A Networked System for Self-Management of Drug Therapy and Wellness

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ABSTRACT
Background: A networked wellness system is under development to document actual ingestions of oral medications, to differentiate types/doses of drugs taken simultaneously, and to provide these data along with other metrics to patients and providers for individually tailored care. *Methods:* After ingestion, an edible sensor (embedded in drug) is activated by stomach fluid and communicates to a wearable monitor that identifies the sensor as unique and records ingestion time/date. The monitor also collects physiologic data and communicates via mobile phone to a secure server that integrates the data with other wireless devices (e.g. blood pressure, weight). Summary reports are generated periodically for patient and physician review. *Results:* No adverse effects were observed in animals using repeated, exaggerated doses of sensors. Two drug-sensor form factors have been tested in 3392 human ingestions with no major and very few minor adverse effects. Sensitivity was 97.0% and specificity was 97.7% when compared to directly observed ingestion. The system identified and differentiated up to 4 simultaneously ingested sensors with an identification accuracy of 100%. Data integration with multiple devices and report generation have been piloted successfully. *Conclusions:* Pre-clinical and early clinical system safety appear satisfactory; data integration and communication appear to be feasible. By providing context-rich information and fostering communication, this system may enhance patient-provider relationship and care coordination.

Categories and Subject Descriptors
B.4.1 [**Input/Output and Data Communication**]: Data Communication Devices.

General Terms
Measurement, Design, Experimentation

Keywords
Adherence, physiologic metrics, chronic care management

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1. BACKGROUND
It is estimated that one third to one half of all patients worldwide do not take their medications properly, wasting billions of dollars in unnecessary healthcare expense. In the U.S. alone, patients who do not take their medications as prescribed cost the healthcare system an estimated $290 billion in avoidable medical spending every year [1]. Patients with chronic diseases – which constitute more than half of all Americans – are particularly challenged, with spotty adherence practices that leave them vulnerable to otherwise unnecessary hospitalizations and additional medical risks. Although there are many indirect methods used currently to confirm adherence to a medication (for example pill count, prescription refill rate, 'smart' pill bottle), there is no gold standard other than directly observed therapy, i.e., watching a patient swallow each dose of medication [2, 3, 4, 5]. While highly reliable when performed appropriately, directly observed therapy is not practical for broad use.

A system that provides secure, reliable, real-time information to patients via their mobile phones and to providers via their clinical decision and support systems would ensure that complete and accurate medication data are shared among key stakeholders in the chain of care. A networked wellness system (Proteus Biomedical, Inc., Redwood City, CA) is under development to (i) integrate adherence data, physiologic metrics and consumer input, (ii) allow patients to access and share data with physicians, family members and/or caregivers, and (iii) provide a platform for targeting feedback and providing tailored management for wellness promotion. This capability eliminates the ambiguity plaguing all other indirect adherence measurement methods mentioned above. More importantly, it forges a direct link between clinically actionable metrics (taking, dose-day, and dose-time adherence) and the critical, modifiable behavior (pill taking). In addition, the system can measure a variety of physiologic parameters (heart rate, heart rate variability, activity, body position) on an ambulatory and periodic basis, and can aggregate at the database server level parallel physiologic metrics obtained with peripheral devices such as wireless blood pressure cuffs, glucometers, and weight scales. These combined data streams allow therapeutic events to be viewed in the context of a person's physiology, thereby providing important links between treatment, behavior, wellness, and therapeutic response.

The concept of biomedical telemetry from ingestible electronics was proposed in the 1960s in a series of lectures aimed at educating biologists, physicians, and engineers about the use of radio to sense and transmit biological signals from animals and humans [6]. In the earliest days, researchers measured gastric

pressure using a swallowable “endo-radiosonde” that was tethered to the subject's tooth. In another effort, core body temperature telemetry from a tortoise was demonstrated using an ingested circuit. Since then, ingestible electronics have been developed by both academic and industry groups [7, 8]. Today, sophisticated and complex ingestible electronic systems are in various stages of clinical and commercial development. Procedures such as capsule endoscopy, which uses a small wireless camera to take and transmit pictures of the digestive tract, are widely utilized. In contrast, the networked wellness system summarized in this manuscript takes a different approach, employing comparatively simple micro-electronic edible sensors, which can be produced in high volume at ultra-low cost. This enables cost-effective incorporation of silicon wafer-based edible sensors into chronically administered oral pharmaceuticals for medication adherence monitoring.

The focus of this manuscript is to describe the components of the networked wellness system and its theory of operation. Pre-clinical and early clinical results are presented as preliminary safety and technical performance assessment.

