>
<th>The same</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>14 [23%]</td>
<td>7 [11%]</td>
<td>29 [49%]</td>
<td>7 [11%]</td>
<td>1 [2%]</td>
<td>0 [0%]</td>
<td>1 [2%]</td>
<td>1 [2%]</td>
</tr>
<tr>
<td></td>
<td>12 [30%]</td>
<td>6 [15%]</td>
<td>14 [35%]</td>
<td>6 [15%]</td>
<td>1 [3%]</td>
<td>0 [0%]</td>
<td>0 [0%]</td>
<td>1 [3%]</td>
</tr>
<tr>
<td></td>
<td>2 [10%]</td>
<td>1 [5%]</td>
<td>15 [75%]</td>
<td>1 [5%]</td>
<td>0 [0%]</td>
<td>0 [0%]</td>
<td>1 [5%]</td>
<td>0 [0%]</td>
</tr>
</tbody>
</table>

### Duration of privacy experience

<table>
<thead>
<tr>
<th></th>
<th>Less than 1/2 hour</th>
<th>1/2 - 1.5 hours</th>
<th>1.5-3 hours</th>
<th>&gt;3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>5 [8%]</td>
<td>31 [52%]</td>
<td>10 [17%]</td>
<td>14 [23%]</td>
</tr>
<tr>
<td></td>
<td>4 [10%]</td>
<td>23 [58%]</td>
<td>6 [15%]</td>
<td>7 [17%]</td>
</tr>
<tr>
<td></td>
<td>1 [5%]</td>
<td>8 [40%]</td>
<td>4 [20%]</td>
<td>7 [35%]</td>
</tr>
</tbody>
</table>

### Frequency of privacy need

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Frequently</th>
<th>All the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>1 [2%]</td>
<td>36 [60%]</td>
<td>6 [10%]</td>
<td>17 [28%]</td>
</tr>
<tr>
<td></td>
<td>1 [3%]</td>
<td>25 [42%]</td>
<td>3 [8%]</td>
<td>11 [27%]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 [55%]</td>
<td>3 [15%]</td>
<td>6 [30%]</td>
</tr>
</tbody>
</table>
### Table 5. Key qualitative findings.

