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**Update on Oral Medication Adherence Monitoring Technologies within U.S.**

**Clinical Research: A Systematic Literature Review**

By

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Executive Master of Public Health

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B.A., University of North Carolina at Chapel Hill, 2013

Thesis Committee Chair: Kelley Chester, DrPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Master of Public Health

In Executive Master of Public Health

2019

## **Abstract**

### **Update on Oral Medication Adherence Monitoring Technologies within U.S.**

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Medication adherence is defined as the extent to which a prescribed dose, frequency and timing of a medication are followed (Davidson, et al., 2015). Non-adherence can lead to disease progression, additional physician visits, longer hospital stays, and increased mortality (Wimbiscus, 2019). According to several studies, overall adherence estimates range from 17% to 80% with an average of around 50% (Wimbiscus, 2019). Within the clinical research setting, the efficacy and safety for investigational drugs are dependent on the medication adherence of clinical trial participants. Hence, medication nonadherence can skew results of clinical therapy trials (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013).

The factors contributing to poor medication adherence can be complex and multifactorial. Due to these varied barriers, there is a need to enhance adherence monitoring through more innovative, practical, personalized, and inexpensive technological approaches that capture oral medication adherence. Low adherence is often the broken link between new therapies and improved health outcomes (Vollmer, et al., 2014).

The best technological solution to accurately capture medication adherence has yet to be determined. This systematic review aims to survey recent tech solutions that alleviate medication nonadherence and presents their trade-offs in accuracy, acceptability, feasibility, efficacy, safety, and user authentication. While is no true “gold standard” for monitoring adherence, there are still many opportunities in future studies to explore effective strategies needed to capture adherence and improve compliance behaviors (Foster, Pai, Zhao, & Furth, 2014).

Key words/phrases: adherence; medication adherence; medication compliance

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# I. Introduction

## Introduction and Rationale

Medication Adherence (MA) as defined by the World Health Organization (WHO) is the extent to which the person's medication-taking behavior corresponds with agreed recommendations from a healthcare provider (World Health Organization, 2003). This definition includes the initiation of the treatment, implementation of the prescribed regime, and discontinuation of the medication. Conversely, medication non-adherence refers to the failure of taking medication as prescribed. Medication nonadherence is a huge threat to public health and is a leading problem in treating illnesses, as more than half of individuals with chronic diseases do not correctly take their medication as prescribed (Park, Collins, Shim, & Whooley, 2017).

The benefits of high adherence to prescribed medication are less health complications, more treatment benefit and effect, and helps minimize the drug wastage and reducing healthcare costs (Connor, 2004). Conversely, low adherence to drug therapy can cause increased morbidity, mortality, emergence of drug resistance, accelerated progression of disease, and enormous costs to the healthcare system (Lam & Fresco, 2015). Non-adherence is a complex phenomenon compounded by drug-taking barriers and behavioral factors that significantly affect a patients' compliance with a prescribed regimen. The ability of health care providers and caregivers to identify and quantify nonadherence has significant limitations (Kane, et al., 2013). There is a need to assess innovative device strategies currently available for capturing patients' adherence to oral medication regimen as a means to understand and mitigate the key drivers and predisposing factors for non-adherence.

Today there are a host of device strategies to measure adherence, these range from individual or cognitive-behavioral intervention to medication event monitoring systems (MEMS) to short message service (SMS) or email reminders (Kane, et al., 2013). With each method exhibiting its own benefits as well as limitations for capturing oral medication adherence

accurately. To date, there has been a lack of rigorous evaluation for technologic device methods within a clinical research setting, with most randomized controlled trials (RCTs) frequently relying on self-reported therapeutic compliance to measure medication adherence. In addition, there are few self-reported (e.g. direct questioning) adherence scales that have been tested for reliability and validity (Chisholm, Lance, Williamson, & Mulloy, 2015).

The clinical research arena provides a unique opportunity to assess the value and effectiveness of more technology-based adherence approaches versus the conventional strategies (like paper calendars, pillboxes, or blister packs) due to its controlled and fabricated study environment. Here enrolled subjects within a clinical trial are eligible for participation by satisfying protocol specified inclusion/exclusion criteria. These research subjects are meant to be reflective of the typical (real-world) patient for which these novel therapies will eventually be prescribed and marketed too. It is important to note that the real-world patients do not experience the commercially marketed drug in the same structured matter as an investigational trial subject, where the research team constantly reiterates drug accountability and compliance to subject(s) per the protocol. RCTs are useful in determining the effectiveness of an intervention. However, that does not guarantee the intervention will be implemented similarly (especially as it relates to medication adherence) in a real-world setting. This systematic literature review aims to provide a critical overview and to examine various technology-based adherence devices aimed to enhance oral medication adherence within clinical research.

### Problem Statement

In real-world poor adherence to treatment can lead to increased morbidity and increase the number of hospitalizations (Whiteley, Brown, Lally, Heck, & J, 2018). Nonadherence causes approximately 33% to 69% of medication-related hospitalizations and accounts for \$100 billion in annual health care costs (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Forgetting to take medications is one of the most commonly cited reasons for nonadherence (Buis, et al.,

2017). Luckily, treatment nonadherence is a major modifiable contributor to these poor patient outcomes and increased health care costs (Kane, et al., 2013).

Within the clinical research setting, poor adherence can skew the results of clinical therapy trials (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Nonadherence of clinical research participants can reduce the statistical significance of treatments under investigation and can affect the study validity by increasing the risk of false negative results (Hess, Raebel, Conner, & Malone, 2006). This can have significant ramifications on the efficacy and safety for investigational drugs seeking FDA approval as package labeling and prescription recommendations are dependent on the medication adherence of clinical trial participants.

### Purpose Statement

Given the current state of evidence, the review of evidence (attributes and limitations) from a subset of randomized controlled trials (RCTs) that utilized technology for at least one component of the intervention for accurately capturing medication adherence among research subjects will be examined.

### Research Questions

1. In comparison to conventional non-technologic approaches, will clinical trial subjects enrolled in RCTs experience significant improvements in oral medication adherence with the assistance of innovative oral medication adherence devices?
2. What are the benefits and limitations of currently available oral medication adherence devices that accurately capture medication self-administration?
3. Does medication adherence device strategies have the capability of informing better well-validated scales for assessing drug adherence beyond the scope of clinical trial subjects for real-world clinical practice?

## Significance Statement

Currently, the utilization of conventional (i.e. non-tech) MA approaches are susceptible to a high degree of missing data and inaccuracies (Buis, et al., 2017). Conversely, methods that are more accurate in capturing true MA tend to be cumbersome, costly, and not easily scalable (Kane, et al., 2013). Other conventional adherence tracking methods like prescription refill data and electronic monitors are still indirect and do not provide data on whether the patient actually took the medication (Kane, et al., 2013). As poor medication adherence to chronic and acute medical conditions continues to be problematic in clinical practice and clinical research. There is a need to promote and simplify oral medication adherence via more innovative devices that capture these endpoints of interest with accuracy and reliability. This examination of oral medication adherence device approaches within clinical trials aims to serve as a microcosm and provide inferences for successful compliance and adherence strategies within real-world clinical practice.

## Definition of terms

- Medication adherence (MA) is a medication-intake behavior that is defined as the extent to which a dose, frequency and timing of a medication are followed as prescribed (Davidson, et al., 2015).
- Medication nonadherence (MNA) is defined as the extent to which a dose, frequency and timing of a medication is not followed as prescribed. Meaning, medication non-adherence includes in-consistency, missing doses, and failing to re-fill a prescribed medication.
- Medication Event Monitoring Systems (MEMS) are technologic interventions that include the following smart pill bottles, smart pill organizers, blister pack devices, and home assistant pill dispensers.
- Ecological Assessment is defined as the monitoring and data collection of behavioral or biometric variables of interest.

- Heart Disease is used interchangeably with the term cardiovascular disease. Heart disease describes a range of conditions that affect the heart. In addition, to those that can lead to a heart attack, congestive heart failure, chest pain (angina) or stroke.
- Mobile Health (mHealth) for the purposes of this paper is defined as both text messaging and smartphone mobile apps.

## II. Review of the Literature

### Introduction

This report utilizes the WHO's 5 dimensions of medication adherence (condition, patient, therapy, health system, and socioeconomic) as a classification system for the factors driving nonadherence. In broader terms, the multifactorial causes of nonadherence outlined in this report are categorized as patient-related factors, physician-related factors, and health system/team-related factors (Brown & Bussell, 2011). To gain a better understanding of the barriers and facilitators to adherence of medication and treatment, we will examine some common factors that negatively impact oral medication adherence (i.e. non-adherence) according to the WHO's 5 dimensions of medication adherence. An in-depth literature review of the various indirect and direct monitoring technologies such as mHealth, medication event monitoring systems (MEMS), and mixed methods was conducted. These novel technologic approaches to improve non-adherence are outlined below.