2. SYSTEM DESCRIPTION

An edible sensor system is under development for electronically confirming medication adherence, gathering physiologic metrics, and communicating these data to patients and providers for individually tailored care. The system consists of two major components: an edible sensor embedded in a drug product, and a wearable health monitor.

2.1 Edible Sensor

The edible sensor consists of an integrated circuit (IC) in the center, surrounded by a friable disc. A photograph of the edible sensor is shown in Figure 1(a).

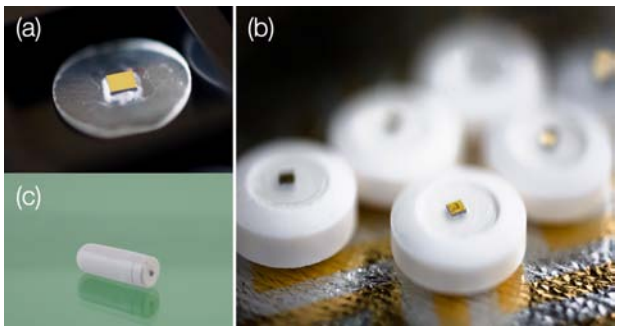

Figure 1. Edible sensor for electronically confirming adherence to oral medications. (a) A closer view of an edible sensor; (b) Edible sensor attached directly to a tablet. (c) Edible sensor co-encapsulated with a drug product using a sensor-enabled capsule carrier.

The edible sensor has at its core a conventional silicon IC measuring 1.0 mm x 1.0 mm x 0.45 mm. The IC is coated with a copper salt on one side and magnesium on the other. The levels of silicon, copper, magnesium, and other minerals present in the sensor are far below levels commonly present in the diet. The friable disc is 5.0 mm in diameter and 200 μm in thickness. It is made from common cellulose-based pharmaceutical excipient materials. The overall weight of the edible sensor is approximately 5 mg.

A battery typically consists of 3 components: an anode, a cathode and an electrolyte. Prior to ingestion, the edible sensor is considered "inert" because no electrolytic solution is present to complete the battery circuitry. After a sensor is ingested, the stomach fluid and the surrounding tissue provide the electrolyte for the sensor. The copper salt and magnesium act as cathode and anode respectively. The combined electrochemical redox reaction at these electrodes produces a voltage of 1-2 V across the IC.

The voltage is stored on the IC using an on-chip capacitor and diode. The voltage created by this redox reaction also activates the circuitry on the IC. Once activated, the on-chip circuitry regulates the current between the anode and the cathode layer, thus modulating the rate of the electrochemical reactions at each of the two layers. By varying the rate of these electrochemical reactions, a time-varying electric potential is established throughout the body. Unique identifying information, similar to a serial number, is encoded on the IC such that the modulated electric potential has the same encoded signature detectable by a wearable health monitor worn on the body. The wearable health monitor interprets the information from the edible sensor, identifies it as unique, and records the sensor ingestion event with corresponding date, time, and sensor signature. This communication process remains entirely within the body; it is unnoticed by and not detectable beyond the patient consumer.

The edible sensors are designed to communicate for a finite period of time, approximately 7 minutes. The friable disc of the sensor, which serves to increase the minimum dimension of the electrolyte and thus increase the variation in voltage detected at the skin, gradually softens as it goes through normal gastric transit. Small amounts of soluble species such as magnesium and copper ions are released to the body, while the bulk of the edible sensor is ultimately eliminated from the body via normal excretion.

The edible sensor is designed to be effectively and economically embedded in a pharmaceutical solid dosage form in a manner that allows both the sensor and the drug product to fulfill their intended functions with no loss of performance. To date, two drug-sensor form factors have been developed and tested in clinical trials. First, an edible sensor is directly attached to an existing tablet dosage form (a placebo or an active drug tablet) using a pharmaceutical grade edible adhesive material. A photograph of this form factor is shown in Figure 1(b). Second, an oral medication in the form of a tablet, capsule, or powder can be co-encapsulated with a special sensor-enabled capsule carrier. This capsule carrier consists of a capsule body, and a placebo "stopper" with an edible sensor affixed to it. This form factor can accommodate a wide range of oral medication form factors and sizes, allowing virtually any oral medications to be used with the system without modification of the finished drug product. A photograph showing a sensor-enabled capsule carrier is shown in Figure 1(c).

2.2 Wearable Health Monitor

The wearable health monitor is a miniaturized skin-patch device capable of documenting communication coming from multiple

edible sensors, and reporting a variety of physiologic parameters. Ideally, the wearable health monitor will adhere to the torso of a patient consumer in a similar fashion as a small adhesive bandage. Over the course of the development process several clinical versions of the wearable health monitor have been developed, ranging from a larger device worn via a belt clip to an on-body device that can be adhered to a patient's body. Figure 2 illustrates some of these early versions of wearable health monitor.