<table>
<thead>
<tr>
<th>Ethical Domain</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| **Autonomy**              | • Autonomy transgression is not a major concern for EAM users or non-users.  
• Monitoring may lead to a sense of "obligation" to be adherent, but this obligation is typically perceived positively. |
| **Privacy**               | • Although ethics community members were concerned that the device could reveal more than intended, EAM users did not share this concern.  
• EAMs may reveal excess adherence information to providers.  
• Participants were occasionally reluctant to reveal adherence information to researchers. |
| **Confidentiality**       | • Although HIV was stigmatized in this community and many participants kept HIV status secret, disclosure could also help combat stigma.  
• EAMs protected HIV status from being disclosed by hiding ARVs.  
• EAMs threatened HIV status disclosure by looking unique or drawing attention.  
• Disclosure concerns were a driver of EAM non-use.  
• EAMs may facilitate wanted disclosure.  
• UARTO participation may lead to status disclosure. |
| **Trust and Relationships** | • Trust between participants and researchers/providers was highly valued in this setting.  
• Because of its value, participants were often willing to deceive clinicians and researchers to maintain trust.  
• Providers' and researchers' trust in participants was often founded in adherence.  
• Adherence monitoring may enhance trust by holding EAM users accountable, and letting researchers check on their adherence. |
| **Dependence**            | • Some EAM users describe becoming dependent upon the device to adhere to medication.  
• Ingrained adherence behaviors limit perceptions of dependence upon the device.  
• To address dependence, participants should be given ample warning before a monitoring study closes, according to the researcher ethics community. |
| **Ancillary Care Obligations** | • Most UARTO participants and researchers felt that it was the study's responsibility to address non-adherence for individual participants.  
• Research assistants were also expected to perform adherence-unrelated activities for participants, such as facilitating visits to clinic. |
| **Opt-in versus Opt-out** | • Most participants endorsed opt-in use of EAMs for clinical care.  
• The research ethics community concluded that mandatory EAM use would not be permissible |
<p>| <strong>EAM use in clinical care</strong> | • The research ethics community was accepting of ethical guidelines to guide EAM use in research, if these guidelines were acceptable and tailored to local contexts. |</p>
<table>
<thead>
<tr>
<th>Table 6. Reasons to and to not use EAMs.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reasons to Use EAMs</strong></td>
<td><strong>Representative Quotation</strong></td>
</tr>
<tr>
<td>Protects drugs from the environment</td>
<td>The device keeps well our drugs. It’s portable and the drugs inside are safe. (Male EAM user, age 38)</td>
</tr>
<tr>
<td>Protects drugs from other people</td>
<td>[The EAM] helps me because the way my husband is not HIV positive I would worry that he removed my drugs and threw them a way. But I know that he does not know how to open the device. You know at first they used to say that they are drugs for the pigs so I imagine that he would be inquisitive to open it and see exactly how these drugs look like. But now am convinced that this cannot happen because I told him that whatever he does here they will be watching him on the computer so he cannot touch it. (Female EAM user, age 46)</td>
</tr>
<tr>
<td>Helps organize drugs</td>
<td>You see it has two chambers: one has Septrine and another one has ARVs. They pack them for me properly. I do not even look at the manufacturer bottles. For me, I find my drugs packed well so when it’s time to swallow I just pick from each chamber. (Male EAM user, age 38)</td>
</tr>
<tr>
<td>Reminder to take medications</td>
<td>It keeps well my drugs and it reminds me to take my drugs. I: How does it remind you? R: When I look at it I remember to take my drugs. (Female EAM user, age 39)</td>
</tr>
<tr>
<td>Prevents disclosure</td>
<td>When you have such a bottle [the drug manufacturer’s bottle], someone can easily see it and know what you have because they have writings on them, but when you have the device no one can know. (Male EAM user, age 38)</td>
</tr>
<tr>
<td>Serves as a status symbol</td>
<td>One day it gave me a lot of prestige. I was at home. You see for me I have a funny father. He looked at it and said “wow, you have such a great phone”. So I opened to take my drugs and it showed the blinking light and he asked me that “surely is that a phone?” I told him that it’s not a phone. I told him that for me, I am the luckiest among all HIV patients because I have Wisepill. I explained to him how it works. I told him I can even go to church with it. (Female EAM user, age 43)</td>
</tr>
<tr>
<td><strong>Reasons to Not Use EAMs</strong></td>
<td></td>
</tr>
<tr>
<td>Disclosure</td>
<td></td>
</tr>
<tr>
<td>From the device</td>
<td>I refused to use it because the way they explained it I knew that it would draw attention from people especially when it lights when opened. (Male EAM non-user, age 52)</td>
</tr>
<tr>
<td>As a result of real-time monitoring</td>
<td>Imagine the nature of my job when I am there like loading cows on the truck and there you are calling me to find out why I did not take my medication on time. This may cause some kind of tension because remember I do not want my boss and my workmates to know that I have HIV. But with this one when my time to swallow comes I go somewhere, I remove my medicine, and I take it. Even if I delay like 10 minutes no problem no one will call me to find out why. (Male EAM non-user, age 52)</td>
</tr>
<tr>
<td>Device too delicate</td>
<td>Another thing is that I realized that it is so delicate when I saw it. I saw that it can fall down and get spoilt, so I decided to leave it and stay with my manufacturer’s bottle where I keep my drugs. (Male EAM non-user, age 47)</td>
</tr>
<tr>
<td>Stopped taking ART</td>
<td>I stopped taking the drugs so I did not need the device. That is why I brought it back. (Female EAM non-user, age 33)</td>
</tr>
<tr>
<td>Others opening/tampering with the device</td>
<td>That device first of all, I refused it because my children used to open it out of curiosity and whenever I came here they would say that I was opening it at odd times and I was disturbed so I decided to return it because it was causing me headache. Even I would go visiting and whenever I put my luggage in the guest room people begin to open the device secretly trying to find out what it is and again it caused problems when I came here so I decided to leave it so that I can have peace. Ever since I left the device now I have peace and I take my drugs well. So briefly that’s why I refused the device. (Female EAM non-user, age 48)</td>
</tr>
<tr>
<td>Not useful to the participant</td>
<td>There is no big reason why I did not use Wisepill. It’s just that I did not see its use. I realized that there was no big use for it and I would be better off without it. It was just going to add more weight in my bag for nothing so I refused it. (Female EAM non-user, age 41)</td>
</tr>
</tbody>
</table>
Table 7. Summary of key ethical principles and questions to guide EAM use.

<table>
<thead>
<tr>
<th>Key Ethical Domains</th>
<th>Underlying Principles</th>
<th>Intrinsic Considerations</th>
<th>Setting/Population Features</th>
<th>Device/Implementation Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Privacy</td>
<td>• Individuals have a right to control information about themselves, including information about their adherence.</td>
<td>• To what extent does informed consent address revelation of unanticipated information about participants or patients?</td>
<td>• Are participants concerned about revealing adherence information to researchers or providers?</td>
<td>• What type of information about participants is the device able to reveal?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• What types of information do individuals prefer to keep private from providers/researcher?</td>
<td>• What data security features exist to protect adherence information?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• What implications would revelation of adherence or other information via the device have on trust or relationships?</td>
<td></td>
</tr>
<tr>
<td>Confidentiality</td>
<td>• Individuals’ right to keep health information from people outside of patient-provider or participant-researcher relationships must be protected.</td>
<td>• Individuals may not be able to fully anticipate risks to confidentiality arising from device use.</td>
<td>• To what extent is the disease that EAMs are used to study stigmatized in the local setting?</td>
<td>• Does the device or study/clinical processes related to monitoring draw attention from others?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• What benefits does voluntary disclosure of health information to friends/neighbors/etc. provide to individuals?</td>
<td>• To what extent is the device associated with a specific disease process within a given community or locale?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• What harms in the individual’s daily life (e.g. relationship with spouse) would breach of confidentiality cause?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• To what extent do concerns about loss of confidentiality vary in the target population?</td>
<td></td>
</tr>
</tbody>
</table>
**Trust and Relationships**

- In monitoring of health, trust may be defined as confidence that individuals' will adhere to certain behaviors, in addition to belief that their words match their actions. Those being monitored may value the former definition as much as the (classical) latter definition.

