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## Ingestible Biosensors for Real-Time Medical Adherence Monitoring: MyTMed

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### Abstract

Medication nonadherence complicates the management and treatment of chronic disease. Nonadherence to medications is associated with significant mortality, accelerated disease progression, and increased health care costs. My/Treatment/Medication (MyTMed) is a novel adherence monitoring system that obtains direct measures of medication adherence/nonadherence. MyTMed consists of 1) a “digital pill” with a radiofrequency emitter that activates on contact with gastric pH; 2) a relay Hub that captures the radiofrequency signal and transmits it to 3) a cloud based server that connects patient and physicians via a bidirectional interface. In our increasingly mobile world, MyTMed is able to provide medication ingestion data and deliver interventions in real time that support adherence. We describe the patient-centered design of MyTMed as well as the behavioral theory supporting the interface architecture.

### 1. Introduction

Chronic diseases demand unremitting adherence to medications. Unfortunately, rates of adherence fluctuate. For example, rates of nonadherence approach 50 percent; the failure to take medications as prescribed leads to worsening disease, greater numbers of hospital admissions, and unnecessary increases in healthcare costs.[1, 2] Up to 69 percent of patients admitted to hospitals for medication related events will be nonadherent to their medication regimens.[3] Patients who are nonadherent to their medication regimes tend to be admitted to a hospital longer than patients who take their medications as prescribed.[4] Moreover, clinical investigations at the proof-of-concept stage to assess new medication regimens cannot be interpreted without valid adherence data because null findings may arise not from lack of drug efficacy but from poor adherence.

Unfortunately, “medication adherence” is often determined as the number of missed doses over a specified time period, often weeks or even months. Nascent periods of nonadherence are therefore missed through this imprecise and often aggregated assessment strategy. Even worse, current methods of assessing medication adherence are indirect, relying on patient

initiated self-report, announced and unannounced pill counts, pharmacy refill measures, electronic measurement of pill bottle opening, and plasma drug levels.[5] The validity and precision of these tools vary, and each confers a different set of advantages and disadvantages depending upon the context of its use. Moreover, current measures of adherence assess adherence over periods of time—weeks to months.[6, 7] By the time nonadherence is detected, behaviors associated with nonadherence are ingrained, making interventions difficult.

The introduction of ingestible biosensors systems that can seamlessly integrate into existing medication regimens provides the ability to retrieve medication ingestion events in real time. An ingestible biosensor that fits into a broader network of biosensors (body sensing network) or a suite of mobile health (mHealth) technologies can provide unobtrusive, direct evidence of medication ingestion.[8–10] Adherence and nonadherence data can therefore be placed in the context of a patient's daily activities, and small changes in medication taking patterns can be elucidated with relevant interventions delivered in real time.

My/Treatment/Medication (MyTMed) is an ingestible biosensor system that is part of a research program seeking to measure, understand and improve real time antiretroviral therapy (ART) adherence in HIV-infected stimulant using individuals.[11] Inconsistent adherence to ART results in progression of disease and increased rates of drug resistance. This problem is particularly acute for HIV-infected stimulant users who are among the worst in ART adherence in the HIV population.[12, 13] A successful medication adherence system must be unobtrusive and maximally acceptable to its users in an ever-changing mobile environment. This paper describes the MyTMed system, the theoretical framework behind it, and its potential applications for medication adherence monitoring and research.

## 2. The MyTMed System

MyTMed comprises of a constellation of innovative mobile technologies and dynamic, personalized behavioral interventions to monitor and support medication adherence. At the heart of MyTMed is a digital pill that consists of a standard gelatin pill capsule with a unique radiofrequency emitting tag (FIGURE 1).

When a patient swallows the digital pill, the gelatin capsule dissolves in the stomach, releasing the study medication (FIGURE 2). Contact with gastric pH activates the tag, generating a unique radiofrequency signal that is broadcasted to a hip mounted receiver (The Hub). The Hub acts as a relay, using short message system (SMS) protocols to transmit a packet of data including ingestion time and event to a HIPAA compliant cloud based web server. Information from the cloud based web server is interpreted by a patient-facing interface, allowing for real time interactions between patient-physician dyads in the face of adherence and nonadherence. Transmission from the radiofrequency tag on the digital pill is unique, correlating with the coencapsulated medication. In the event that a patient ingests two digital pills at once, two separate, unique radiofrequency signals are received by the Hub, delineating two separate ingestion events. Radiofrequency transmission lasts for approximately 30 minutes as the digital pill transits the gastrointestinal system, and the insoluble radiofrequency tag is excreted.