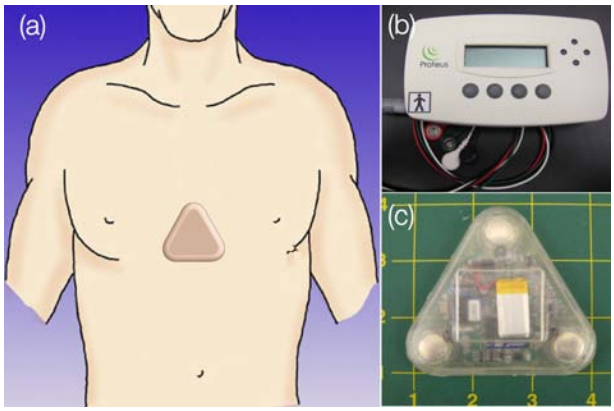

Figure 2. Wearable health monitor is designed to communicate with the ingested edible sensors and to collect physiologic data such as activity and heart rate. (a) Placement of a wearable health monitor on the body. (b) First generation clinical version of a wearable health monitor. The monitor measures 155 x 93 x 27 mm, and weighs 300 grams. (c) Second generation clinical version is triangular in shape, approximately 85 mm per side and 8 mm in height. It is a 2-piece device with an adhesive electrode base, connected to the monitor itself via snap connectors.

The wearable health monitor serves to collect data from different sensors both internal and external to the body. It is adhered to the patient's body using an adhesive electrode base comprised of three biocompatible, electrocardiogram (ECG)-style Ag-AgCl electrodes. These electrodes allow the monitor to sample the patient's biopotentials where the electrodes are attached. Low-frequency biopotentials are sampled to produce an ECG for heart rate assessment. A communication channel is also established for interfacing with sensors within the body (e.g. an ingested edible sensor). In addition, the monitor can assess the impedance across each electrode pair by applying a low-amplitude, alternating current and measuring the resulting voltage. This feature is useful for verifying and confirming monitor attachment to the patient consumer.

Within the current clinical version of the wearable health monitor, there is a custom-made printed circuit board and a rechargeable battery, which is capable of powering the monitor for approximately seven days. Functionally, the monitor consists of five main blocks including a data-logging engine, signal chains for high frequency sensor data, signal chains for low frequency sensor data, a communications subsystem, and various internal sensors such as an accelerometer for activity assessment.

After the sensor data are sampled, analyzed, and compressed, they are stored in the internal memory of the monitor. One of the design goals is to configure the wearable health monitor such that it periodically and automatically connects to a general-purpose computing device (e.g. a mobile phone) over a wireless link, transmits stored data via this link to a secure server, and then clears the memory of the monitor to free up space for further data collection. Prior to implementing this wireless data transfer scheme, a wired upload station approach has been developed and validated.

2.3 Peripheral Devices and Data Integration

In addition to the electronic medication adherence and physiologic data collected by the edible sensors and wearable health monitor, metrics such as blood pressure and body weight can be captured and integrated into the wellness system using a set of third-party, peripheral wireless devices (Carematix, Inc. Chicago, IL). For example, a wireless sphygmomanometer and weight scale can be set up at a patient consumer's home, along with a base station that communicates with these wireless monitoring devices. Once the base station receives a measurement from a monitoring device, it pushes the measurement via a phone or a personal computer to a centralized, secure data server. At the server level, data from these third-party, peripheral devices are integrated with those from edible sensors and wearable health monitor (Figure 3). Using this regime, a comprehensive set of electronic medication adherence, physiologic (e.g. heart rate and activity), and health monitoring (e.g. blood pressure and body weight) data are aggregated and seamlessly integrated. Ideally prior to dissemination, data would be processed and examined to verify their authenticity and validity. Once validated, they can be

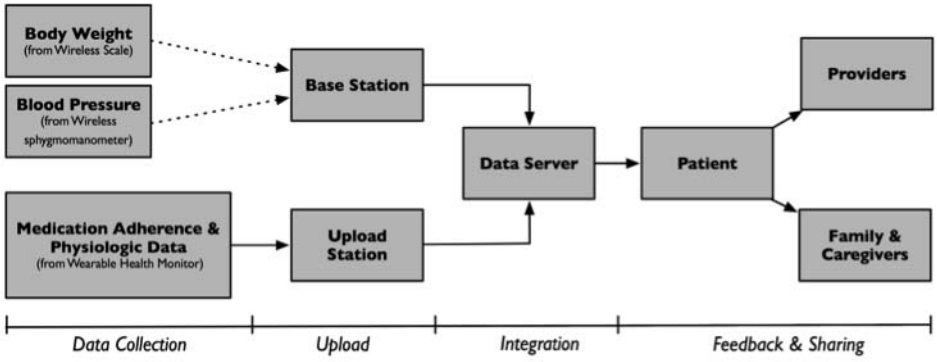

Figure 3. A block diagram showing medication adherence and physiologic data collection, integration, and sharing using a networked wellness system.

disseminated to designated stakeholders including patients, their family members/caregivers, and healthcare providers.