- Trust may be a foundation of individuals' relationships with researchers or providers.

- Do potential device users trust researchers/providers at baseline?

- To what extent, if any, does monitoring imply mistrust for the target population?

- To what extent is the relationships between EAM-users and researchers/providers founded upon maintenance of optimal adherence?

- Will individuals attempt to deceive researchers/providers in order to maintain "trust"?

- To what extent does use of the device facilitate development of close relationships between users and researchers/providers (e.g. by inducing frequent contact, home visits, etc.)?

**Dependence**

- In a practical sense, dependence is harmful when interventions upon which individuals are dependent are removed.

- Researchers may have a responsibility to address dependence when it arises as a byproduct of study participation.

- What additional tools are locally available to individuals to assist with adherence, should the device no longer be available?

- What structural barriers to adherence exist within the target community? How does the EAM bypass them, if at all?

- What factors related to EAM use/monitoring provide inducement to adhere?

- To what extent is dependence based upon the device alone, versus the spectrum of activities related to monitoring/study participation/EAM-based clinical care?

- What plans/resources are in place to address dependence at the conclusion of research studies?

- To what extent does the EAM provide benefit beyond factors related to adherence (e.g. in protecting medications from contamination or detection)?
### Ancillary Care Obligations
- Researchers may have an obligation to provide care when need for it arises from study-related monitoring.
- While ancillary care obligations are founded upon normative arguments, individuals' expectations for ancillary care and risks associated with this care (e.g. disclosure) and costs may guide how it is provided.
- To what extent are individual instances or patterns of non-adherence considered a health risk?
- What costs would be associated with addressing dependence?
- What validated tools could be used to build intrinsic motivation to adhere?
- What kinds of health concerns or hazards does the device have the capability to detect and reveal?
- What interventions could effectively and feasibly address detection of dangerous non-adherence?
- How frequently do devices detect actionable health hazards, and what resources would be needed to address them?

### Autonomy
- Individuals have the freedom to make decisions about their behaviors, including how they take their medications.
- Individuals may not value the freedom to be non-adherent, and may willingly forfeit this freedom.
- Individuals may value an "obligation" to be adherent in order to motivate them to take medications.
- What aspects of autonomy do target users value, in terms of health behaviors and decision-making?
- To what extent is the obligation to adhere perceived negatively?
- To what extent can the device reveal actions that could be construed as "embarrassing" or "non-normative"? To what extent would this limit individuals' ability to pursue these actions?
- To what extent do EAM-based interventions aimed at improving adherence "force" individuals to take medications?

### Motivation to Participate in Study
- Study participation must be relevant
- Individuals often
- What motivates relevant
- To what extent is
<table>
<thead>
<tr>
<th>Research*</th>
<th>voluntary, and free from undue incentivization.</th>
<th>participate in research for reasons other than altruism.</th>
<th>individuals to participate in a research study?</th>
<th>To what extent does a longitudinal study provide a previously-nonexistent social support network for participants? What plans exist to address loss of benefits of this network when a study closes?</th>
<th>monitoring itself a motivation to participate in a study?</th>
<th>What benefits of a research study are intended?</th>
<th>What mechanisms exist to provide ongoing analysis of benefits that participants receive, and to examine whether they provide undue inducement to participate in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>When to use EAMs</td>
<td>Individuals with capacity should be allowed to make an informed, autonomous decision about using an EAM for clinical care.</td>
<td>Opt-in and opt-out enrollment strategies theoretically both preserve autonomy.</td>
<td>To what extent do participants accept paternalism in making healthcare decisions?</td>
<td>What amount of information do participants want and need about an intervention in order to be considered &quot;informed&quot;?</td>
<td>What inducements exist to advocate for widespread or universal use of the device within a target population?</td>
<td>What efficacy does the device/monitoring have on individuals' and communities' health?</td>
<td></td>
</tr>
</tbody>
</table>

*Data not specifically discussed in this thesis.*
Figure 1. The Wisepill device. (Source: Haberer AIDS Behavior 2010 (24))
Figure 2. Location of Mbarara, Uganda. (Source: Google Maps)
Figure 3. Schematic of hypothesis generation. Arrows indicate how hypotheses for each set of interviews were informed.