Horizon Scanning report No. 14

Ingestible sensor to monitor the adherence of long term drug therapy

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Methods

Agenas is a public body. Its mission is to promote innovation and development within the Italian national healthcare service and provide an Early Awareness and Alert (EAA) service by Horizon Scanning (HS) activities in the field of new and emerging health technologies.
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A full description of the methods used for the production of the present HS report can be found at www.agenas.it

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Limitations

This report is based on information available when the searches were made and does not contain data on subsequent developments or improvements of the evaluated technology. The observations made on effectiveness, safety or cost-effectiveness of the technology evaluated in the report are to be considered temporary.

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Declaration of Conflict of Interest

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Name of the technology / procedure: **Ingestible sensor to monitor the adherence of long term drug therapy**

Target population

The device is for patients affected by chronic pathologies requesting lifelong or long term therapeutic treatments. In particular, the technology could be used in patients (especially elderly people) with multiple treatments in which no-adherence to drug therapy may result in serious adverse events.

Description of the procedure and technology

Poor adherence to long-term therapies severely compromises the effectiveness of treatment making this a critical issue in population health from the perspective of quality of life and of health economics [WHO 2003]. Direct and indirect methods for monitoring adherence to drug therapy are now available for the long-term therapies. Direct methods are intended to control directly the assumption of the drug by the patient while the indirect methods are based on systems that help the patient to remember the ingestion event or to monitor the ingestion.

Object of the present report is a technology that detects the actual adherence to the prescribed treatment, by the patient, through a small sensor ingested together with the drugs. The sensor can be encapsulated either directly into drug or within a placebo tablet and, once ingested, it is activated by the gastric juices and it creates an electric field detected by a wearable sensor applied to the skin of the patient.

The recorded data are transmitted from the wearable health monitor on a mobile device (smartphone, tablet, pc), which, in turn, forwards the information to a centralized and protected server [http://www.proteus.com/technology/digital-health -feedback - system].

The different stakeholders involved in the care process can access the data on the server to analyse the adherence to drug therapy, respecting the privacy of the patient. The system can be counted among both direct methods, when the sensors are encapsulated in drugs therapy, and indirect methods, when the sensors are encapsulated in an inert substance and is taken with other drugs.

Clinical importance and burden of disease

Chronic diseases can be very different: heart diseases, stroke, cancer, diabetes, respiratory diseases, neurological and neurodegenerative diseases, musculoskeletal disorders, vision and hearing defects and genetic diseases, are only a few examples. They can also be of viral origin, such as AIDS and hepatitis. Most of these diseases are associated with an aging population. Chronic diseases are characterized by having symptoms that persist over time, sometimes steadily, and with phases of partial remission and exacerbation. Therapies for these diseases can lead to improvements but are inconclusive. According to the WHO, in Europe chronic diseases cause at least 86% of deaths and 77% of the disease burden [WHO, 2011]. For this reason the fight against chronic disease is a public health priority, both in richer countries

than in poor ones. In 2011 in Italy about 60% of the population suffered from chronic diseases, , distributed as follows [Istat Serie Storiche]: Chronic bronchitis, emphysema and respiratory failure, bronchial asthma: 6.1%; Osteoarthritis, arthritis: 17.1%; heart diseases (including myocardial infarction): 3.6%; Diabetes: 4.9%; Allergic diseases: 10.3%, Hypertension: 15.9%. Almost 39% of the population, in 2012, suffers from at least one chronic disease. Models based on improving care for chronic diseases already exist and are being implemented in many countries. Given the high degree of co-morbidity, treatment aimed at the total health needs of the patient is likely to be a more promising strategy with respect to the treatment of individual diseases. Patient compliance is an important issue in therapy, indeed, the active participation of the patient in the management of the disease can facilitate the achievement of health goals.
In current clinical practice, a good compliance to antihypertensive therapy appears to be effective in the primary prevention of cardiovascular events [G Corrao et al, 2012].

Products, manufacturers, distributors and approval

The device identified to monitor the compliance in long term drug therapy is the “Proteus Personal Monitor” that includes the “Ingestion Event Marker (IEM)” produced by Proteus Digital Health, Inc.
The technology (system) consists of the following elements:

- “Ingestion Event Marker”, it is an ingestible sensor, with dimensions of 1.0 mm x 1.0 mm, composed of an integrated circuit set in a hard crumbly based on cellulose of about 5.0 mm on which are placed an anode and a cathode. The sensor is ingested together with drugs. Some prototypes involve the insertion of the sensor directly into the tablet.
- “The Proteus Personal Monitor”, it is a wearable patch applied to the torso of the patient that captures and records the pulses transmitted by the ingestible sensor. The wearable sensor may be equipped with additional accessories for the detection of physiological parameters, such as ECG, temperature and movement of the patient.
- A software through which the wearable sensor communicates with any other computer devices. The software manages and detects the ingestion events.