### Medication Nonadherence

Types of medication nonadherence are broadly categorized as unintentional or intentional. Unintentional nonadherence involves intending to take a medication as instructed but failing to do so for some reason like forgetfulness or carelessness (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Unintentional nonadherence can be influenced by patient characteristics, treatment factors, and patient-provider issues (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013).

Conversely, intentional nonadherence involves making a decision to not take a medication as instructed based on perceptions, feelings, or beliefs (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Intentional nonadherence reflects a rational decision-making process by the patient. Where he/she weighs the benefits of treatment against any adverse effects of the treatment (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013).

There are several factors that can potentially influence (negative or positive) adherence for patients within research studies. Some factors associated with adherence include provider relations, side effects, forgetfulness (cognitive deficits and memory problems), beliefs about medication necessity, establishing routines for taking medication, social support, complex prescribed medication regimen, cost, and medication knowledge (Hale, Jethwani, Kandola, Saldana, & Kvedar, 2016). Choosing the “best” tech-based approach and measurement strategy to obtain an approximation of adherence behavior must take all these consideration into account (WHO, 2003). Most importantly, the strategies employed must meet basic requirements of acceptability, usability, feasibility, user authentication, safety, and accuracy.

### Disease-Specific Factors

Across all areas of medicine, medication nonadherence is identified as one of the major challenges in promoting public health (Kane, et al., 2013). Making the distinction between the types of condition, acute as opposed to chronic, and communicable (infectious) as opposed to non-communicable, diseases are critical in order to properly understand the type of care needed (World Health Organization, 2003). For instance, chronic conditions, such as HIV/AIDS or TB, may be infectious in origin but will require the same kind of care as many other chronic non-communicable diseases like hypertension, diabetes and depression. Depending on the disease or condition being addressed with the oral medication regimen might have a profound effect on medication adherence. Among research studies of patients with cancer, depression and negative expectations of results were also shown to have a negative relationship to adherence (Johnson,

2015). The following sections outline some disease-specific characteristics that contribute to medication nonadherence among populations.

### Patient-Related Factors

There are several patient-related factors that contribute to medication nonadherence in the United States. These factors include, but are not limited to a lack of understanding of their disease, lack of involvement in the treatment decision-making process, inadequate medical/health literacy, beliefs/attitudes concerning the effectiveness of the treatment, previous experiences with pharmacological therapies, lack of motivation, lack of family/social support are all predictive of nonadherence (Brown & Bussell, 2011). Therefore, there is an ongoing need to develop novel and engaging digital approaches that address these patient related factors of nonadherence (Whiteley, Brown, Lally, Heck, & J, 2018).

### Therapy-Related Factors

Physicians who prescribe complex drug regimens often fail to account for potential medication nonadherence (Brown & Bussell, 2011). The avoidance of prescribing numerous medications and behavioral modifications at one time would help prevent the patient from feeling overwhelm. In instances where it may be necessary to prescribe more than one drug or intervention during a given clinic encounter, providers should provide rationale that would encourage patients to inform their physicians of any plans to change medications and/or alter medication taking behavior (Brown & Bussell, 2011).

Adverse effects or side-effects have been known to be contributing factor for non-adherence, especially when it comes to oral anticancer drugs that have a number of immediate and long-term adverse effects like fatigue, mouth sores, and/or nausea (Wimbiscus, 2019). Among oral anticancer drugs, the influence of therapy related side effects were found to be predominant factors for significantly impacting medication non-adherence (Verbrugge et al., 2013).

## Health System & Team

The fragmented health care system has posed barriers to medication adherence by limiting the health care coordination and the patient's access to care (Brown & Bussell, 2011). The insurance and pharmacy bureaucracy can often discourage unnerved patients dealing with a diagnosis, often causing them to give up all together (Wimbiscus, 2019). Health information technology within the system is not widely available, preventing clinicians the necessary tools and information to properly assess and understand the individual's medication-taking behaviors (Brown & Bussell, 2011).

Within the health team, insufficient communication among physicians may contribute to medication nonadherence as correspondence between hospitalist and primary care physicians occurs in less than 20% of hospitalizations (Brown & Bussell, 2011). As a result, this inadequate communication contributes to medication errors and potentially avoidable hospital readmissions (Brown & Bussell, 2011). Conversely, substantially improved adherence of patients have been witnessed from patients who report a good relationship with their physician (Brown & Bussell, 2011). These multifactorial failures are present at every point along the supply chain within the healthcare system. Hence, we cannot underestimate the importance of the role of the physicians in the medication adherence equation.

## Socioeconomic Factors

The cost of treatment in the United States can be quite expensive. As a result, insurance and financial concerns can be quite overwhelming for some patients having to juggle their insurance plan's co-pay structure and out-of-pocket limits (Wimbiscus, 2019). Hence, these socioeconomic pressures can drive some patients to non-adherence like deciding to take one pill every other day or every third, or even cut the pills in half (Wimbiscus, 2019).



## Adherence Monitoring Approaches

Various technology-enabled devices and systems have emerged to address MNA. Patient medication adherence can be assessed with direct and/or indirect measures. Examples include drug assays or markers, self-report, pill counts, electronic monitoring systems, and review of pharmacy records or administrative data (Hess, Raebel, Conner, & Malone, 2006). Many measures and methods have been used to assess/evaluate adherence with the focus on the accuracy of patient medication adherence, yet no gold standard measure has been applied (Hess, Raebel, Conner, & Malone, 2006).

There are numerous methods for measuring adherence and no single method performs well on all criteria. Appropriate adherence tools can be characterized into two main categories, subjective and objective measures (Lam & Fresco, 2015). Objective (or direct measures) involve secondary database analysis, electronic medication packaging devices, pill count, clinician assessments and self-report.

### Indirect Monitoring

Indirect monitoring for medication adherence provides subjective measures that generally provide explanations for the patient's nonadherence. These methods are typically targeted at improving a patient's adherence as a medication taking behavior. Characteristics of these approaches are automated medication reminders tailored to treatment schedule, provides real-time information about medication adherence, can utilize assessments to provide periodic assessment of medication side effects, and can provide tailored education, recommendations, and encouragement based on adherence and ecological assessment data (Himmelhoch, et al., 2017).

Indirect monitoring can also use these administrative data sets all assume that all medication obtained is consumed by the patient. As a result, this provides an overestimation of actual adherence and only provides a value of the medication obtained by the participant (Hess,

Raebel, Conner, & Malone, 2006). Indirect monitoring devices (trays, vials and phone apps) provide pill intake reminders like a blinking light, buzzer, and/or SMS (Davidson, et al., 2015).

### *mHealth*

Mobile health (mHealth) strategies delivered via smartphones that integrate text message reminders and mobile phone apps are a low-cost and effective web-based way to improve oral medication adherence. The application of this wireless technology to healthcare is a rapidly-growing field in preventative medicine and chronic disease management (Davidson, et al., 2015). This tech strategy has the potential to address nonadherence by providing reminders for medication taking and refilling, tracking biometric results, offering education, and facilitating social interactions that provide support and motivation (Morawski, et al., 2018).

Cell phone use is widespread, with text messaging even more common (Buis, et al., 2017). The availability of smartphone health apps has expanded quickly. From 2012 to 2015 (just 3 years) there has been a 515% increase in adherence apps available for download, with an estimated 107 apps currently available for hypertension alone (Morawski, et al., 2018). Hence, these type of adherence interventions possess high acceptability, feasibility, ease of use, are easily scalable, low-cost, and clinically promising (Ben-Zeev, et al., 2016; Whiteley, Brown, Lally, Heck, & J, 2018). Mobile phone-based monitoring is an attractive option due to their ubiquity, connectivity, computational power, and portability (McGillicuddy, et al., 2013). Adolescents and young adults aged 18-29 years have high rates of mobile phone use with 98% owning a smartphone (Whiteley, Brown, Lally, Heck, & J, 2018).

Not all mHealth interventions are created equal. As smartphone devices with programmable apps offer more opportunities for innovative interactive strategies for improving adherence beyond the use of text messages alone (Himmelhoch, et al., 2017). There is an increasing number of mobile phone apps available to support people in taking oral medications and improve

medication adherence. However, little is known about how these mobile apps differ in terms of features, quality, and effectiveness (Santo et al., 2016).

### Direct Monitoring

Adherence monitoring should be performed routinely to ensure therapeutic efficacy, avoid unnecessary dose and regimen changes, contain health care costs, and prevent resistance to therapy from developing (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). These type of measures document a more precise record of a patient's medication-taking behavior.

Prescription refill histories are an indirect method of measuring medication adherence as it examines the proportion of days covered (PDC) that is defined from pharmacy dispensing records (Vollmer, et al., 2014).

