A Digital Health Solution for Using and Managing Medications

Wirelessly Observed Therapy

By Lorenzo DiCarlo, Greg Moon, Allison Intondi, Robert Duck, Jeremy Frank, Hooman Hafazi, Yashar Behzadi, Timothy Robertson, Ben Costello, George Savage, and Mark Zdeblick

Taking oral medication on a prescribed schedule can be a nuisance, especially for elderly individuals and busy people with lots of things on their minds. Nonetheless, taking medication as prescribed is important for maintaining health and well-being. In cases where medication use is part of a clinical trial, taking prescribed medication is important to the entire investigation and outcome of the study, including the determination of whether a drug is effective and safe.

Several approaches are currently used to assess medication taking. The most reliable method is directly observed therapy (DOT), which consists of a clinician observing and documenting the date and time of the patient's swallowing each dose of medication. In some cases, this is done by video recording of the patient taking the medication. Although highly reliable when performed appropriately, this method is resource intensive, time consuming, and costly. Other indirect methods for monitoring adherence include patient questioning, patient pill diaries, pill counts, daily weighing of pill containers, and prescription refill rates. Electronically documenting the date and time when the cover of a pill container has been opened is another option. Each of these methods, however, is limited in scope and provides only an estimated measure of actual drug intake, as none of them reliably record whether the patient has actually ingested the medication. Not surprisingly, a study by Laine and colleagues [1] in 1998 showed that such methods are inaccurate.

For this reason, researchers at Proteus Digital Health, Inc. have developed a digital health technology that determines when medications have been ingested and can wirelessly provide this information in a confidential way to patients and designated caregivers, health providers, and researchers (Figure 1). In this article, we describe the current system and its performance in a preliminary clinical study. Our goal is to further develop and commercialize this system for documenting and communicating medication use to assist in the care of patients and to benefit clinical trials that evaluate new drugs.

The system consists of an ingestible sensor, the Ingestible Event Marker (IEM), and an externally worn adhesive monitor, the Proteus Personal

PILLS COURTESY OF STOCK.XCHNG/RICHARD DUNSTAN.
MAN COURTESY OF STOCK.XCHNG/WEDWARD.

Digital Object Identifier 10.1109/MPUL.2012.2205777
Date of publication: 24 September 2012