The ingestible sensor is integrated in an inert tablet that dissolves in the stomach. The redox process is activated by stomach acids acting as an electrolyte. The redox process actives the sensor where are positioned the anode and cathode generating an electric field not related to stomach pH [http://www.proteus.com/technology/digital-health-feedback-system] [FDA K113070]. The signal remains, therefore, contained in the body of the patient and detected through the skin by an adhesive sensor on the torso that records the date and time of the assumption [Belknap 2013]. The ingestible sensor remains active 5-7 minutes and the wearable patch for a period of seven days. The telemetry data, time and day of ingestion, can be downloaded to electronic devices via Bluetooth and then monitored by accessing a central server. The CE mark obtained in August 2010 includes the Ingestible sensor and wearable sensor; the U.S. FDA market clearance, as a medical device for co-ingested applications, was obtained in July 2012. The system is not recorded in the Italian Register of Medical Devices (RDM) of the Ministry of Health.

Product name [Manufacturer]	Distributor	CE Mark	RDM	FDA
Proteus Personal Monitor – Ingestion Event Marker (IEM) [Proteus digital health,Inc]		☑	☐	☑

Setting

The ingestion and wearable sensors can be used in an outpatients or home setting. Transmission of data is ubiquitous but analysis takes place in a medical setting. Currently the technology works through the concomitant ingestion of both the sensor and the therapy's drug. No information is available about the potential interference of electromagnetic source with technology.

☑ Home	☐ Hospital	☑ Outpatient
☐ Accident and Emergency	☑ Other: the use could be in any setting	

Roll out in Italy

The technology, belonging to Class II medical devices, cannot be used in Italy because as there registration in the Italian General Repertory of Medical Devices (RDM). According to the Decree of Ministry of Health issued on 21 December 2009, only medical devices of Class I are exempt from this requirement.

☐ Pre-marketing	☐ On the market for 1-6 months	☐ On the market for 7-12 months
☐ On the market for more than 12 months	☑ Not identified	

Comparators

The Gold Standard to monitor adherence to drug regimens is Directly Observed Therapy (DOT). Different comparators are possible according to the direct or indirect methods used by the device to detect the adherence to therapy. Direct methods include: a) the ingestion of pills/drugs from patient at presence of health worker; b) surveillance systems; c) monitoring of patient biological data changes linked to drug usage or a specific disease. Indirect methods include: a) pill count; b) electronic alert system; c) innovation blister; d) questionnaires; e) prescription monitoring; f) pharmacological concentration monitoring.

Effectiveness and safety

We carried out a literature search on different databases to identify primary and secondary studies of efficacy and safety of "Proteus Personal Monitor – IEM" published from 2008 to date, in English and Italian language.
The searches on EuroScan and CRD (DARE & HTA) databases were performed on 12 November 2013 and aimed at identifying the secondary studies on "Proteus Personal Monitor – IEM", according to the inclusion criteria.

Clinical studies on the efficacy and safety of "Proteus Personal Monitor – IEM" were searched, according to our inclusion criteria, in the following databases: MedLine, EMBASE and Cochrane Library (18 November 2013).
To identify ongoing clinical trials we consulted the *clinicaltrial.gov* database (12 November 2013) by combining the key words sensor AND "medication adherence" OR "digital health feedback system" OR WOT.
Searches results are:

- EuroScan and CRD (DARE & HTA) databases: 12 documents, they were all excluded as they not consider the technology assessed in this report;
- MedLine, EMBASE and Cochrane Library databases: 391 articles. After reading the titles and abstracts, 8 clinical studies were considered eligible to full text analysis and, among these, 3 studies were excluded for these reasons: one study considered the individual variables that influence the drug responses of patient; one study considered only the cost elements; one study was a meeting presentation.
- *clinicaltrial.gov* database: three clinical studies were identified (Table 1), 2 are complete and 1 is in the recruiting phase.

The following outcome measures were identified for the 5 clinical studies (Table 2):

- PDA (Positive detection accuracy): the number of detected ingestible markers divided by the number of functional ingestible markers administered.
- Taking adherence: the number of marker-enabled medications detected by the system divided by the number of marker-enabled medications prescribed.
- Scheduling adherence: the percentage of doses taken within a predetermined time window.
- Safety: detection of adverse events.