Adopting more innovative and technological approaches to adherence monitoring comes with perceived barriers to like initiation obstacles, knowledge barriers, and privacy and security issues (Haun, et al., 2014).

Medication adherence (or compliance) is measured by a variety of methods, with no one method of adherence reigning superior in all aspects to another method (Chisholm, Lance, Williamson, & Mulloy, 2015).

Among various medication adherence improve methods like patient self-reports, pill counts, biological monitoring, refill rates, and electronic monitoring (MEMS), there are limitations that exist for these methods can only approximate adherence measures. Patient self-reports rely on memory and are prone to inaccuracies and recall bias (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Pill counts can be unreliable as noncompliant subjects can fail to return bottles or dump pills before to a accountability count (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Biological monitoring (blood or urine samples) are either impractical, invasive, or intrusive and does not measure adherence unless the time and dose administered before sampling is verified (Dayer, Heldenbrand, Anderson, Gubbins, & Martin,

2013). Refill rates and MEMS monitoring cannot determine whether patients have actually taken the medication (Table 1). For instance, with a MEMS the process of cap removal from a smart pill bottle does not necessarily reflect dose ingestion (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013).

*Table 1: Limitations of Conventional Medication Adherence Capture Methods*

Conventional MA Methods	Limitations
Patient self-reports	Rely on memory and are prone to inaccuracies and recall bias
Pill Counts	Can be unreliable as noncompliant subjects can fail to return bottles or dump pills before to an accountability count
Biological monitoring	Are either impractical, invasive, or intrusive and does not measure adherence unless the time and dose administered before sampling is verified
Pharmacy refill rates	Cannot determine whether patients have actually taken the medication

### *Medication Event Monitoring Systems (MEMS)*

Medication event monitoring systems (MEMS) also referred to as Electronic Medication Packaging (EMP) devices are considered to be the “gold-standard” test of reliability for medication-event monitoring. The MEMS integrates a small microcircuit into a lid for a medication vial, which records the time and date whenever the lid is opened (Stoner, Arenella, & Hendershot, 2015). MEMS monitors are capable of storing up to 3800 medication events (Stoner, Arenella, & Hendershot, 2015). In addition, over 700 peer-reviewed publications have used MEMS to compile drug dosing histories and assess compliance in patients within various clinical settings (Stoner, Arenella, & Hendershot, 2015). Companies developing smart pill boxes, bottles, and caps that alert patients and other stakeholders when doses are missed. May sometimes compete with a pharmacy’s blister pack product (mobihealthnews.com).

Wireless-enabled pill bottles (Appendix 3) have created the opportunity to monitor medication adherence in real-time (Reese, et al., 2017). This new technology measure adherence

and facilitates automated communication that allows remote monitoring for large populations at reasonable cost while providing encouragement (Volpp, et al., 2017).

Automatic pill dispensers and smart pill organizers, such as the Maya MedMinder® (Appendix 2) often incorporate a remote monitoring component (via mobile health technology) that facilitates patient-provider communication, increases adherence to medical regimens, optimizes control of medical conditions, improves health outcomes, and reduces costs in some chronic illnesses (McGillicuddy, et al., 2013). These personnel-based services are often available with an associated service fee. For instance, the MedMinder® device cost \$45 per month that would prove prohibitive to a large fraction of a target population (McGillicuddy, et al., 2013). Smart pill organizers (like the MedMinder® device) have mechanisms to document medication adherence in real-time. This capacity provides timely reinforcement and motivational feedback based on adherence levels.

Medication delivery units (MDU), such as EMMA® (Appendix 6) delivers medications from single-dose blister cards according to schedules programmed remotely by prescribing pharmacies. The blister cards containing 30 wells are inserted via a loading tray in the front of the device and the user interacts with a touchscreen interface to dispense medication (Ligons, Mello-Thoms, Handler, Romagnoli, & Hochheiser, 2014).

MEMS caps have no mechanism to intervene in real time as the adherence data is only available after being downloaded during an onsite visit (McGillicuddy, et al., 2013).

MEMS are useful for calculating adherence rates for dose taking and dose timing and often are viewed as the best method to measure adherence (Dayer, Heldenbrand, Anderson, Gubbins, & Martin, 2013). Clinical studies utilizing electronic medication packaging devices (i.e. electronic pillboxes) suggest that the mean adherence to medication are higher than the gold standard of a good adherence level cut-off point.

### *Ingestible Biosensors*

ID-Cap system is a technological capture approach that provides an objective measure of medication ingestion and report verified medication adherence data at the dose level in real-time (Flores, et al., 2016). This system is classified as an ingestible event monitoring system as it has the capability to detect the presence of an ingested solid oral dosage from inside the gastrointestinal (GI) tract (Flores, et al., 2016). An ID-Cap system consists of an ingestible microsensor that is embedded in an oral dosage form that communicates digital messages to an external wearable reader to confirm ingestion once the sensor is activated by stomach fluid (Flores, et al., 2016). Adherence data (timestamp of ingestion) is then transmitted to a secure, centralized database via a mobile phone network.

DHFS provides a reliable and not overly intrusive means of assessing medication-taking and patient adherence status in real-time (Kane, et al., 2013). Further studies are needed to evaluate the usability of the system with respects to specific patient populations, clinical applications and outcomes, economics of therapeutic interventions, clinical trials, and potential complementation of existing strategies (Flores, et al., 2016).

### *Vision-Based Systems*

Directly observed treatment ensures adherence but is not feasible or cost-efficient for large scale and real-world implementation (Himmelhoch, et al., 2017). Vision-based systems as a tech-based approach for oral medication adherence is based in computer vision and image processing research. This approach monitors medication intake via vision modules for identifying and tracking inhabitants, motion, gestures, and subjects. The aim of this system is track if the right medication is being taken by the correct user. Several of these approaches have utilize various algorithms for skin color distinction/classification in order to distinguish between skin and non-skin colors. Detection and tracking techniques focus on hand/face (hand over mouth) occlusions and hand/hand (bottle twisting) occlusions (Appendix 5).

VOT has great potential with advancing computer technology and new features, such as facial recognition capabilities, for reducing scalable barriers of time and resources needed to monitor patients remotely (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014). Mobile DOT has great scalable potential to large populations since the cost for patients to use this strategy is minimal (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014). Lastly, since mobile DOT targets multiple barriers, it may be a successful approach for a wide age range (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014).

### *Mixed Methods*

Measuring adherence alone or simply reminding patients about oral dosing does not significantly improve adherence in the long-term (Whiteley, Brown, Lally, Heck, & J, 2018). Some adherence interventions may employ a mixed methods approach by combining some form of supportive adherence correspondence (i.e. provider communication) and/or external behavioral influencer beyond the integrated device. Adherence counseling emphasizes patient education, self-monitoring, direct patient feedback, and individualized problem-solving (Kalichman, et al., 2016).

By incorporating various technological methods (like mobile apps, wearable sensors, and MEMS device) has the capability for improving and capturing real-time medication adherence accompanied with personalized feedback to help motivate patient self-efficacy, automated summary reports, and biometrics of interest (like blood pressure) that can easily be uploaded to provider networks (McGillicuddy, et al., 2013).

It is not uncommon to witness mixed methods in today's RCTs that incorporate conventional and mHealth approaches to assess oral medication adherence. For instance, many studies in this review measured adherence using unannounced pill counts assessed via a phone call combined with self-report as measured by a smartphone application. In addition, several reviews document that utilizing mobile phone technology (primarily involving SMS) has shown

to be effective in improving medication adherence for a number of medication conditions (e.g. diabetes, asthma, HIV, obesity, psychiatric) (Kreyenbuhl, et al., 2019).

### Summary of current problem and study relevance

As poor medication adherence to chronic and acute medical conditions continues to be problematic in clinical practice and clinical research. There is a need to promote and simplify oral medication adherence via more innovative devices that capture these endpoints of interest with accuracy and reliability. This examination of oral medication adherence device approaches within clinical trials aims to serve as a microcosm and provide inferences for successful compliance and adherence strategies within real-world clinical practice.