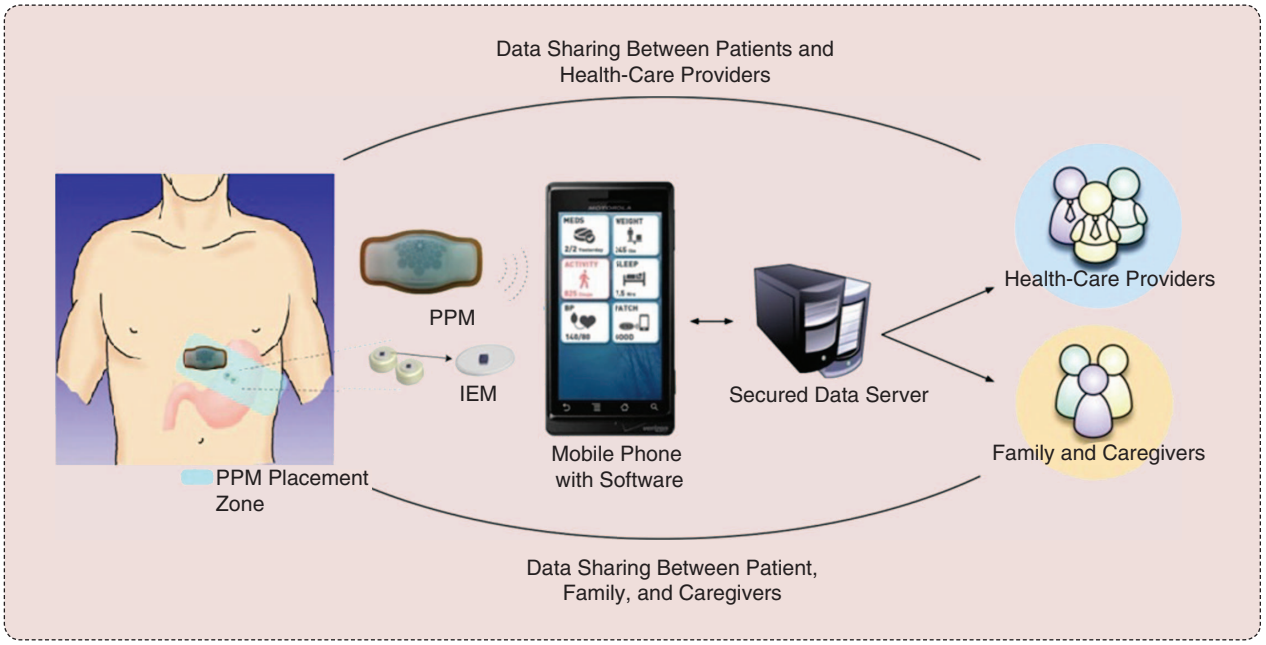

FIGURE 1 Overview of the fully developed raisin system for wirelessly observed therapy. Data that are collected and stored by the system can be accessed by patients and others who are designated by the patient.

Monitor (PPM). Together, the IEM and PPM can be used to directly confirm whether, when, or how many doses of prescribed medication are actually taken and can provide information related to activities of daily living.

The IEM is approximately the size of a grain of sand and is composed of materials that are safe to be ingested (Figure 2). The IEM can be incorporated with medication in several ways during manufacturing: within a tablet, on the surface of a tablet with a transparent or an opaque-colored covering, or inside a capsule. When the IEM is ingested, it combines the electrolyte coating on its surface with the electrolytes found in the stomach fluid to form a biogalvanic battery. The ensuing current is modulated by the IEM and creates an electric field that propagates through the body tissues to the skin surface. When the