### 2.1. No alteration of drug structure by radiofrequency signals

Existing radiofrequency signals emitted by the digital pill will penetrate the co-encapsulated medication prior to acquisition by the Hub. A theoretical concern that radiofrequencies may alter the chemical structure or alter the chiral composition of medications has remained unfounded.[14] Studies applying radiofrequency waves to insulin and chemotherapeutics have shown no effect in structural composition. [15, 16]

### 2.2. Dissolution of radiofrequency tag containing gelatin capsules

Encapsulation of medications within gelatin capsules pose the theoretical concern that drug dissolution, pharmacokinetics and pharmacodynamics will be altered. Gelatin capsules can act as a barrier, preventing access to the gastric pH required to dissolve a medication. Several avenues of evidence suggest that gelatin capsules will not alter the pharmacokinetics or pharmacodynamics of an encapsulated medication. First, gelatin capsules are used widely throughout medication formularies and rapidly disintegrate in an aqueous media. Second, reformulation of ART medications, namely Saquinavir, into gelatin capsule formats have not been shown to alter the pharmacodynamics of the drug.[17] Third, gelatin capsules have been used to improve palatability of saquinavir and L-thyroxine without discernable change in pharmacodynamics.[17, 18]

### 2.3. Retention of radiofrequency tags

The radiofrequency emitting portion of the digital pill ( $1\times1\times0.3\text{mm}$ ) is made of small amounts of silver, zinc, and magnesium – approximately the size of a sesame seed. Metal components are coated with an epoxy resin to prevent absorption as the tags transit the gastrointestinal tract. Because tags are insoluble, the risk of tag retention in the gastrointestinal tract, although theoretical, is minimal.

Greater than a decade's worth of experience with much larger ( $31\times11\text{mm}$ ) ingestible video capsule endoscopes have demonstrated a retention rate of less than two percent.[19, 20] Clinically significant signs and symptoms of obstruction do not occur until the bowel lumen approaches 5mm, an unlikely event in patients using ingestible biosensors. In most cases of retained video capsule endoscopy pills, patients remain asymptomatic with treatment consisting of oral fluid administration.[21] In cases where patients electively underwent surgical removal for video capsule endoscopy pills, findings consisted of mild stricture and ulceration at the site of the retained pill.[22] Given the significantly smaller dimensions of the insoluble portion of the digital pill, we believe that retention and subsequent complications will be negligible.

## 3. Design Considerations for Ingestible Biosensor Systems

### 3.1. Technical Considerations

MyTMed utilizes SMS protocols to relay ingestion data through the Hub to the cloud based interface. Other systems utilize ambient wireless local area networks (WiFi) to bridge the medication ingestion event to a workable interface that allows for patient-physician interactions.[9] Utilizing SMS through the control channel that exists in most mobile phones and smartphones allows MyTMed to function in low resource areas that have poor WiFi

connectivity. Although smartphone applications (apps) have been developed to encourage medication adherence, the presence of these apps on a smartphone can pose a risk of discovery to a study subject in the event of theft or unauthorized access to their device. Interventions sent through SMS/MMS protocols consume less power than apps, enabling their use even in low power situations.[23]

Novel mHealth interventions must have adequate security to guard against intrusions and unauthorized access to protected health information (PHI). The Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health Act (HITECH) list guidelines for ensuring PHI is safe and accessible only to patients and their health care providers.[24, 25]

Potential points of data interception for an ingestible biosensor system include ingestion data packets from the radiofrequency sensor, SMS relay to the cloud based server, and interventions sent from the interface.[26, 27] Methods to mitigate security breaches include using proprietary radiofrequencies to mask ingestion data, placing the Hub in close proximity to the radiofrequency signal minimizing the distance of transmission and the potential for interception, and creating personalized intervention messages.

### 3.2. Masking Patient Participation in a Real-World Scenario

Smartphone applications and ingestible biosensor components deployed in the real world should remain hidden and unobtrusive to prevent participant discovery. Digital pills with exposed radiofrequency tags, medication adherence smartphone apps and relay devices may lend clues that a patient is participating and interacting with an ingestible biosensor. Divulging this information can be damaging for patients who wish their disease or medication ingestion remain confidential.

We have taken several measures to make MyTMed unobtrusive, yet usable. First, the use of an opaque gelatin capsule masks the radiofrequency tag, preventing discovery of patient participation in a medication adherence trial. Second, the MyTMed interface functions through SMS (text messages) and MMS (multimedia images) signals, avoiding the presence of an app that could be accessed and mined for ingestion and intervention data if the patient's phone was stolen. Third, MyTMed intervention messages are selected by the participant and personalized. Text and multimedia messages are confidential, anonymous and may contain unrelated content that the user recognizes as a trigger to access adherence information.