Table 2: Summary of Oral Medication Adherence Device Methods

Technology Approaches	MA Improve or Capture	Advantages	Disadvantages
Mobile Health (mHealth) – short message service (SMS) and/or mobile applications (smartphone apps)	Improve intervention	<ul style="list-style-type: none"> <li>• Low-cost (cost-efficient)</li> <li>• Intuitive interface (acceptability)</li> <li>• Ubiquity</li> <li>• Connectivity</li> <li>• Computational power</li> <li>• Portability</li> <li>• Scalable (availability)</li> </ul>	<ul style="list-style-type: none"> <li>• Simple text messages (SMS) and app-based functions; have not been leveraged by pharmacies to improve patient outcomes</li> <li>• Accessibility (only available to individuals with smartphones)</li> <li>• Reminders lose efficacy over time (alarm fatigue), whereas the influence of provider notification is more enduring</li> </ul>
Smart Pill Organizers	Capture intervention	<ul style="list-style-type: none"> <li>• Electronic pill box</li> <li>• Monitor medication adherence in real-time</li> <li>• Innovative cameras/sensors to monitor the contents of each medication bin enables remote monitoring center to follow-up with patients</li> </ul>	<ul style="list-style-type: none"> <li>• Limited and inconsistent data supporting the effectiveness of these devices</li> <li>• Cost may be prohibitive for wide-scale application</li> <li>• Monthly subscription (~\$45 per month) for remote monitoring services</li> <li>• Size of a small microwave oven; “too bulky”</li> <li>• The process of removing medication from the tray does not necessarily reflect dose ingestion</li> </ul>
Smart Pill Bottles	Capture intervention	<ul style="list-style-type: none"> <li>• Low-cost (cost-efficient)</li> <li>• Low-resource</li> <li>• Easily scalable</li> </ul>	<ul style="list-style-type: none"> <li>• Limited data about their ability to improve the quality of medication in various therapeutic areas especially in real-world naturalistic settings</li> <li>• The process of cap removal does not necessarily reflect dose ingestion</li> <li>• no real-time monitoring – adherence data is only available after being downloaded at time of onsite visits</li> </ul>

Bio-ingestible Sensors	Capture intervention	<ul style="list-style-type: none"> <li>• Monitor medication adherence in real-time</li> <li>• Accurate measurement of medication adherence for oral drug therapy at the dose level (high detection accuracy; high user authentication)</li> </ul>	<ul style="list-style-type: none"> <li>• Limited reader battery life</li> <li>• Durability of the reader when dropped or exposed to fluids</li> <li>• Design elements that impact patient acceptability and use (e.g., an adhesive patch on the skin – skin irritation)</li> </ul>
Virtually Observed Therapy (VOT)	Capture intervention	<ul style="list-style-type: none"> <li>• Scalable (mHealth components)</li> <li>• Monitor medication adherence in real-time</li> <li>• Patients submit videos electronically from mobile device to the secure study website (non-intrusive)</li> <li>• Video observation provides an accurate assessment of adherence (high user authentication)</li> </ul>	<ul style="list-style-type: none"> <li>• Patient must own a mobile phone with video recording capabilities</li> <li>• Remote monitoring (personnel intensive)</li> </ul>
Home Assistant Pill Dispenser	Capture intervention	<ul style="list-style-type: none"> <li>• Monitor medication adherence in real-time</li> <li>• Combination of an electronic medication management, reminder, and telemedicine monitoring system</li> </ul>	<ul style="list-style-type: none"> <li>• This technology presents significant usability challenges (particularly for the cognitively impaired)</li> <li>• The process of removing medication from the tray does not necessarily reflect dose ingestion</li> </ul>
Mixed methods	Improve and/or capture intervention	<ul style="list-style-type: none"> <li>• Social support</li> <li>• Mechanical reminder system</li> <li>• Targeted education</li> </ul>	<ul style="list-style-type: none"> <li>• Patient facing tech and machine learning and distributed computing</li> </ul>

Table 2 (Continued)

### III. Methodology: Data Collection and Analysis

#### Introduction

Given the current state of evidence, the review of evidence (attributes and limitations) from a subset of randomized controlled trials (RCTs) that utilized technology for at least one component of the intervention for accurately capturing medication adherence among research subjects will be examined.

It was hypothesized that technology-based medication adherence monitoring methods are more effective than conventional practices in accurately capturing oral medication adherence among randomized clinical trial (RCT) participants. These qualifying RCTs were identified via ClinicalTrials.gov (CT.gov). CT.gov is a publicly accessible descriptive registration database of clinical trials as required by U.S. law (available on <http://www.clinicaltrials.gov>). In addition to providing study characteristics (study description, study design, arms and interventions, outcome measures, and eligibility criteria) this web-based database also includes a summary of the study results (if available) and does not include patient identifying information. This systematic review surveys the findings of eleven (n=11) identified publications that examined medication adherence capture mechanisms and presents their technologic attributes and limitations.

#### Literature Search Methodology

This systematic review entailed three rounds of exclusionary implementation prior to the resulting five qualified RCTs. Initially, I queried ClinicalTrials.gov (a registry of clinical trials) on 29-Mar-2019 for qualifying RCTs using a combination of the following selected search field parameters within the *Advanced Search* feature of the *Find Studies* webpage of CT.gov: conducted in the U.S.A. (selected “United States” for CT.gov locations/country), classified as Interventional studies (Clinical Trials), within the specified time parameters (RCT opened on or after 01/01/2010 to 01/01/2019), and with *medication adherence* or *medication compliance* entered for the specific condition or disease. This CT.gov query was ran twice, once with *medication adherence* as the condition or disease name and again with the search

term *medication compliance* as the condition or disease name. This resulted in a total of records four hundred and fifty-three records identified (n=453). Duplicate CT.gov clinical trials records were excluded (n=205).

The first round of exclusionary implementation was based on review of CT.gov study title and abstract/summary. Manual sorting of the 248 retrieved records was conducted to exclude records that did not include: results reported on a technologic medication adherence intervention(s) as the primary outcome (n=148) or a technologic medication intervention related to oral medication (n=25).

The second round of exclusionary implementation was based on successfully locating accompanying peer-reviewed journal articles for the identified RCTs. For the qualifying clinical trials that did not have a publication linked in the CT.gov registered record, I subsequently searched PubMed and Cochrane Library from 10-Apr-2019 to 10-May-2019 for English language publications (full-text only and not abstracts) related to the identified clinical trial records (via CT.gov), using combinations of keywords from the CT.gov abstract/summary, principal investigator/co-investigator(s), and sponsors/coordinating site(s) (if applicable). Of the qualifying RCTs examining technologic oral medication adherence approaches within the specified time parameters (n=75), this publication query yielded 29 articles for full-article review.

The third round of exclusionary implementation was based on a full-text comparison review of the RCT interventional approach and the systematic review inclusion criteria. As a result, the remaining publications were excluded that did not include: access to full publication text (n=1), a fully executed RCT beyond prototype feasibility study (n=1), and a technologic approach aimed to accurately capture oral medication adherence across any specified disease group or demographic (n=16). Of the 29 articles extracted, eleven (n=11) articles reporting on six interventions met inclusion criteria and were included in this in-depth systematic review (Figure 1).

## Data Extraction and Quality Assurance

Beyond study characteristics (author names, title, date of publication, journal) and intervention characteristics (type of MA intervention device, disease/condition of treatment), the resulting systematic review articles (n=11) were carefully reviewed for six adherence measures of interest (accuracy, acceptability/participant satisfaction, feasibility, usability, safety, and user authentication). Subsequently, these adherence measures were assessed based on the systematic review data extraction codebook (Appendix A). Quality assurance was guaranteed via double data entry. The resulting systematic review articles (n=11) were extracted twice to ensure reliability.

## Analysis Plan

Of 11 randomized controlled trials (RCTs) directed at capturing medication adherence among recipients of oral medication regimens across an array of different medical conditions, only 81.8% (9/11) of the reviews concluded that their respective approach would be appropriate for the originally proposed aims. This relevant data from the eligible studies were collected in a Microsoft Excel spreadsheet. All outcome data was verified.

For articles that actually reported on any of the adherence measures of interest (accuracy, acceptability/participant satisfaction, feasibility, usability, safety, and user authentication), the respective articles were coded appropriately to align with the evidence and assessments by the article author(s). Subsequently, for review articles that did not report on one or more of the adherence measures of interest then these were coded based on the most appropriate category that supported the coding scale case definitions (Appendix A).