2.4 Data Feedback and Sharing

As shown in Figure 3, once the electronic medication adherence and physiologic data are integrated and validated at the server, the next step is data dissemination to appropriate stakeholders. First and foremost, these data belong to the patient consumer and are sent to him/her directly, discreetly, and securely. With the consumer's permission, the same set or a subset of the gathered data can be shared with their designated person(s) including family members/caregivers, and healthcare providers. Data can be viewed and shared in a multitude of ways. Some of the data dissemination methods that are currently being implemented include web-based access using a computer or a smartphone, email notification, and text messaging.

3. SAFETY ASSESSMENT

3.1 Pre-Clinical Study in Animals

Prior to assessing the networked wellness system clinically, system safety was evaluated in pre-clinical animal models. One of the main objectives of the pre-clinical program was to demonstrate edible sensor ingestion safety and to provide *in-vivo* dose-response information. To that end, a 14-day repeated dose, oral gavage toxicology study was conducted in rats.

Eighty-four Sprague-Dawley rats of 6-7 weeks old were used in a toxicology study conducted at an established research facility (Charles River Laboratories Intl. Inc. Wilmington, MA) under Good Laboratory Practice. All materials used in the assembly of an edible sensor were included and defined as the test item. Test item was first incubated in extraction vehicles to produce the gavage fluids. In order to produce gavage fluids that reflect realistic product-use exposures to an edible sensor, physiologic extraction vehicles were employed. Specifically, test items were extracted with simulated gastrointestinal fluids, with extraction time in each fluid reflecting transit times through these gut compartments in humans.

All extracts were administered as a gavage within 24 hours of extraction completion. Water was used for the untreated control group. Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was used for the vehicle control group.

Table 1. Dosing groups for the 14-day repeated dose oral gavage toxicology study in rats.

Group	Description	Human Daily Dose Equivalent (# Edible sensors per day)
1	Untreated control	De-ionized water
2	Vehicle control	SGF and SIF
3	0.33 X	10
4	1X	30
5	10 X	300
6	100 X	3,000
7	1,000 X	30,000

Five dosing groups plus two control groups were utilized in this study (see Table 1). The 1X group (Group 4) represents the projected maximal daily ingestion scenario by human, estimated at 30 edible sensors per day. The 10X, 100X and 1,000X groups were included to assist in the generation of a dose-response profile for the edible sensor. Animals received a single, daily oral gavage dose for 14 days, using a constant dose volume of 10 ml gavage fluid/kg body weight. Doses were administered to non-fasted animals.

Clinical observations were made pre-, during, and post-study that included mortality/moribundity check, body weight, food consumption, and ophthalmoscopy. Blood samples were obtained from the animals after 14 days of dosing to evaluate hematology, coagulation, and biochemistry. Animals were euthanized post-study and examined for any gross lesions during gross necropsy. Organ weights were obtained from all animals. A veterinary pathologist prepared histopathology slides for review from the control group and the 1000X group (30,000 edible sensors exposure per day) tissues.

3.2 Clinical Studies in Humans

To assess the safety of edible sensor ingestion and the use of the system in humans, a series of clinical studies have been conducted in healthy volunteers, patients with tuberculosis, and patients with heart failure.

Clinical study design has been reported elsewhere and is summarized in Table 3 [9, 10, 11]. The edible sensors used in these studies were administered in the following form factors: sensors attached to placebo tablets (healthy volunteer study), sensors attached to placebo tablets co-ingested with active drug tablets (tuberculosis study), and sensors co-encapsulated with furosemide tablets (heart failure study). In each study, a safety assessment was conducted per protocol by evaluating the frequency and nature of adverse events (AEs) occurring during the active and the follow-up phase of the study. An adverse event was defined as "any undesirable medical event occurring in a subject, whether or not the event is considered related to the investigational device". Study investigators were asked to further classify all AEs based on the criteria listed in Table 2.