The study by *Au-Yeung et al, 2011* is an overview of 4 prospective observational studies on 4 populations over 19 months.
111 patients were recruited on a voluntary basis, with different diseases (30 with tuberculosis, 8 with heart failure, 43 with hypertension, 30 healthy). The main outcomes of all studies concerned the technical performance and safety of the technology. Studies comparing the technology with DOT (Directly Observed Therapy). Data from 111 patients were used for safety assessment and data from 103 of them were used for assessment the technical performance of the device.
On the total number of markers ingestions 8.5% was excluded for technical reasons and, on the total remaining, 50.4% was administered with directly observed ingestion while the 49.6% was administered in an unsupervised at-home setting, using a marker-enable medication form. Using the results from DOT, the PDA was equal to 97.1%. Three different ingestion methods were used: 1) the sensor is ingested alone; 2) the sensor is ingested with the drug; 2) the sensor is encapsulated in the drug and ingested. The results were described as follows: a) the PDA is equal to 96.7%; b) PDA equal to 98.1%; c) PDA equal to 96.7%. Regarding to the markers ingested, using the "unsupervised at-home setting", the study wanted to capture the adherence to therapy assessing the average of both level adherence and scheduling adherence; the results are respectively to 85.4% and 68.5% in patients with heart failure and 90% and 82.8% in hypertensive patients while identification accuracy is equal to 100%.
Sixty nine adverse events are reported (defined as "any undesirable medical event occurring in a subject, whether or not the event is considered related to the investigational device"), in 45 subjects, 67 of whom were non-serious and 2 serious but not associated with the technology. From the above described study, *Belknap R. et al, 2013* extracted and reported in a subsequent publication results exclusively from the population affected by tuberculosis (30 patients).They received therapy with DOT to detect the accuracy and safety. The study is a prospective, non-randomized and descriptive. The primary analysis has resulted a

PDA equal to 95% and the identification accuracy equal to 100%. Regarding to safety, the study found 11 adverse events in 8 patients, including 3 related to technology (skin rash).

DiCarlo 2012 provides an overview to demonstrate that the compliance of drug therapy could have a relevant impact on clinical study results carried out on pharmacological development, characterized from assumption that the drug therapy ingestion is equal to prescription therapy.

The study reports the results of different published studies carried out to 2012 and also reports the results of one study carried out on 10 patients, not published, from which the accuracy (PDA) is equal to 99.3% when the technology is compared to DOT.

Kane J.M. et al, 2012 report a small scale observational study, carried out in 4 weeks, on 28 patients (12 with bipolar disorders and 16 affected by schizophrenia). The primary aim is to compare the accuracy of the technology with directly observed therapy, while the secondary aim is the characterization of adherence and the physiological metrics. 27 of which 28 patients completed the study. The results are: PDA compared to DOT is equal to 94%; the taking adherence is 74%; the scheduling adherence is 67% for drug therapies to take into 2 hours. Regarding the safety no adverse events and no anticipated adverse effects were detected; nine no-serious adverse events were detected in 6 subjects and for 5 subjects of them, 6 adverse events were related to technology (skin rash).

The study of *Eisenberger et al, 2013* assesses the accuracy, use and safety of the technology, combined to different enteric-coated mycophenolate sodium in kidney transplants patients. It is an uncontrolled pilot study, with 20 transplanted patients recruited.

The outcomes are described as follows: PDA is equal to 100% when the technology is adopted during the DOI (directly observed ingestion) while, when it is no adopted during the DOI, is equal to 68%; the taking adherence, independently to the number of drugs ingested daily, is 99.4%; the scheduling adherence is to 84.5%; regarding the safety no significant adverse events and no reject events were registered (only 7 patients detected a skin rash).

Three clinical studies resulting from clinicaltrial.gov database focused on the technology produced by Proteus Digital Health Inc, composed by a ingestion sensor and a wearable sensor. One study is randomized and is still ongoing; it compares the system efficacy to monitor the ingestion of drug therapy with directly observed therapy.

The other two studies, single-arm, have been completed but has not reported any publications relating to results of studies on the clinicaltrials.gov website.

The primary outcome of all studies is the ability of the system to detect the accuracy of drug ingestion in three populations of patients with different chronic conditions: schizophrenia or bipolar disorders, kidney transplant, and tuberculosis. Secondary outcomes are safety of the system, taking adherence and scheduling adherence and evaluation of experience, the satisfaction level and ease of use of the technology in patients.

Two studies were carried out in USA and another one (NCT01320358) in Switzerland. The three studies were funded by Proteus Digital Health, Inc., Novartis e mHealth UCSD, though the manufacturer was involved in all studies.