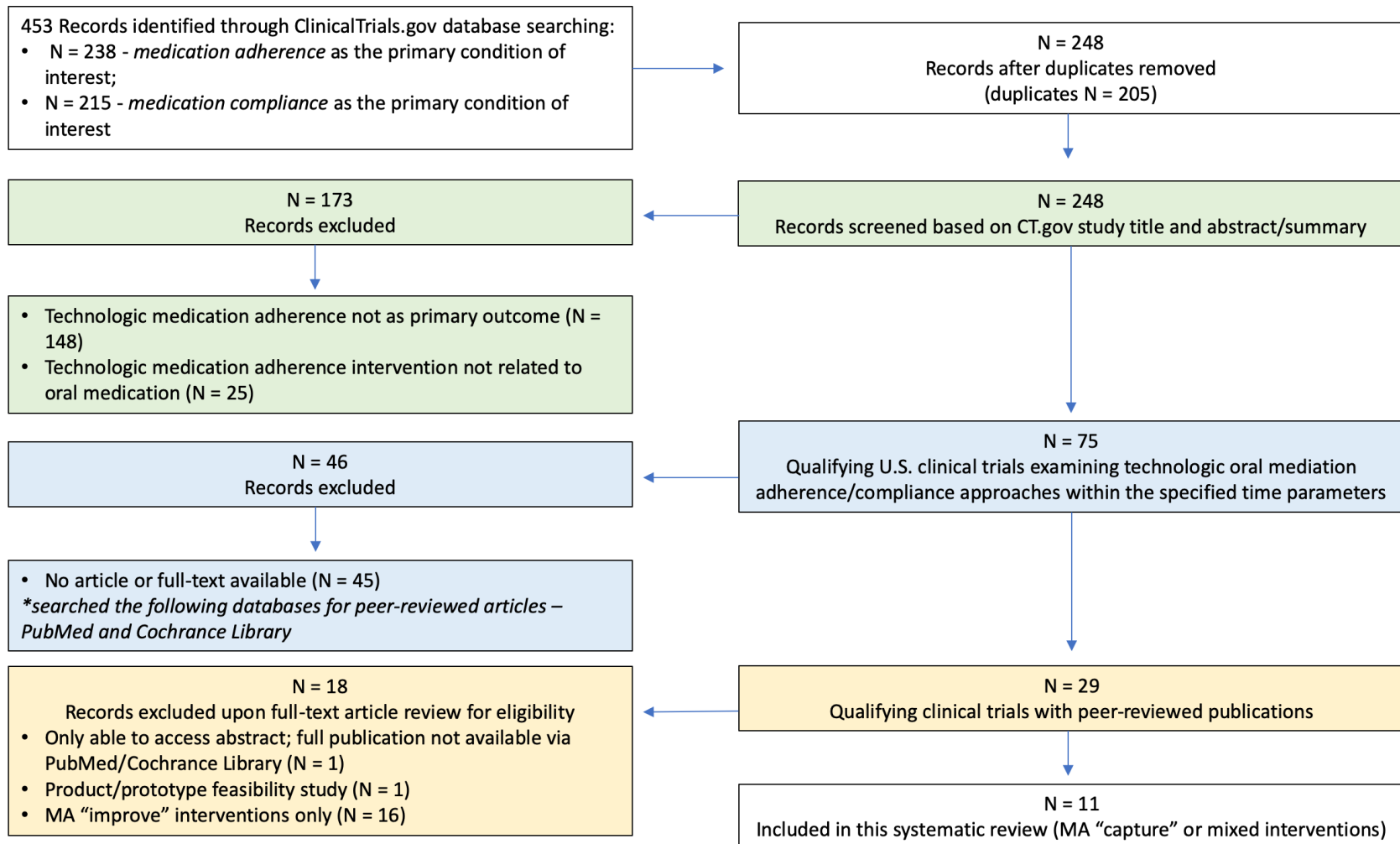


Figure 1: Flow diagram of the study selection process

This flow diagram represents the number of records identified, screened, included and excluded during the study selection process. A literature search was conducted in Pudmed and Cochrance Library databases up until 10-May-2019.

## IV. Results

### Introduction

An analysis of 11 studies, reporting 6 different intervention approaches, shows that technologic medication adherence devices can vary greatly. A descriptive overview of the peer reviewed articles (n=11) selected for data extraction are as follows (Table 3).

### Study Characteristics

The one smart pill organizer intervention, by Hale et al. describes a randomized controlled pilot study for the MedSentry® MEMS. This study included 25 participants living with chronic heart failure in the United States who were either randomized to standard of care (SOC) or use of the remote medication monitoring system for 90 days. The study aim was to determine whether remote medication monitoring would be associated with fewer unplanned hospitalization and emergency department (ED) visits, increased medication adherence, and improved HRQoL compared to SOC (Hale, Jethwani, Kandola, Saldana, & Kvedar, 2016). The study results support smart pill organizers as a promising medication monitoring technology system. Reporting that MEMS monitoring was associated with an 80% reduction in the risk of all-cause hospitalization and a significant decrease in the number hospitalization in the intervention arm compared to the SOC arm (Table 3).

The one smart pill botte intervention, by Volpp et al. describes a randomized 2:1 clinical trial with a 12-month intervention using electronic pill bottles (Vitality GlowCaps®) or SOC. This study included 1509 participants who were currently prescribed at least 2 to 4 study medications (statin, aspirin, b-blocker, antiplatelet agent) for a recent (1-180 days) acute myocardial infarction. The study aim was to determine whether a system of medication reminders delays subsequent vascular events in patient following an acute myocardial infarction compared with SOC. The study results did support any significant improvement of medication adherence or vascular readmission outcomes for acute myocardial infarction survivors (Table 3).

The one virtually observed therapy (VOT) intervention, by Creary et al. describes a pilot study for an innovative electronic directly observed therapy (DOT) approach. This study included 15 participants who children with sickle-cell disease, had been prescribed hydroxyurea for  $\geq 6$  months, and had daily access to a smartphone or computer. The study aim was to determine if electronic directly observed therapy or VOT was feasible, acceptable, and could achieve  $\geq 90\%$  hydroxyurea adherence. The study results reports an overall median observed hydroxyurea adherence of 93.3% with electronic DOT (Table 3). This study illustrated the merits of mobile DOT (or VOT) as a multi-dimensional strategy that uses alert messages, videos, feedback, and incentives (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014).

The two articles reported on bio-ingestible sensor interventions. The first, by Flores et al. describes an open-label, single-arm, exploratory study with an ID-Cap System (consists of an ingestible microsensor that communicates digital messages to an external wearable reader to confirm ingestion). This study included 20 participants who were healthy volunteers. The study aim was to determine the performance, reliability, usability, and safety of the ID-Cap system for remote monitoring of 20 ingestion events over four weeks (Appendix E). The ID-Cap system study reports 97.75% (391 detections/400 expected ingestion events) for overall adherence to the prescribed study capsules (Table 3). The second, by Kane et al. describes an open-label, single-arm, observational study with a digital health feedback system (DHFS) that incorporated physiologic assessments (activity level and sleep duration/disruption) with bio-ingestible sensor ingestion. This study included 28 participants who were ambulatory with schizophrenia or bipolar disorder. The study aim was to determine the feasibility and safety this DHFS over 28 days. The study reports a mean adherence rate of 74% and 67% of doses taken within 2 hours of the prescribed dosing time (Table 3).

The one home assistant pill dispenser intervention by Ligons et al. describes an open-label, single-arm study with medication delivery unit called EMMA® (Appendix G). EMMA® delivers medications from single-dose blister cards according to schedules programmed remotely by pharmacies. This study included 19 participants residing in an assisted living facility (median age was 87.1 years of



age) who presented with various levels of cognitive statuses. The study aim was to determine the relationship between cognitive status (older adults) and the usability of a medication delivery unit (EMMA®). Each subject was assessed for cognitive status and video coding allowed for quantification of usability errors during the observed testing sessions. The study reports a significant relationship between Mini-Mental State Exam (MMSE®) scores of 24+ (no cognitive impairment) and successfully completed MDU tasks (average of 69.0%). This is compared to average of 34.7% for completed MDU tasks in the cognitively impaired group (MMSE® score <24) (Table 3).

The five articles reported on mixed method interventions. The first, by Reese et al. describes a randomized controlled trial with smart pill bottles (adherence monitoring) and customized reminders (mHealth). This study included 120 participants who were kidney transplant recipients and prescribed tacrolimus for the 180-day trial. The study aim was to determine the percentage of correctly taken tacrolimus doses as estimated by pill-bottle openings. Each subject was randomized 1:1:1 to adherence monitoring with customized reminders, adherence monitoring with customized reminders plus provider notifications, or adherence monitoring (control). The study reports mean adherence of 78%, 88%, and 55% in the reminders, reminders-plus-notifications, and control arms (Table 3). The second, by Davidson et al. describes a randomized trial for an intervention program called SMASH (Smartphone Medication Adherence Stop Hypertension) that incorporates a smart pill organizer (Maya Medication MedMinder®) and physiologic monitor to assess blood pressure (BP). This study included 38 participants who were either African American or Hispanic and diagnosed with uncontrolled hypertension for the 6-month trial. The study aim was to determine MSA efficacy for this program that promotes and assists in maintaining medication adherence and BP monitoring. The study reports significant reductions in resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) for the SMASH group versus the SOC group across all time points (Table 3). The third, by McGillicuddy et al. describes a randomized controlled trial with a smart pill organizer, physiologic monitor to assess BP, and smartphone app (mHealth). This study included 20 participants who were hypertensive kidney transplant patients for the 3-month trial. The study aim was to determine the feasibility, acceptability, and preliminary outcomes of this mHealth medication

and BP self-management system. Each participant in the intervention group received a Bluetooth capable BP monitor and had the reminder function of their smart pill organizer enabled along with notifications sent to their smartphone. Participants in the control group only had the smart pill organizer with disabled reminder function to monitor their adherence. The study reports significant improvements in medication adherence and significant reductions in clinic-measured SBP across the monthly evaluations (Table 3).