Table 2. Adverse event classification

Category	Classification
Seriousness	☐ Serious Adverse Event (SAE) ☐ Non serious
Anticipated	☐ Anticipated ☐ Unanticipated
Severity	☐ Mild ☐ Moderate ☐ Severe
Relatedness	☐ Related – Device-related – Study procedure-related ☐ Possibly related – Device-related – Study procedure-related ☐ Unrelated ☐ Unknown

4. TECHNICAL ASSESSMENT

Three prospective, observational device feasibility clinical studies were conducted over the course of 18 months at four clinical sites in the U.S. Subject population included healthy volunteers, patients with tuberculosis, and patients with heart failure. Each clinical study protocol was reviewed and approved by an independent institutional review board. Each study was monitored by the study sponsor (Proteus Biomedical, Inc.) according to Good Clinical Practice guidelines.

Detailed clinical study protocols used in these studies have been reported elsewhere [9, 10, 11]. A summary of subject selection criteria, study procedural highlights, duration, and outcome metrics are summarized in Table 3 for reference.

To assess the technical performance of the networked wellness system, a number of key outcome metrics were defined, which have been used throughout the clinical validation program of the system. These key metrics and their definitions are as follows:

- *System sensitivity*: The number of detected edible sensors divided by the number of edible sensors administered. Assessed in conjunction with directly observed ingestion.
- *System specificity:* The number of non-detected negative controls divided by the number of negative controls administered plus any incidence of false positives.
- *Identification accuracy*: The number of correctly identified edible sensors divided by the number of edible sensors detected.
- *Taking adherence of sensor-enabled medication*: The number of sensor-enabled medication detected by the system divided by the number of sensor-enabled medication prescribed (in heart failure pilot study only).
- *Scheduling adherence of sensor-enabled medication*: The percentage of doses taken within a pre-determined time window collectively determined by the study subject and the coordinator pre-study. A sensor-enabled medication was considered taken "on-time" when ingested within ± 1 hour and ± 2 hours of the specified time for a twice-daily and once-daily dosing regimen, respectively (in heart failure pilot study only).

System sensitivity, specificity, and identification accuracy were calculated for edible sensor ingestions administered at a directly observed ingestion setting across all subjects and by population. The analysis excluded instances where there were (i) data collected from subjects during training prior to the observation phase of the study, (ii) user errors in properly activating monitor prototypes prior to sensor ingestion, (iii) malfunctions in prototype software or hardware, or (iv) unsatisfactory placement or location of the monitor prototype, as indicated by a measured electrode impedance of 1000 ohms or greater. Measurements were also assumed to be independent. A 95% confidence interval (CI) was determined using the method of Clopper-Pearson. For the remaining outcome metrics, descriptive statistics (n, mean, median, standard deviation, median, minimum, and maximum) and 95% confidence intervals were determined when appropriate. α, the level of statistical significance, was set at 0.05.

5. SAFETY RESULTS

5.1 Pre-Clinical Study in Animals

No unscheduled deaths were reported in this pre-clinical study. The changes in body weights between the animals in the water control group (Group 1), vehicle control group (Group 2) and the dosing groups (Groups 3 to 7) were not statistically significant. No abnormalities in food consumption were observed in any of the dosing groups. Edible sensor exposure led to no abnormal clinical observations or ophthalmologic pathology. Gross necropsy and histopathology findings were normal.

Alanine aminotransferase (ALT) in the blood chemistry samples showed a statistically significant pair-wise difference between the 1X treatment group (30 sensors/day) and the untreated control

Table 3. Summary of clinical study designs.

Population	Healthy	Tuberculosis (TB)	Heart Failure (HF)
Selection Criteria	• 21 years of age or above • In general good health • Negative urine pregnancy test	• 18 years of age or above • Received 10 days of treatment for active TB • Negative urine pregnancy test	• 18-80 years of age • NYHA Class II or III HF • Taking furosemide once or twice daily, <40 mg/day • Implanted with a CRT or an ICD
Procedural Highlights	• Pre-study day overnight fast • 12 doses/day • 2-4 edible sensors/ dose • Non-functional, "negative control" sensors were given • Effects of different foods and drinks on sensor performance were evaluated	• Co-ingestion of edible sensors with TB medication during scheduled Directly Observed Therapy (DOT) visits • 2-4 edible sensors/ DOT visit • Non-functional "negative control" sensors were given • DOT was done either in-clinic or at the subject's home	• Daily ingestion of sensors co-encapsulated with furosemide tablets and a placebo • Daily weight and blood pressure measurements using wireless devices provided • 2 sensors/ weekly clinic visit • Review study data with provider and designated caregiver post-study
Study Duration	2 days	10 DOT visits within 2 weeks	28 days
Outcome Metrics	System sensitivity, System specificity, Sensor identification accuracy	System sensitivity, System specificity, Sensor identification accuracy	System sensitivity, Taking and scheduling adherence, Blood pressure, Body weight Measurement taking frequency, Summary report generation

group in females (p=<0.05). An elevation of 1.1 times the upper limit of normal ALT range was observed. The observed difference was not considered to be clinically relevant however, as the increase was extremely small and a dose-dependent effect was not observed in any of the higher dosing groups. Thus, there was no compelling evidence for edible sensor-related dose dependency in clinical chemistry.