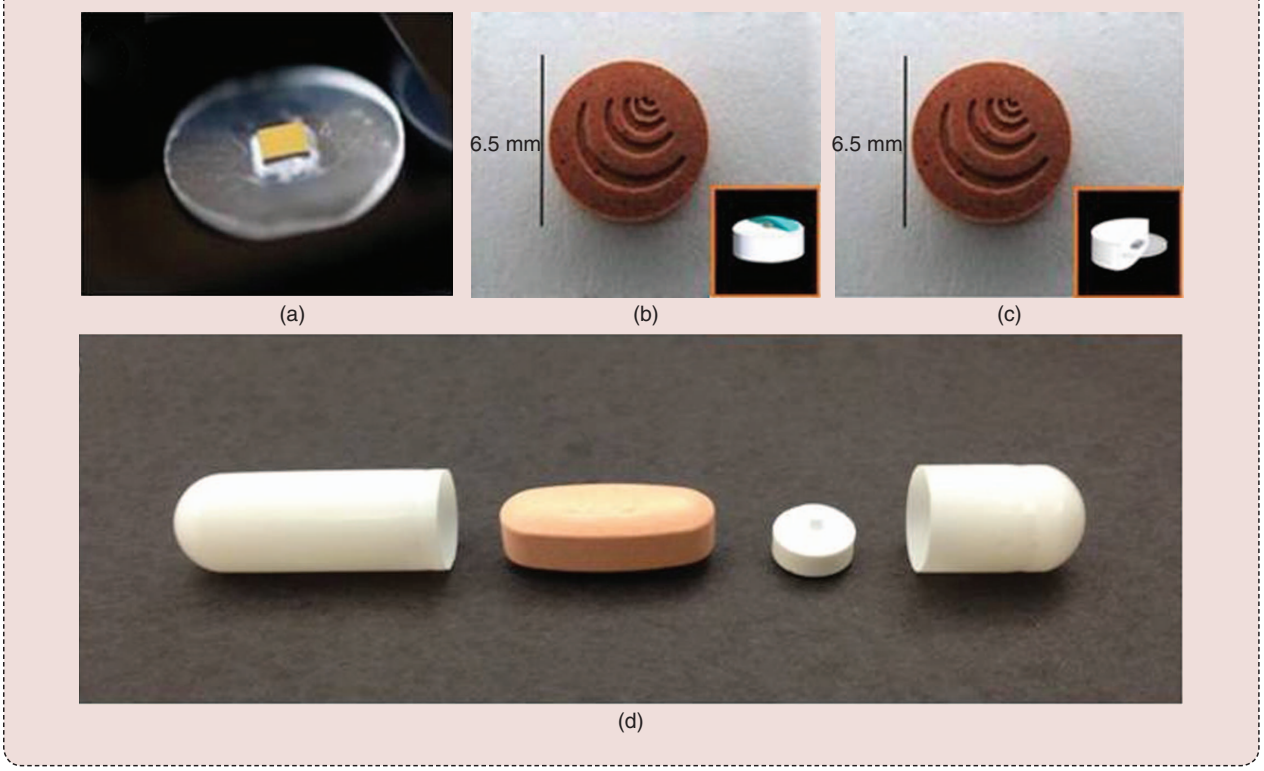

FIGURE 2 (a) The IEM, (b) IEM on a tablet surface, (c) IEM within a tablet, and (d) IEM within a capsule.

current reaches the skin surface it is detected, decoded, recorded, and date- and time-stamped by the adhesive monitor, which acts as a receiver. In this manner, the body becomes the battery electrolyte, and it becomes the antenna for the IEM to communicate to the sensor on the torso. This mimics another well-known process where bioelectric signals from the cells of the heart reach the electrodes of an electrocardiograph on the surface of the body. The IEM's current is less than that of a human heartbeat, and each IEM's identifier is unique. This makes it possible to differentiate multiple IEMs from one another when they are ingested at the same time. Each ingested IEM communicates its identifier for approximately 5–10 min and can be detected only when the monitor is adherent to the user's skin, thus providing personal privacy for data recording. The IEM then becomes inactive and gets excreted subsequently in the feces. Because of its small size, there are currently no gastrointestinal contraindications for its use.

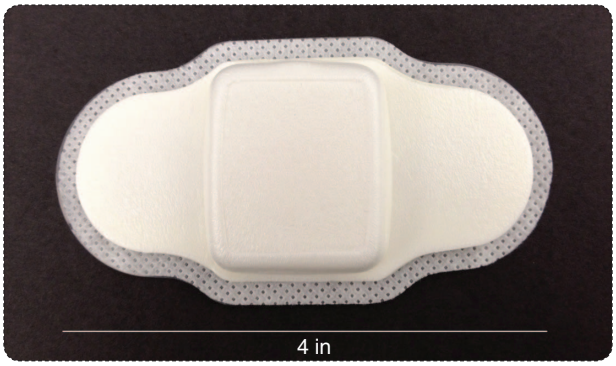

FIGURE 3 The PPM.

The PPM is a miniaturized, ambulatory, battery-operated data-logging device that has been designed for seven-day wear during any and all daily activities, including bathing and swimming (Figure 3). In addition to detecting when an IEM has been ingested, the PPM can record biometrics, such as heart rate, activity, and sleep and sleep quality. The PPM also assesses skin impedance to confirm that the PPM is attached properly to the skin of the user.

In addition to detecting ingested sensors, the PPM brings together data streams from different biometric sensors within the monitor itself. The electronic module contains a printed circuit board with electronic integrated circuits and a lithium-ion battery encased in a watertight housing. Functionally, electronic module consists of a data-logging engine, signal chains for high-frequency (HF) IEM sensor data, low-frequency (LF) data (e.g., bioelectric and accelerometer data as well as on-patch diagnostics), and a communications subsystem. A preprogrammed sequence of measurements consists of acquisition of data from different biometric sensor inputs. Measurements are written in a data record to an onboard flash memory, processed, and stored before being forwarded. Between sensor measurements, the device enters a low-power mode to conserve battery life. Figure 4 shows a functional block diagram of the electronics module.