The fourth, by Whiteley et al. describes an open-label, single-arm pilot study with a iPhone adherence gaming app and a smart pill bottle to measure adherence. This study included 20 participants who adolescents and young adults (mean age of 22 years) and were diagnosed with HIV. The study aim was to develop an immersive, action-oriented iPhone gaming intervention to improve antiretroviral medication and treatment. Each participant reported medication nonadherence and acceptability scoring via client service questionnaires and session evaluation forms. The study determines that apps and mobile phone games can have significant impacts for engaging adolescents in interventions who otherwise may not be willing or able to participate in prevention programs (Table 3).

The fifth, by Stoner et al. describes a randomized controlled trial examining a smart pill bottles with daily SMS medication reminders. This study included 76 participants who were treatment-seeking with an alcohol use disorder. The study aim was to evaluate whether a mobile health intervention could improve naltrexone adherence. Each participant in both arms received a smart pill bottle, a prepaid smartphone, and received daily SMS querying medication side effects, alcohol use, and craving. However, participants in the intervention arm received additional medication reminders and adherence assessments via SMS. Ultimately, the study did not provide significant support for the efficacy of text messaging to improve adherence to pharmacotherapy for alcohol use disorders (Table 3).

Table 3: Oral Medication Adherence Device Interventions, 2010-2019

Citation (First author, year of publication) Study name (if applicable)	Population sample size	Technology Study type	Intervention (I) Control (C)	Results
Creary, 2014	N=15  Sickle cell disease	Virtually Observed Therapy (VOT)  Open-label; single-arm	I: participants submit MSA videos daily and received electronic reminder alerts, personalized feedback, and incentives  C: N/A	This study demonstrated that VOT is feasible, acceptable, and can achieve high hydroxyurea adherence with an overall median of 93.3%.
Davidson, 2015 SMASH program	N=38  Hypertension	Mixed Methods  Small-scale efficacy RCT	I: Smart pill organizer (Maya MedMinder®) that provides reminders and SMS along with physiologic monitor  C: SOC	The study reports significant reductions in resting SBP and DBP for the SMASH group versus the SOC group across all time points.
Flores, 2016	N=20  Healthy volunteers	Bio-ingestible sensors  Open-label; single-arm	I: ID-Cap System  C: N/A	The ID-Cap system study reports 97.75% (391 detections/400 expected ingestion events) for overall adherence to the prescribed study capsules.
Hale, 2016	N=25  Heart Disease	Smart pill organizer  Randomized controlled; pilot study	I: MEMS monitoring (MedSentry®)  C: SOC	MEMS monitoring was associated with an 80% reduction in the risk of all-cause hospitalization and a significant decrease in the number hospitalization in the intervention arm compared to the SOC arm.

Kane, 2013	N=28  Schizophrenia or bipolar disorder	Bio-ingestible sensors  Open-label; single-arm; pilot study	I: DHFS that incorporated physiologic assessments with bio-ingestible sensor ingestion  C: N/A	The study reports a mean adherence rate of 74% and 67% of doses taken within 2 hours of the prescribed dosing time.
Lignons, 2014	N=19  Elderly (cognitive impairment)	Home Assistant Pill Dispenser  Open-label; single-arm; pilot study	I: EMMA®  C: N/A	The study reports a significant relationship between MMSE® scores of 24+ and successfully completed MDU tasks (average of 69.0%). This is compared to average of 34.7% for completed MDU tasks in the cognitively impaired group (MMSE® score <24).
McGillicuddy, 2013	N=20  Hypertension	Mixed Methods  RCT; pilot study	I: smart pill organizer, physiologic monitor to assess BP, and smartphone app (mHealth)  C: smart pill organizer	The study reports significant improvements in medication adherence and significant reductions in clinic-measured SBP across the monthly evaluations
Reese, 2017	N=120  Immunosuppressant therapy (organ transplant)	Mixed Methods  RCT; pilot study	I: Smart pill bottle with customized reminders I: Smart pill bottle with customized reminders & provider notifications  C: Smart pill bottle	The study reports mean adherence of 78%, 88%, and 55% in the reminders, reminders-plus-notifications, and control arms.

Stoner, 2014	N=76  Substance Abuse	Mixed Methods  RCT	I: Smart pill bottle with daily SMS medication reminders  C: Smart pill bottle with additional SMS medication reminders	The study does not provide significant support for the efficacy of text messaging to improve adherence to pharmacotherapy for alcohol use disorders.
Volpp, 2017 HeartStrong Study	N=1509  Heart Disease	Smart pill bottle  2:1 randomization ratio	I: MEMS monitoring (Vitality GlowCaps®)  C: SOC	The intervention did not significantly improve medication adherence or vascular readmission outcomes for acute myocardial infarction survivors.
Whiteley, 2018	N=20  HIV/AIDS	Mixed Methods  Open-label; single-arm; pilot study	I: iPhone gaming app (mHealth) and smart pill bottle  C: N/A	The study determines that apps and mobile phone games can have significant impacts for engaging adolescents in interventions who otherwise may not be willing or able to participate in prevention programs.

Table 3 (Continued)

SOC Standard of Care; MMSE® Mini-Mental State Exam; RCT Randomized Controlled Trial; MSA Medication Self-Administration; MDU Medication Delivery Unit; BP Blood Pressure; SBP Systolic Blood Pressure; DBP Diastolic Blood Pressure; DHFS Digital Health Feedback System; EMMA® Electronic Medication Management Assistant; MEMS Medication Event Monitoring System; SMS Short Message Service

## Analysis of Major Themes and Findings

A review of 11 studies noted a number of themes that informed our analysis of oral medication adherence device methods. These results are summarized in Table 4 (see below).

### Accuracy

Of the 11 peer-reviewed articles examined, only 45.5% (5/11) of the studies used a high-quality measure of adherence (coded as high accuracy in Table 4). These medication adherence device methods included virtually observed therapy (1/5), smart pill organizer (1/5), bio-ingestible sensors (2/5), and a mixed methods approach (1/5) that incorporated mHealth and a smart pill organizer. The accuracy of medication adherence monitoring was determined to be inconclusive for 36.4% (4/11) of the studies examined. Most of these approaches (3/4) utilized a smart pill bottle with the remaining method being a smart pill organizer. Both interventions utilizing smart pill organizers and smart pill bottles for medication adherence monitoring tracking can electronically monitor, measure, and securely relay adherence pill bottle openings to the study team with data about the time a participant opens their smart medication device. However, the process of cap removal does not necessarily reflect dose ingestion and can often be a challenging outcome measure to report for many of these studies that utilized that MEMS method.

### Acceptability and Participant Satisfaction

Of the 11 peer-reviewed articles examined, 81.8% (9/11) of the study approaches were identified as favorable medication adherence device methods (Table 4). These medication adherence device methods included virtually observed therapy (1/11), home assistant pill dispenser (1/11), bio-ingestible sensors (2/11), and a mixed method approach (5/11). Acceptability and participant satisfaction were determined to be not favorable for 9.09% (1/11) of the studies examined. This was seen with the smart pill organizer approach (1/11). In addition, acceptability and participant satisfaction scoring was not collected for 9.09% (1/11) of the studies examined in this systematic review. The corresponding approach was with the smart pill bottle (1/11).

Acceptability and participant satisfaction scores were available from 90.9% (10/11) of the studies examined in this systematic review. Of the designated favorable adherence device methods, 88.9% (8/9) of these methods incorporated some form of mHealth interface functionality. A commonality of these approaches is the adoption, promotion and integration of behavioral strategies via health messaging, emphasizing healthy habits, tracking goals, and giving incentives for behavior change (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014). The utilization of mobile phones for these methods represent an ideal medium to improve medication adherence because of their availability, acceptability, patient-centered approach among research participants. In addition, for their ability to enhance the ecological validity of assessments and treatments as they are collected in real-time and in the individual's natural setting (Kreyenbuhl, et al., 2019).

#### Feasibility

Of the 11 peer-reviewed articles examined, 54.5% (6/11) of the study approaches were identified as feasible medication adherence device methods (Table 4). These medication adherence device methods included the virtually observed therapy (1/11), bio-ingestible sensors (2/11), and a mixed method approach (3/11). In addition, 18.2% (2/11) of the study approaches were identified as not feasible medication adherence device methods. These medication adherence device methods included a smart pill bottle (1/11) and a mixed method approach (1/11). And lastly, 27.3% (3/11) of the study approaches were identified as inconclusive on the feasibility outcome measure. These medication adherence device methods included a smart pill organizer (1/11), a home assistant pill dispenser (1/11), and a mixed method approach (1/11).