### 3.3 Patient Acceptance

Success of an ingestible biosensor system like MyTMed relies on patients accepting and using the digital pill and Hub. Patients who are mistrusting of the healthcare system likely possess a high risk of medication nonadherence, and may be unwilling to accept ingestible monitoring systems. Several lines of evidence show that patients with distrust of our healthcare system, and established nonadherence will accept MyTMed. First, HIV infected drug users have indicated that they will accept monitoring technology when assured of confidentiality.[28, 29] Second, 96% of patients with schizophrenia or bipolar disorder successfully completed a pilot study utilizing an ingestible biosensor administered in

conjunction with antipsychotic medications.[30] Third, deployment of wearable biosensors has been accepted and successful among patients with a history of cocaine abuse.[31]

## 4. The MyTMed Interface

The MyTMed interface is an elegant, bidirectional system that allows patient-physician dyads to engage in real-time, collaborative efforts to improve ART adherence. The interface pulls adherence and nonadherence data from the cloud-based server through Health Level-7 (HL7) messaging through Mirth. Specific ingestion data and timestamp from a hub corresponding to a unique patient is downloaded through HL7 and interpreted by Mirth. This information is stored and interpreted on a secure database to generate bidirectional text and multimedia messages for patient-physician dyads to communicate episodes of adherence and nonadherence. The patient-facing portion of the interface is accessible through SMS or MMS protocols on a mobile phone or smartphone and adherence data is accessible through a downloaded database on the physician-facing portion of the interface. Ultimately, the MyTMed interface is able to respond to real-time medication ingestion data with timely interventions that will help support adherence.

### 4.1. Behavioral Interventions to Support Adherence

Few behavioral theories support the use of long lasting interventions in a mobile setting.[32] The interventions in MyTMed are centered around an informational-motivational-behavioral (IMB) framework.[33] The IMB model was originally developed for HIV-risk reduction interventions. Interventions using this model first provided information about HIV transmission, then strategies to increase motivation for risk reduction, and finally behavioral skills needed for that risk reduction [28]. It has subsequently been successfully and widely applied in behavioral research, including for improving ART adherence.[34, 35]

Informed by the IMB framework, MyTMed presents up to date, accurate information on medication adherence, and delivers an intervention aimed at driving personal motivation to improve adherence behavior.

To adapt the IMB approach to the mobile environment our intervention is delivered in a dual stage process designed to maximize acceptance and adoption. Called the teaser and tie-in, this process allows us to deliver evidence-based informational and motivational content that will trigger behavioral change. The teaser consists of a text message paired with a multimedia image that will capture the participant's attention. Content of the teaser will be determined by focus groups of HIV infected methamphetamine individuals permitting a personalized flavor to teasers (see below). Once the participant clicks on the teaser, they are directed to a tie-in- a second image with a personalized, meaningful theme that reflects the effects of ART adherence. Tie-ins will contain both informational and motivational content designed to initiate or maintain behavior change in the form of continued medication adherence.

## 5. Focus Groups

User input, including qualitative data about digital and mobile health acceptability, is essential for designing wearable technology [30]. Our team has conducted formative research with the target population assessing their current use of adherence reminder systems and their interest in digital and app-delivered adherence systems [31].

Two sets of focus groups were conducted with 22 participants. The first two groups asked about prior use of reminder systems and characteristics that would make them willing to use an adherence system. Applied thematic analysis [32] including response coding and use of NVivo [33] qualitative data analysis software was conducted. (TABLE 1)

Our prior research suggests that this population uses and wants novel medication reminder systems. They value medication adherence tools and recognize that they often face significant barriers to adherence. Using an ingestible biosensor system poses a logical evolution in grassroots medication adherence among HIV infected methamphetamine users. Additional input from HIV infected stimulant users will be critical to development of an interface and intervention that will be readily accepted and effectively used. Future research plans include additional qualitative focus groups to specifically assess responses to the ingestible sensors, the wearable interface and the tips and teasers of this intervention.

## 6. Discussion

MyTMed is a novel medication adherence system that can be easily adopted into existing body sensing networks to help patients take their medications as prescribed. Current measures of adherence largely rely on indirect measures of ingestion. MyTMed, with its digital pill, documents medication ingestion at the moment at which it happens, eliminating recall bias or distortion. Better evidence of medication ingestion can lead to design of improved interventions and strategies to sustain medication adherence. Overencapsulation of a medication with the MyTMed system is easy to accomplish, allowing for multiple iterations of our concept across a variety of chronic diseases.