In sum, laboratory findings from the 14-day repeated dose oral gavage toxicology study in rats indicate that there were no differences between the control groups and the edible sensor treatment groups, including the exaggerated dosing group of 1,000X (equivalent to the exposure of 30,000 edible sensors per day). There was no evidence of an adverse dose-dependent edible sensor-related toxicological effect observed in this pre-clinical study.

5.2 Clinical Study in Humans

A total of 63 subjects, including 25 healthy volunteers, 30 patients with tuberculosis, and 8 patients with heart failure were enrolled and completed three clinical studies. Study subjects' demographic and baseline characteristics are summarized in Table 4.

Safety assessment was conducted for each study per protocol. A total of 15 adverse events were reported in these 63 subjects. There were 2 serious adverse events reported: both SAEs were described by the investigator as severe and unrelated to the study device and procedure. There were no unanticipated device adverse effects. The most commonly observed "related" and "possibly related" AEs were described as mild skin rash associated with the commercial electrodes placed on a subject's body. No definitive edible sensor-related AEs were reported.

6. TECHNICAL PERFORMANCE

A total of 3392 edible sensors were administered to 29 males and 34 female subjects age 21-80 with a body mass indices from 16 to 47 kg/m^2. Of the 3392 ingestion events, data from 3277 events (96.6%) were available for statistical analysis. 2788 of these edible sensors were given in a directly observed setting that allows the assessment of system sensitivity. The remaining 489 edible sensors were taken in a non-clinical, at-home setting; data from which were used to characterize subjects' off-site medication taking behavior such as taking and scheduling adherence. An additional 219 "negative controls", i.e. placebo tablets with no edible sensors, were given to assess system specificity.

The overall system sensitivity versus directly observed ingestion from these three studies was 97.0% (95% CI = 96.3-97.6%, N = 2788); system specificity was 97.7% (95% CI = 94.8-99.3%, N = 221). Sensitivity and specificity by study population are shown in Figure 4. System sensitivity was unaffected by subject's BMI in healthy volunteers and TB patients (p=0.336 and p=0.731, respectively)[1]. Meal type was also found to be not significantly associated with sensitivity (p=0.151)[2]. The system identified and differentiated up to four simultaneously ingested sensors with an identification accuracy of 100% (95% CI = 99.9-100%, N = 2641) [9, 10, 11].

Table 4. Subject demographics.

Population	Healthy	TB	HF
# Center	1	2	1
# Subjects enrolled	25	30	8
Gender, n (%)			
Male	6 (24%)	16 (53.3%)	7 (87.5%)
Age (year)			
Mean (SD)	33.2 (10.0)	44.9 (14.1)	67.9 (13.3)
Min, Max	21, 62	22.5, 79.5	46.0, 85.0
BMI* (kg/m^2)			
Mean (SD)	27.5 (7.4)	23.5 (4.1)	28.2 (5.5)
Min, Max	17.8, 44.6	16.0, 31.1	21.0, 34.2

*BMI = Body mass index

In the pilot study with heart failure patients, subjects were instructed to take 1-2 sensor-enabled furosemide (based on the regimen prescribed by their physicians) and 1 sensor-enabled placebo daily. The mean taking adherence of furosemide and placebo across subjects were 88.6% (95% CI = 78.8-93.4%, N = 8 subjects) and 83.4% (95% CI = 73.5-93.3%, N = 8 subjects), respectively. The system was successful in identifying and differentiating sensors associated with furosemide from those that were linked with a placebo. Subject's scheduling adherence varied from 10.8% to 89.3%, median value was 82.5% (N = 8 subjects).

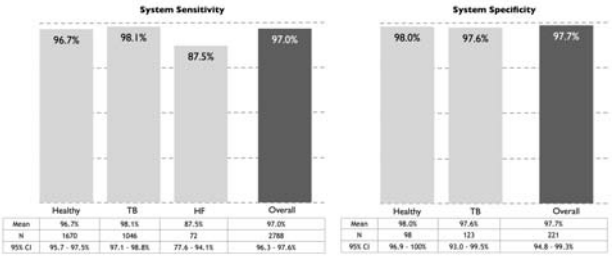

Figure 4. Networked wellness system sensitivity and specificity in confirming medication adherence compared to directly observed ingestion.