Potential benefits to patients

The use of a technology able to directly and non-invasively detect the level of adherence reducing the number of variables that could influence negatively the adherence, could represent an important element in terms of compliance assessment for appropriate therapies.

☐ Mortality reduction or increased survival	☐ Reduction of the morbidity	☑ Improved quality of life (patient/users)
☐ Improved patient monitoring	☐ Other: Faster wound healing	☐ Not identified

Cost of the technology / procedure

To define the purchasing cost of the technology we sent an *ad hoc* questionnaire to the manufacturer. We asked information on the technical, organizational and economic aspects of the technology. The manufacturer did not provide any information. An email enquiry elicited a brief response. According to the manufacturer website "*the cost of technology depends on context in which it used".*

To date (December 2013) some economic studies assessing the potential economic impact that no-adherence to drug therapy could generate for healthcare system are available. The study by Fine R.N. et al (2009) on transplantations showed that the costs even if the data on economic impact are very poor, could be estimated taking into consideration the additional costs of diagnostic tests, immunosuppressive costs and general cost of transplant procedure. A WHO report (2003) estimated the economic impact of non-adherence to therapy in patients with chronic disease from $100 to $300 billion per year. *Au-Yeung and DiCarlo* compared the wireless with DOT to assess the drug adherence to treat the tuberculosis. The purpose of the study was to assess the potential cost saving by using WOT (wirelessly observed therapy) when compared to DOT (directly observed therapy). A model to compare the costs of monitoring the standard of care treatment for tuberculosis utilizing DOT or WOT was constructed. The outcome was the Failure rate. The cost model suggests that WOT could be funded for the continuation phase of tuberculosis treatment and provide benefits compared to DOT. The results indicate that the tuberculosis treatment using WOT could be funded in countries in which the use of DOT is limited or when the disease is drug-resistance.

☐ Increased costs compared to alternative treatments	☐ Increased costs due to increased demand	☐ Increased costs due to the required investments
☐ New costs	☐ Other:	☑ Not identified

Potential structural and organisational impact

Structural impact

The technology does not require any structure except for data storage (server). It is unclear whether the server comes with the device and is hosted by the healthcare facility that adopts the technology or by the manufacturer.

☐ Increase in requirement of instruments	☐ Always be used	☐ Can be used only under specific circumstances
☐ Decrease in requirement of instruments	☐ Other:	☑ Not identified

Organisational impact

As the technology is used at home or in a medical ambulatory the healthcare system must organise health workers to monitor and report the information gathered to promptly identify non-compliance. Health systems should provide training for workers and patients but no study provided this information.

☐ Increase in the number of procedures	☑ Re-organisation required	☑ Training required for user
☐ Reduction in the number of procedures	☐ Other:	☐ Not identified

Conclusions

“Proteus Personal Monitor – IEM” to monitoring the adherence of long term drug therapy is a technology which has been recently introduced on the market. The new CE mark of some element of the system and the recent FDA approval on the basis of very little evidence available, do not look promising for the introduction of this technology in our national healthcare system. The literature research showed that the clinical studies carried out on Raisin System Pills, are feasibility studies that assess the detection accuracy of the ingestible sensor. The studies have been carried out on small scale and some assess a small number of patients focusing on populations affected by a specific chronic disease. The detection accuracy was high compared to direct observation. No serious adverse events were reported, but one rare harm is a skin rash. The majority of authors are affiliated to manufacturer and the studies are funded from manufacturer. There are no results reported from the ongoing trial The cost of technology is impossible to define because the manufacturer did not provide this information. Available economic studies do not allow to do some consideration because taking into account only macro-categories of expenditure linked to chronic disease and no-adherence of them.

Future prospects

The technology stays in its early phase in which the use of the sensor is useful to monitor the behaviour of patients. According to information from the manufacturer, in the next years the technology will evolve because the sensor will be integrated directly in the drug tablet and this could allow definition of the real assumption/ingestion of drug. This will allow detecting, directly, the assumption of prescribed drugs and guaranteeing a real monitoring of adherence to specific treatment, improving the quality of data. On the basis of low quality and sparse evidence it is not possible to recommend the introduction of “Proteus Personal Monitor – IEM” in a potential programme of adherence monitoring for long term drug therapy. To assess the potential impact of the technology on clinical practice, it is necessary design independent comparative studies on accuracy, efficacy, safety and cost effectiveness using better methods than at present.