The medication adherence device approach that displayed the highest feasible probably was mixed methods approach, 27.3% (3/11). This combination of mHealth and MEMS are able to capitalize on the scalable and cost-effective attributes of mHealth while addressing the need for enhanced adherence capture mechanisms. mHealth's feasibility strengths lie in its ability to leverage the existing mobile technology infrastructure and the commonality of mobile phones, where utilization among U.S. adults is about 94% (Davidson, et al., 2015).

A major feasibility limitation of the device methods examined in this systematic review is the interventions do not change patient behavior, meaning adherence rates can return to baseline shortly after the monitoring ends. Hence, the most successful and feasible adherence methods are the interventions that couple these less-complex MEMS technologies (like smart pill bottle caps) with behavioral intervention approaches to improve motivation for treatment. Monitoring adherence alone or merely reminding patients about pill tablet ingestion does not significantly improve adherence in the long term.

### Usability

Of the 11 peer-reviewed articles examined, 81.8% (9/11) of the study approaches were identified as possessing a low ease of use for their respective device method (Table 4). These medication adherence device methods included the virtually observed therapy (1/11), smart pill organizer (1/11), bio-ingestible sensors (2/11), and a mixed method approach (5/11). In addition, 18.2% (2/11) of the study approaches were identified as possessing a high ease of use for their respective device method. These medication adherence device methods included the home assistant pill dispenser (1/11) and smart pill bottle (1/11).

When examining this outcome measure within the systematic review, it became evident the importance of product design and user interface. For studies that conducted qualitative data collection on their respective device method via interviews, they were able to capture the importance of device design features in the both the smart pill bottle and smart pill organizer approaches. Some study participants referring to the smart pill bottle caps as “clucky” or “annoying because I can’t just carry it; it’s too big” (Whiteley, Brown, Lally, Heck, & J, 2018). Hence, by keeping the end-user experience in the forefront of device design more novel and engaging digital approaches for enhancing medication adherence can be realized.

### Safety

Of the 11 peer-reviewed articles examined, 100% (11/11) of the study approaches were identified as a low risk measure of adherence (Table 4). This article coding designation was based on the whether the study had no adverse events, including serious adverse events that are considered unexpected and



related to trial participation (Appendix 1). In addition, study participant risk is minimal if the device methodology is not very invasive. Literature reviews on technology-based healthcare interventions recommends that these interventions minimize their obtrusiveness (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014). The medication adherence device methods that were deemed low risk included virtually observed therapy (1/11), smart pill organizer (1/11), smart pill bottle (1/11), home assistant pill dispenser (1/11), bio-ingestible sensors (2/11), and a mixed method approach (5/11).

#### User authentication

Of the 11 peer-reviewed articles examined, 54.5% (6/11) of the study approaches were identified as utilizing a low user authentication for their respective device method (Table 4). These medication adherence device methods included smart pill organizer (1/11), smart pill bottle (1/11), home assistant pill dispenser (1/11), and a mixed method approach (3/11). In addition, 45.5% (5/11) of the study approaches were identified as utilizing a high user authentication for their respective device method. These medication adherence device methods included virtually observed therapy (1/11), bio-ingestible sensors (2/11), and a mixed method approach (2/11).

*Table 4: Systematic Review of Oral Medication Adherence Device Methods*

Citation (First author, year of publication)	Disease (indication)	Digital therapeutic approach (intervention)	Accuracy	Acceptability /Participant Satisfaction	Feasibility	Usability	Safety	User Authenticatio n
Creary, 2014	Sickle cell disease	Virtually Observed Therapy (VOT)	High Accuracy	Favorable	Feasible	Low ease of use	Low risk	High
Davidson, 2015	Hypertension	Mixed Methods – Smart pill organizer (capture); mHealth (improve)	Inconclusive	Favorable	Not feasible	Low ease of use	Low risk	High
Flores, 2016	Healthy volunteers	Bio-ingestible Sensor	High Accuracy	Favorable	Feasible	Low ease of use	Low risk	High
Hale, 2016	Heart Disease	Smart Pill Organizer	High Accuracy	Not Favorable	Inconclusive	Low ease of use	Low risk	Low
Kane, 2013	Schizophrenia Bipolar Disorder	Bio-ingestible Sensor	High Accuracy	Favorable	Feasible	Low ease of use	Low risk	High
Lignons, 2014	Cognitive impairment (elderly)	Home Assistant Pill Dispenser	Low accuracy	Favorable	Inconclusive	High ease of use	Low risk	Low
McGillicuddy, 2013	Hypertension	Mixed Methods – Smart Pill Organizer (capture); mHealth (improve)	High accuracy	Favorable	Inconclusive	Low ease of use	Low risk	High
Reese, 2017	Immunosuppr essant therapy (organ transplant)	Mixed Methods - Smart pill bottle (capture); mHealth (improve)	Low accuracy	Favorable	Feasible	Low ease of use	Low risk	Low
Stoner, 2014	Substance Abuse	Mixed Methods – smart pill bottle (capture); mHealth (improve)	Inconclusive	Favorable	Feasible	Low ease of use	Low risk	Low

Volpp, 2017	Heart Disease	Smart pill bottle	Inconclusive	Not collected	Not feasible	High ease of use	Low risk	Low
Whiteley, 2018	HIV/AIDS	Mixed Methods – Smart Pill bottle (capture); mHealth (improve)	Inconclusive	Favorable	Feasible	Low ease of use	Low risk	Low

Table 4 (Continued)

## V. Discussion

### Introduction

This systematic literature review examined recent advances in the field of technology-based oral medication adherence approaches within clinical research. A CT.gov query of relevant trials (date parameters 01/01/2010 through 01/01/2019) was conducted using specific search terms (medication adherence and medication compliance) that yield 248 records after duplicates were removed. Manual sorting of these 248 retrieved records to exclude methodology that did not satisfy the inclusion criteria yielded 30 articles for systematic review. An analysis of these 11 studies reported on 6 different intervention approaches and showed that technologic medication adherence devices can vary greatly.

### Summary of study

The aim of this systematic review was to conduct an in-depth review of the medication adherence monitoring tracking technologies currently available. Our review of 11 clinical trials found not one intervention to be effective at improving long-term oral medication adherence and health outcomes. It is our understanding that medication adherence is largely behavioral. In addition, the literature shows that the most effective interventions incorporated a multi-faceted approach by employing technological aspect along with behavioral component (like counseling).

In addition, for the adherence interventions examined in this systematic review (4/5) the studies that used mixed methodology resulted in improved medication adherence. However, with a limited sample of available clinical trials to review more diverse interventions are warranted for different demographics and conditions.

### Discussion of key results

Medication adherence (as a health behavior) resides primarily in the domain of the patient (Brown & Bussell, 2011). In addition, adherence is a multi-faceted public health issue that requires a

multifactorial and individualized solution that improves patient education and adherence behavior (Wimbiscus, 2019).

The most successful and feasible adherence methods are the interventions that couple these less-complex MEMS technologies (like smart pill bottle caps) with behavioral intervention approaches to improve motivation for treatment. These behavioral intervention approaches are often best delivered via mHealth strategies. As with mHealth technology, cost effectiveness of these approaches would be expected to increase as the cost of technology decreases (McGillicuddy, et al., 2013). However, alarm fatigue is a potential threat to mHealth strategies. As the content of the mHealth intervention patients might find these methods to be too effortful, formulaic, or repetitive and disengage as a result (Ben-Zeev, et al., 2016). Monitoring adherence alone or merely reminding patients about pill tablet ingestion does not significantly improve adherence in the long term.

### Limitations

For the purposes of this systematic review, medication adherence improvement strategies were not examined. As the primary goal was to examine innovative adherence device methodology that could accurately capture medication ingestion. However, research suggest that indirect approaches that emphasize patient knowledge, self-monitoring, counseling, accountability, and a personalized program can contribute to improvement in medication adherence (Park, Collins, Shim, & Whooley, 2017).

Many of the articles examining mHealth in this systematic review did not give participants an option and issued smartphones with unlimited service to standardize and control the intervention experience. If participants are given the option to use their own smartphones, then the intervention cost would be reduced as individual across socioeconomic classes increasingly already have smartphones. Hence, making this technological intervention even more feasible when paired with a MEMS as a mixed methodology approach.

It is important to note that the small sample of review articles (n=11). In addition, to the inclusion criteria requiring potentially qualifying studies to have a publication at the time of the systematic review.

These may have led to a biased study sample. Hence, the prevalence of technologic medication adherence capture methods may not be fully representative of all current methods currently available to U.S. clinical research studies and should be interpreted carefully.

Despite these limitations, the results of the study provide recommendations for future testing of innovative technologic interventions that incorporate principles to improve health behavior and promising strategies to accurately capture oral medication adherence (Kreyenbuhl, et al., 2019).