Although our concept is exciting and feasible, it has several limitations. Our conceptual framework for MyTMed has yet to be deployed in a real world setting. We anticipate patients will accept MyTMed based on previous discussions with our study population (HIV infected stimulant users).

## 7. Conclusion

Ingestible biosensors provide direct evidence of medication ingestion that can be interpreted to detect nascent periods of medication adherence and nonadherence. Real time medication adherence data will allow patients and providers to hone in on episodes of nonadherence before behaviors of nonadherence become integrated into daily routine.

Iterative technology development, improved wireless connectivity, and an expanded knowledge of factors that lead patients to accept, adopt and interact with an ingestible biosensor system will lead to improved methods of measuring medication adherence.



An initial 15 patient pilot of MyTMed and the concepts outlined in this paper will take place in early 2016–2017.

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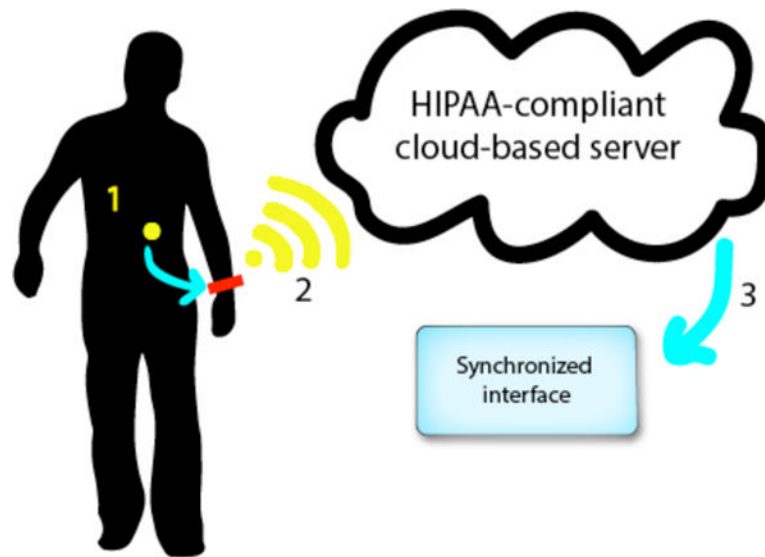
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**FIGURE 1.**

MyTMed digital pill showing (A) empty pill capsule, (B) medication inserted into gelatin pill and (C) fully assembled digital pill.



**FIGURE 2.**

The ingested digital pill (1) activates the Hub (2) that sends a message to the cloud based server. Information is pulled from the server into the interface (3) that delivers behavioral interventions to support adherence to patients.

**TABLE 1**

Sample focus group responses to app delivered adherence

Code	Participant Response
Current methods used for adherence	<p>Participants reported using:</p> <ul style="list-style-type: none"> <li>• Blister packs</li> <li>• Pill boxes</li> <li>• MEMs Cap</li> <li>• Reminder apps</li> <li>• Alarms and reminders</li> <li>• Family and friends providing reminders</li> <li>• Medical staff provided reminders</li> </ul>
Challenges to adherence	<ul style="list-style-type: none"> <li>• Forgetting</li> <li>• Ignoring alarms</li> <li>• Depression</li> <li>• Drug and alcohol use</li> <li>• Travel</li> <li>• Tired of taking so many meds</li> <li>• “I’ve looked up a lot of stuff on the HIV. There’s nothing. There’s HIV apps but it’s about how you get infected and stuff. They’re really simple and stupid. You know what I mean? There’s no med adherence apps.”</li> </ul>
Willingness to use mobile and novel adherence systems	<ul style="list-style-type: none"> <li>• “Honestly, I can’t wait to see what you come up with. I can’t wait to see it and hopefully I try it and I like adherence. Anything that has to do with taking my meds, I like to try ‘em.”</li> <li>• “I was in another [study]...it was about adherence. We had this bottle. It had an electronic top. Whenever you take your medicine, they would know that...that helped me a lot with the medication adherence”</li> <li>• Sometimes people ... stray. So therefore, if the doctor is gonna call you, you can just not even answer the phone. I still would like it so that the doctor would be able to log it and say, ‘Okay. You’ve done 90 percent medication adherence for the last three months because I see record of it. Let’s talk about why 10 percent of it, you didn’t do.’ ... To be able to track it in the hospital on his computer, say, ‘Yeah. I see you’ve been taking your meds.’ Or, ‘No, you haven’t been taking your meds.’ When you sit down face-to-face, have a conversation with your doctor.</li> </ul>