Table 1: Summary of the registered studies identified on clinicaltrials.gov

Official title and Registration number	Design	Purpose	Outcome	Phase	N° patinets	Start date - Completion Date
Event Marker Ingested To Trigger Event Recorder 3.0 Psychiatry Study (EMITTER 3.0 PSY) (NCT01804257)	*Single group assignment*	*"Feasibility study of using a digital health feedback system (DHFS) to monitor medication-taking and physiologic and behavioural parameters in patients with bipolar disorder or schizophrenia"*	• *Positive detection accuracy (PDA)* • *System safety*	*NR*	*28*	*May 2010* *May 2011*
Reliability, Safety and Usability of the Transplantation Sensor System Combined With Myfortic® in Adult Kidney Transplant Patients (NCT01320358)	*Single group assignment*	*"To evaluate the reliability, safety and usability of the Transplantation Sensor System when the Ingestible Event Marker (IEM) is given in combination with ECMPS 360 mg tablets in adult renal transplant recipients"*	• *Accuracy and precision in detecting directly observed ingestion* • *Adherence (taking and scheduling) to prescribed medications* • *Incidence and severity of adverse events* • *Satisfaction and usability of the System by patients*	*II*	*30*	*April 2011* *November 2011*
Wirelessly Observed Therapy in Comparison to Directly Observed Therapy for the Continuation Phase of Tuberculosis Treatment (NCT01960257)	*Randomized Parallel assignment*	*"To find out if using these new technologies works as well as the standard method of observing in person when patients take their tuberculosis medications"*	• *Positive Detection Accuracy (PDA)* • *Percentage of Witnessed Doses* • *Subject experience with the DHFS and the usability of the system* • *Subject satisfaction with the DHFS system.*	*IV*	*100*	*October 2013* *June 2015*

Legend: mg=milligrams

Tabella 2: Summary of included studies

Title of study	Study design	Objective	Outcome	N° of patients
Au-Yeung KY, et al, 2011. Early clinical experience with networked system for promoting patient self-management. The American Journal of Managed Care.	4 prospective, observational studies	To assess the patient adherence of long term drug therapy at home or medical ambulatory using a network system compared to DOT.	PDA: 97,1% e 96,7% (encapsulated sensor) Taking adherence: 85,4% (patients with heart failure); 90% (patients with hypertension) Scheduling adherence: 68,5% (patients with heart failure); 82,8% (patients with hypertension) Safety: 69 AE in 45 patients (2 serious but no linked to technology)	111
Belknap R, et al, 2013. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLOS ONE, Vol.8, Issue 1.	Prospective, non-randomized, descriptive study	To assess the accuracy, safety and acceptability of system from patients using DOT.	PDA: 95% Taking adherence: - Accuratezza di identificazione: 100% Scheduling adherence: - Safety: 11 AE in 8 patients (3 linked to technology)	30
DiCarlo LA, 2012. Role for direct electronic verification of pharmaceutical ingestion in pharmaceutical development. Contemporary Clinical Trials 33 (2012) 593-600	Overview + Prospective, non-randomized single arm (no published)	To demonstrate the relevant impact of adherence to drug therapy on reliability of clinical results on pharmacological development.	PDA: 99,3% Taking adherence: - Scheduling adherence: - Safety: -	10
Kane JM, et al, 2013. First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. J Clin Psychiatry 74:6.	Observational study	To compare the accuracy of medical device with DOT.	PDA: 94% Taking adherence: 74% Scheduling adherence: 67% Safety: 9 AE on 6 patients (6 linked to technology)	28
Eisenberger U, et al, 2013. Medication adherence assessment: high accuracy of the new ingestible sensor system in kidney transplants. Transplantation, Vol.96, Number 3.	Pilot study no controlled c	To assess the accuracy, use and safety of technology when compared with specific enteric-coated.	PDA: 100% (vs DOI) 68% (no DOI) Taking adherence: 99,4% Scheduling adherence: 84,5% Safety: 7 patients, AE linked to technology	20

Legenda:

AE: Adverse events
DOT: directly observed therapy
DOI: directly observed ingestion

Evidence searches

Searches of the databases were carried out using the following keywords to indicate:

- ***the technology of interest:*** ingestible sensor system, medication event monitoring device, ingestible sensor based system, Wireless Observed Therapy, WOT, digital health feedback system, DHFS, Raisin system, monitoring adherence therapy system, digital
- ***the pathology of reference:*** medication adherence monitoring, confirming medication ingestion, medication compliance monitoring, treatment compliance monitoring

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Glossary

DOI: Directly observed ingestion

DOT: Directly observed therapy

AE: Adverse event

FDA: Food and Drug Administration

PDA: Positive Detection Accuracy

RDM: Repertorio Dispositivi Medici

WOT: Wireless observation therapy