### Implications

Assessing non-adherence can be challenging, particularly in a non-experimental setting. The use of technology may provide an innovative, practical, personalized, and inexpensive approach to promote medication adherence (Creary, Gladwin, Byrne, Hildesheim, & Krishnamurti, 2014). The development of effective, efficient, and non-intrusive approaches to improve MSA and capture adherence monitoring is critical to public health success as limited health care resources are increasingly diminished by growing demand (McGillicuddy, et al., 2013).

### Recommendations

The value and merits of more technology driven adherence solutions will become more apparent from the data provided. As technology joins other connected health devices that can be used independently or in an integrated manner, this will bolster the data available for precision medicine.

The next steps for future research in this arena should include efforts to develop an empirically validated, efficacious, and cost-effective approach dedicated to improving medication adherence (McGillicuddy, et al., 2013). In addition, the development more diverse medication adherence devices are required for different populations, diseases and conditions as the reasons for medication nonadherence are complex and multifactorial (Park, Collins, Shim, & Whooley, 2017).

### Conclusion

As discussed, there are various device approaches readily available to improve and capture medication ingestion, but low adherence still persist. This is suggestive that the underlying explanations

for low adherence vary and that these approaches alone do not effectively address them. Therefore, fusion-based systems that incorporate some effective improve medication adherence strategies like targeted education about the value of the medications (if patients do not understand their benefit), mechanical reminder system (if patient are forgetful), and social support (if patients need external encouragement) along with the merits of more technology drive adherence devices have potential to transform the drug development industry and advance clinical trials.

By promoting adherence strategies that capitalize on effective communication within the physician-patient relationship would be essential. In addition, to employing a patient-centered approach to care that promotes active patient involvement in the medical decision-making process (Brown & Bussell, 2011). This transparency and accuracy of “true” medication adherence will lead to better accountability.

Medication adherence can be measured by a variety of methods, with no one method of adherence reigning superior in all aspects to another method. Based on this systematic review, the most effective adherence interventions include both educational and behavioral strategies. Hence, needs to be a call to action within clinical research to transition from the conventional methods of medication adherence monitoring to more innovative approaches that can increase the rigor and validity of the clinical research industry moving forward.

## Abbreviations

**CT.gov:** ClinicalTrials.gov  
**DHFS:** Digital Health Feedback System  
**DOT:** Directly Observed Therapy  
**EMP:** Electronic Medication Packaging  
**FDA:** Food and Drug Administration  
**HTN:** Hypertension  
**HRQoL:** Health-related Quality of Life  
**IST:** Immunosuppressant Therapy  
**MA:** Medication Adherence  
**MDU:** Medication Delivery Unit  
**MEMS:** Medication Event Monitoring System  
**MNA:** Medication Nonadherence  
**MSA:** Medication Self-Administration  
**PDC:** Proportion of Days Covered  
**VOT:** Virtually Observed Therapy

**RCT:** Randomized Controlled Trial

**SMS:** Short Message Service

**SOC:** Standard of Care

**WHO:** World Health Organization

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## Appendix

### Appendix 1: Variables for Data Extraction

Variable Name	Variable Description	Case Definition*	Coding Scale
Accuracy	The quality or state of being correct or precise.	Defined as a proportion of participants with adequate oral medication adherence (defined as $\geq 75\%$ of prescribed doses taken) If study results are not reported or the intervention was a mixed methods approach that randomized all participants (intervention and control) to arms utilizing a MEMS as the objective measure of adherence, then an inconclusive designation should be assigned.	High Accuracy Low Accuracy Inconclusive
Acceptability / Participant Satisfaction	The quality of being tolerated or allowed.	A “favorable” participant response is defined as a rate greater than 80% (if collected as a study outcome). If participant satisfaction was not collected but it is reported that no study participants prematurely discontinued use of the medication adherence, then this can be indicative of favorable acceptability. However, if such information is not available from the respective article a “not collected” designated should be assigned.	Favorable Not favorable Not collected
Feasibility	The state or degree of being scalable. Meaning, easily or conveniently implemented on both a small and/or large scale.	Designated as “inconclusive” if more research is required to determine efficacy or if the respective systematic review attribute a “feasible” or “not feasible” status	Feasible Not feasible Inconclusive
Usability	The degree to which something is able or fit to be used. Study can report on measures of utilization metrics, range of features, enhanced levels of	Measurement of how easy the finished product is to use by its intended users. A “high ease of use” participant response is defined as a rate greater than 80% (if collected as a study outcome). If device	High ease of use Low ease of use

	functionality. Design is often a battle between trying to deliver functionality and trying to deliver ease of use.	usability was not assessed in the article, then participant acceptability of whether they will use the device/intervention again can be indicative of a “high ease of use” designation. Popular/familiar method; user-friendly	
Safety	The condition of being protected from or unlikely to cause danger, risk, or injury.	If adverse event(s) are reported, the respective medication tool will be designated as high risk. Whereas, tools with no adverse event(s) reported for the duration of the study will be designated as low risk.	High risk Low risk
User Authentication	The act or process of verifying an active human-to-machine transfer of credentials required for confirmation of a user’s authenticity.	A high user authentication is based on the traceable feature of the device. Hence, the invasiveness of the intervention (nonintrusive versus intrusive) would contribute to a high designation for user authentication. This can include the incorporation of biometric monitoring.  The process of removing medications from a tray or removing a pill bottle cap does not necessarily reflect dose ingestion. Hence, these adherence device mechanisms will be designated as low for user authentication.	High Low

\* If the respective article included in the systematic review does not report and/or capture this variable of interest, then the following case definition in the table above will be used for coding purposes.

## Appendix 2: Example of a Smart Pill Organizer

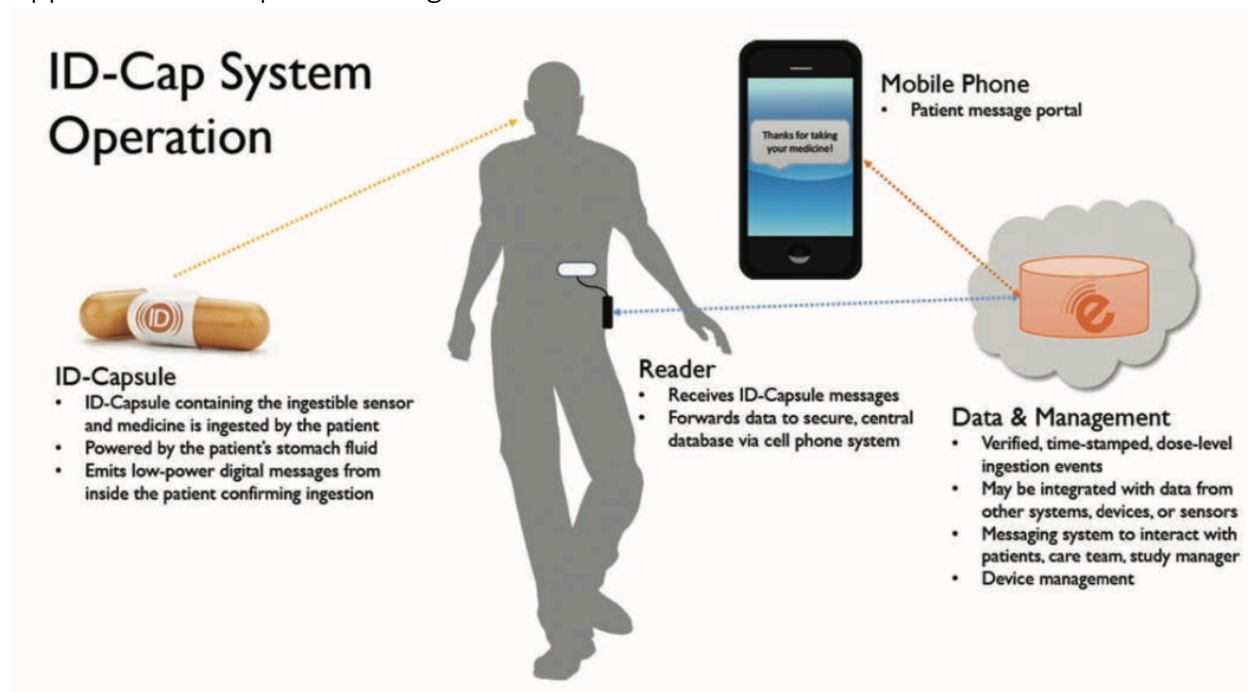


May MedMinder®. Retrieved from <https://www.medminder.com/pill-dispensers-2/maya-pill-dispenser/>

## Appendix 3: Example of a Smart Pill Bottles



## Appendix 4: Example of Bio-ingestible Sensors



*ID-Cap system consists of an ingestible microsensor that communicates digital messages to an external wearable reader to confirm ingestion*

## Appendix 5: Example of Virtually Observed Therapy (VOT)



Retrieved from <https://mhealth.jmir.org/2019/2/e11638/>

Appendix 6: Example of a Home Assistant Pill Dispenser



*Depiction of an Electronic Medication Management Assistant (EMMA®)*