In addition to taking sensor-enabled furosemide and placebo, subjects were asked to take two blood pressure measurements (AM and PM) and one weight measurement daily, using the wireless sphygmomanometer and weight scale provided. Data from wireless devices were successfully integrated into the networked wellness system to monitor subjects' weight and blood pressure along with medication adherence, heart rate, and step count. The mean weight reported was 183.0 lb ± 31.7 lb, ranging from 134 lb to 245 lb. The mean morning systolic/diastolic blood pressure reported was 122.7/69.9 mmHg; that in the evening was 123.1/67.5 mmHg. Subjects took an average of 21.6 out of 28 (77.1%) weight measurements, and 40.6 out of 56 (72.5%) blood pressure measurements prescribed.

[1] The sample size used in assessing sensitivity in patients with heart failure was too small to evaluate the relationship between system sensitivity and subject BMI. Thus, the analysis was not conducted.

[2] Only assessed in the study with healthy volunteers.

Data collected from each subject were successfully integrated for post-study report generation. Data reports were shared with the subjects, their family members and caregivers to gather feedback. As illustrated in Figure 5, the data report presents medication adherence pattern collected from the edible sensors, step count and heart rate gathered from the wearable health monitor, and weight, blood pressure, and heart rate obtained from peripheral wireless devices in a comprehensive manner.

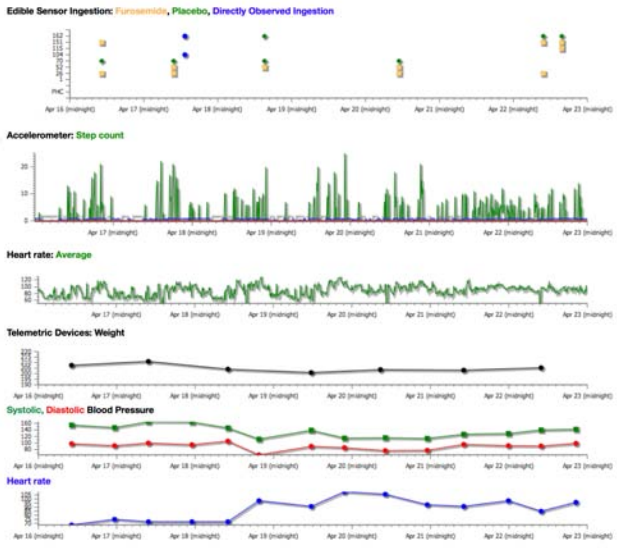

Figure 5. An example of a data report integrating medication adherence, physiologic metrics, and information collected from wireless health monitoring devices.

7. DISCUSSIONS

7.1 Findings To Date

Based on pre-clinical and early clinical experience, the proposed networked wellness system appears to have a satisfactory safety profile.

In the 14-day repeated dose oral gavage toxicology study in rats, there was no evidence of edible sensor-related toxicity even in the highest dosing group, which represents the human equivalent of ingesting 30,000 sensors in a single dosing event daily for 14 consecutive days. In the 3 clinical studies of 63 human subjects, there were no reports of device-related serious adverse events and a low frequency of device-related adverse events.

The majority of the device-related adverse events reported were associated with the wearable health monitor of the system. Specifically, the commercial ECG electrodes and electrode bases caused mild skin rash at the placement site. To mitigate the risk of future AEs of similar type and to increase patient comfort, a number of improvements have been implemented. New adhesive materials designed for longer-term, repeated use have been used. Moreover, the placement zone for the wearable health monitor has been expanded to allow monitor attachment at different places on the body and to avoid repeated attachment at the same location.

In terms of technical performance, the networked wellness system was found to have high sensitivity (97.0%), high specificity (97.7%), and excellent identification accuracy (100%) in electronically confirming adherence. A slightly lower system sensitivity (87.5%) was observed in the heart failure pilot study, however, it was determined to be unrelated to the population. Software issues were encountered during the study, which led to sub-optimal performance. Also, the sample size available for sensitivity analysis was very small (N = 72) when compared to the other two studies (N = 1670 and 1046), resulting in a wide confidence interval. Nonetheless, even when incorporating the findings from this study with the results of other studies, the overall early clinical experience has demonstrated that the system functions as designed, capable of detecting and differentiating up to four simultaneously ingested edible sensors. This enables recording of actual ingestion event and detailed characterization of medication adherence pattern that is not attainable via conventional, indirect, adherence assessment methods such as pill count and prescription refill rate.