Before the PPM is first applied to the skin, it is activated by pressing and holding a button that brings the device out of its storage mode and begins regular operation. The activated PPM brings together various data streams from different sensors, which are then processed and stored. When the PPM comes into proximity of the patient's mobile phone, the PPM's stored

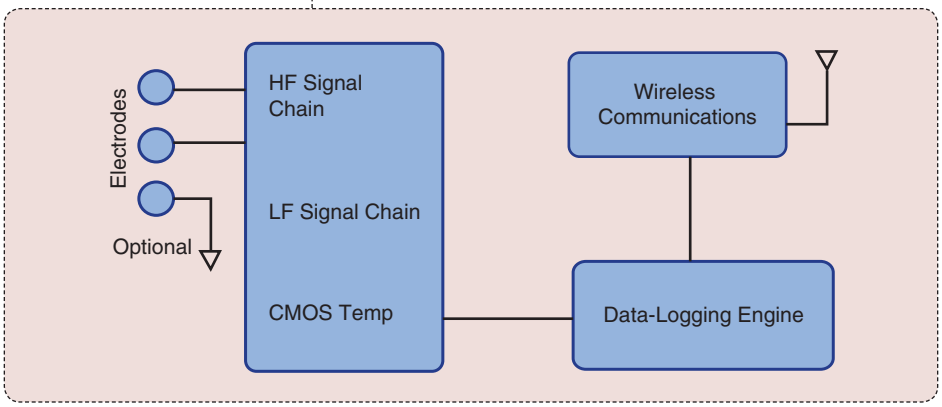

FIGURE 4 Functional block diagram of the PPM.

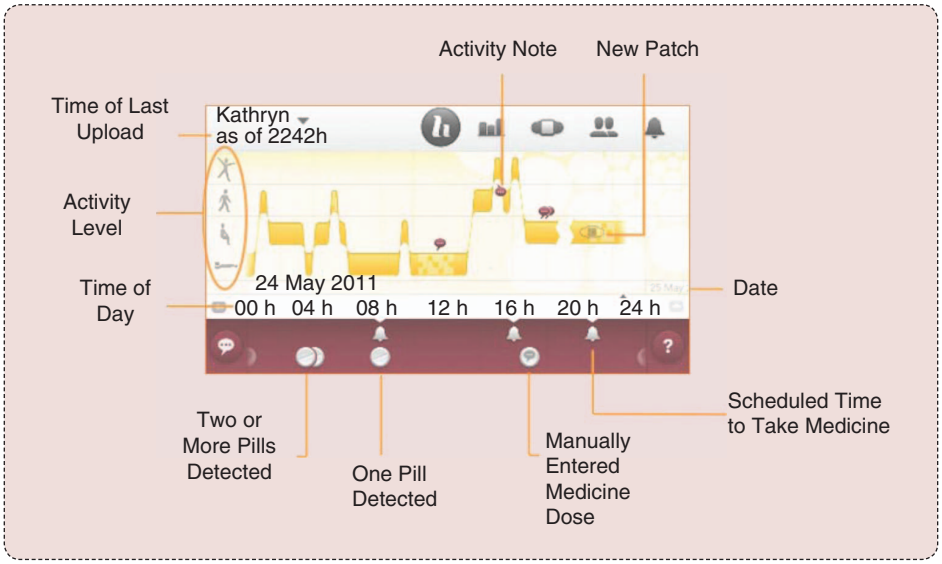

FIGURE 5 An example of a user's display.

TABLE 1. SUBJECT BASELINE DEMOGRAPHICS.

Parameter	Value
Age (years)—Mean ± SD	41.6 ± 11.5
Range	(27–58)
N	10
Gender	
Males	10 (100.0%)
Females	0 (0.0%)
Ethnicity	Eight Caucasian (80.0%) Two Asian (20.0%)
Weight (lb)—Mean ± SD	183.9 ± 19.1
Range	(165–226)
N	10
Height (in)—Mean ± SD	70.2 ± 2.8
Range	(65 –74)
N	10
BMI—Mean ± SD	26.09 ± 4.4
Range	23.7–29.8
N	10

data are encrypted and transmitted via Bluetooth to the patient's phone, and the phone sends the data using industry-standard encryption utilized by banks to a secured, centralized data center for storage and processing. Processed data are then relayed for display to the patient (Figure 5). Some or all of the processed data may also be relayed to other individuals, including medical professionals, as designated by the patient.