Moreover, the heart failure pilot study has demonstrated that data from peripheral wireless health monitoring devices can be integrated successfully into the proposed system. Once integrated, physiologic and medication adherence data can be centralized and displayed concurrently. Based on post-study subject interviews, the majority of the subjects expressed interest in seeing the health-related information provided by the study report and thought it could improve the management of their heart failure condition. Additional comments included suggestions on making future sensor-enabled medications more discrete, making the wearable health monitor smaller with a longer battery life, and an enhanced form factor. Subjects also expressed interest in the idea of getting reminders on the mobile phone when they forget to take their medicines.

7.2 Maintaining Privacy

The potential benefits of any system should be considered with its potential drawbacks. Ultimately it should be the individual consumer who decides whether to utilize it and the consumer should be the owner of the data. To cite an example from another industry, a credit card could be perceived as a tool whose primary purpose is to allow organizations to monitor any and every individual monetary transaction. However, for millions of individuals there is a positive and universal appeal of a credit card as a convenient means of conducting immediate, cash-less transactions that outweighs any negative perceptions. Similarly on the Facebook® website, individuals can and do share personal information, including health-related information, with others who are individually selected by the sharing individual. In order to maintain privacy in both instances, provisions are in place so that individuals decide and direct with whom they wish to share information. Today, individuals already choose to utilize universally available financial and social systems, and accept the tradeoff for privacy when they believe that they are working with a trusted partner. Similar approaches should be feasible for care and wellness systems.

7.3 Future System Enhancements

The networked wellness system has been demonstrated to be capable of capturing adherence electronically, assessing behavior and physiologic information in the context of the pilot studies described above. System enhancements are underway to increase the capabilities of the system in everyday use.

The edible sensor is being enhanced in a number of ways. The size of the signature field is being increased so that every dose of any medication will be given a globally unique identifier, allowing true unit level identification of pharmaceuticals. In addition, provisions are being put in place to hash the unique signature using cryptographic techniques in order to differentiate sensor-enabled medications from counterfeit drugs. A non-destructive interface is also being added to the edible sensor so that it can be tracked through the entire pharmaceutical supply chain to generate an electronic pedigree for each pill.

Additional sensing modalities are being added to the edible sensor, such as core temperature, gastric pH, enteric transit time, and specific molecular diagnostics for particular diseases. These enhancements will extend the edible sensor from being a simple marker of ingestion to a multi-functional data collection platform.

The functionality of the wearable health monitor is also being extended. Additional sensing modalities of interest include acoustic measurements of intra- and extra-corporeal sounds, use of the accelerometer information combined with other data streams to classify patient activity, and detailed measurement and classification of electrocardiograms.

Wireless technology allows data collected by the wearable health monitor and edible sensor to be instantly available throughout the spectrum of care. Ongoing efforts are being made to identify radio link innovations between the wearable health monitor and mobile phone including Bluetooth, BLE, Zigbee, and ANT. Implementing one of these protocols combined with the development of an application-specific integrated circuit will reduce the battery size and component count dramatically, resulting in a small, disposable electronic plaster that can comprehensively characterize adherence and other health parameters.

Finally, perhaps the most exciting area for system enhancement is in the way that data from these various sensor platforms are fused to allow patients to study their own lives and to give them tools to improve their health. Building upon current trends in behavioral research, self-actualization, and human-centered design, the networked wellness system has the potential to become a comprehensive platform for exploring the relationship between objective data on therapy and individual wellness.

7.4 Potential Clinical Applications

In its commercial form, the networked wellness system will wirelessly communicate timely, objective, and actionable adherence and wellness information to patients and other key stakeholders in the chain of care. The envisioned system will offer mobile care management solutions that are patient-centric yet highly scalable. Since adherence and wellness behaviors are universally relevant to disease outcomes, the system will be intended for wide clinical utility, for both acute and long-term applications.

The networked wellness system should be particularly well suited to the management of complex chronic disease, wherein information, interpersonal connectedness, behavioral support, and logistical coordination are essential, especially in between visits to healthcare providers. The system will be capable of being customized for use in multiple therapeutic areas, including cardiovascular, metabolic, neuropsychiatric, and infectious disease. As described previously, the system has already been studied in hypertension and heart failure populations. Additional investigations have been planned in organ transplantation, schizophrenia, diabetes, and HIV/AIDS.

The networked wellness system has the potential to offer significant value to patients, caregivers, providers, and health systems alike, by empowering patients to understand and take charge of their health as never before. The system could also equip family caregivers—the world's largest yet least recognized group of health workers—with tools to manage the day-to-day logistics of their loved-ones' health. It could allow providers to determine whether adherence, as opposed to worsening disease, is the source of a patient's suboptimal clinical status, thereby informing the rational titration of medications. Finally, it may provide improved outcomes and reduced healthcare expenditures by keeping patients on their medications and facilitating the delivery of earlier, more targeted interventions.

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