Recently, a feasibility study was conducted at the Proteus Digital Health campus to determine the system's positive detection accuracy (PDA), which was defined as the number of IEM ingestions detected by the system divided by the number of confirmed IEM ingestions by date- and time-stamped video recordings.

Ten healthy male subjects participated in the study. Each subject was provided inactive pharmaceutical tablets embedded with an IEM, an adhesive monitor that was worn on the left mid-torso, and a mobile phone that was programmed for study-related communication, data upload, and data review. Based on the experience with earlier prototypes, a minimum of 278 ingestions were required to satisfy the scientific requirements of the study. Subjects were instructed to ingest a total of six study tablets daily over an eight-day period. Each ingestion was documented by a date- and time-stamped video recording for comparison with automated system detections of tablet ingestions. Subjects were also instructed to report any side effects.

Eleven subjects were screened, and ten subjects were enrolled in the study. The lone-screen failure was due to known hypersensitivity to adhesives. There were no subject withdrawals during the study. The baseline demographics are summarized in Table 1.

The PDA of the system when compared with ingestion confirmed by video recording was 99.3% (401 of 404 ingested IEMs) (95% CI: 97.7, 99.9%). There were no adverse events reported during the study (see "Reports from Industry").

There have now been more than 250 human subjects who have been studied and more than 5,000 subject days of the system use that has included more than 14,000 IEM ingestions. Subjects included healthy volunteers, and subjects with diabetes, heart failure, hypertension, mental health disorders, such as schizophrenia and bipolar disorder, renal transplantation, and tuberculosis. Clinical studies included women as well as men, and more than 5,000 subject days of system use. Body mass index has ranged from 16.0 to 44.6. To date, the system has had a good safety record. There has been a single occurrence of nausea and vomiting (0.5%) reported after the ingestion of multiple IEM in a single day, and only minor and self-limited skin irritation related to the adhesive backing of the PPM. Newer versions of the PPM causing less adhesive-related skin irritation, and alternatives to an adhesive PPM, are in development.

The IEM and PPM are CE-marked for use in Europe and have FDA-clearance for use in the United States. Based on its performance when compared with DOT, the system holds promise for a reliable, efficient, and effective means of recording, communicating, and managing medication use and activities of daily living.

Reports from Industry

In the IEEE Engineering in Medicine and Biology Society, we are well aware that even though we have a large number of industrially related members and readers of *IEEE Pulse*, a majority of our articles still come from academia. We would like to see more articles related to industrial and commercial activities associated with biomedical engineering that share new developments in the biomedical industry with our members. We encourage authors in industry to submit articles related to new products, new services, and other industry-related activities for publication such as this article from Proteus Digital Health, Inc. Although we cannot publish articles that are essentially advertisements for new products, we encourage potential authors to describe the engineering, life science, and clinical aspects of products and services in their work area. We also like to include a paragraph describing their commercial organization. Potential authors are encouraged to contact the editor (mneuman@mtu.edu) with a description of their proposed article, and if acceptable we will work with them to create the piece.

Lorenzo DiCarlo (ladicarlo@proteusbiomed.com), Greg Moon, Allison Intondi, Robert Duck, Jeremy Frank, Hooman Hafazi, Yashar Behzadi, Timothy Robertson, Ben Costello, George Savage, *and* ***Mark Zdeblick*** *are with Proteus Digital Health Incorporated, Redwood City, California.*

Reference

[1] C. Laine, C. J. Newschaffer, D. Zhang, et al., "Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: A pharmacy claims-based analysis," *Pharm World Sci.*, vol. 20, pp. 73–77, 1998.