Evaluation of ReX® - an innovative digital medication management system, for effective assessment and enhancement of patient’s adherence to therapy.

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Key words:

Adherence rate, Non-adherence, Personalized medicine, Medication management
Abstract:

Background: Medication non-adherence is a major problem in healthcare, imposing poor clinical outcomes and a heavy financial burden on all stakeholders. Current methods of adherence assessment are severely limited: they are applied only periodically, do not relate to actual pill intake and suffer from patient bias due to errors, misunderstanding or intentional non-adherence.

ReX is an innovative drug management system designed to address poor patient adherence and enhance patient engagement with their therapy. ReX controls and tracks pills from the point of packaging right through to the patient’s mouth. ReX generates robust, real-time adherence data. Interactive communication with the system enables patients to report outcomes, complete surveys and receive messages and instructions. ReX includes a reusable Drug Dispensing Unit, disposable Cassette containing pills and a cloud-based, data portal.

Objectives: The objectives of this study were to evaluate: 1) ReX safety 2) acceptance and usability of ReX innovative technology 3) efficacy of ReX in (a) providing pills according to the dose regimen; (b) managing reminders and adherence data; (c) enhancing adherence rates compared to standard of care.

Methods: ReX system components and operation are demonstrated. The ReX system safety, usability and efficacy were evaluated in two human-factor, non-clinical, feasibility studies. Human subjects used ReX for administration of pill-shaped Tic Tac sweets, according to a pre-programmed dose regimen. The first study, comprising 59 subjects aged 18-92 evaluated ReX use and administration of 2 pill intakes. The second study was a self-controlled, “walk around” study, comprising 40 subjects, aged 18-90. Subjects took pills at home, for 4 days each via the device (ReX test) or from standard packaging (Control test).

Results: The first study confirmed the usability and acceptance of the ReX novel approach to pill dispensing. All subjects (100%) successfully managed 2 pill intakes. 81% of subjects rated the ReX device as easy to use. The second “walk around” study confirmed the safety, usability and efficacy of the ReX system. Overall adherence rate in the ReX test was 21% higher than in the Control test (P<0.0001, Confidence=95%). Real-time, personalized reminders, provided in the event of delay in pill intake, contributed to 18% of doses taken during the ReX test (P<0.0001, Confidence=95%). 87% of subjects found the ReX system easy to use and felt comfortable using it for their medications.

Conclusions: ReX’s novel “Tracking to the Mouth” technology was found to be safe, feasible and effective for oral medication therapy.
1. Introduction:

“Medication Non-Adherence” is defined as the extent to which patients fail to take medications and/or follow treatment recommendations as prescribed by their care providers. It is one of the most serious problems in healthcare, imposing heavy financial burden on all stakeholders: insurers, employers, and patients [1].

Overall adherence for medication therapies in developed countries was found to be almost 50% [2]. Forgetting to take medication and misunderstanding instructions are the most frequently reported reasons for non-adherence [3]. It is estimated that non-adherence leads to 125,000 deaths per annum and accounts for 69% of all medical-related hospital admittance, in the U.S [2]. Between $100 and $300 billion of avoidable healthcare costs have been attributed to non-adherence in the US annually, representing 3% to 10% of total U.S healthcare costs [3]. A recent report estimated that non-adherence, in 2016, cost the pharmaceutical industry up to $637 billion in lost sales, of which $250 billion were in the U.S [4]. This estimate points to a far more significant problem than previously believed.

Adherence measurement is a considerable challenge. Existing tools are mainly capable of analyzing (a) whether initial electronic prescriptions were picked up and (b) if patients refilled their prescriptions. Current methods of measuring adherence may be classified as direct or indirect:

- Direct methods - Measurement of the drug level or its metabolite in body fluids. Direct approaches are expensive, limited to periodic assessment and subject to variations resulting from the patient’s condition at the test time.
- Indirect methods – These include patient questionnaires, self-reports, pill counts, rates of prescription refills, assessment of patient’s clinical response and patient diaries. Indirect methods are simple but inaccurate and biased [1].

Patient’s adherence to therapy is most critical in the following cases:

1. High risk drugs - Errors, overdose and abuse may lead to serious health effects, medical emergency and death. The most severe global epidemic is overdose of prescribed opioid analgesics. The economic burden of opioid abuse has been valued at $78.5 billion worldwide [5, 6] causing an estimated 69,000 deaths each year [7].
2. Specialty drugs – These comprise high priced drugs, such as biological drugs, drugs requiring special handling and drugs available only via a limited distribution network. e.g.; a new treatment for Hepatitis C (Olysio and Sovaldi) cost up to $1000 per pill and about $80,000 for full treatment [8]. Adherence to such drugs has a critical impact on treatment success. Specialty drugs rapidly penetrate the market. Their cost therefore has substantial impact on overall healthcare costs [9].
3. Clinical trials – Adherence rate of human subjects to an investigational drug is frequently over-estimated in clinical trials. This rate may increase by 30-40% when using methods involving patient’s behavior (such as self-report and pill count), compared to assessment of drug plasma level [10-12], indicating for unreliable adherence assessment. This is explained by intentional non-adherence, which is common in clinical trials [12]. Non-adherence leads to results which are false or misleading and subvert efforts to determine drug safety or efficacy [13]. Moreover, non-adherence necessitates the enrollment of additional patients in order to achieve acceptable statistical outcomes. This results in estimated additional costs ranging from ~$0.5 million in phase 1 trials to $12 million in phase 3 [14].
Novel technology-based solutions have been developed to remotely record, deliver, manage and monitor drug intake information and the patient’s condition. A range of digital health solutions offer adherence monitoring and an electronic treatment diary. These include connected devices (such as smart bottles and pillboxes), SMS reminders and mobile apps [15]. However, to make a profound change in medication adherence levels, it is essential to implement a comprehensive solution addressing all elements of the medication therapy process.

ReX is an innovative drug management system which monitors the drug from its packaging in the pharmacy through to its administration into the patient’s mouth. Pills are locked in the device and can be released only at the right time, at the specified dose and only to the prescribed patient’s mouth. Pill intake data are recorded and transmitted in real time to caregivers. When a dose is missed, a personalized reminder is immediately provided to the patient. ReX can survey the patient’s wellbeing and be used as a treatment dairy. Here we demonstrate ReX system evaluation in two human feasibility studies, aim to demonstrate its safety, usability and efficacy in adherence assessment and enhancement. The benefit of ReX use over standard of care was evaluated as well as its potential to overcome the limitations of current adherence measurement methods.
2. Methods:

2.1. ReX system design:

ReX is a hand-held, mobile device intended to provide solid oral medication on patient demand, according to a pre-programmed treatment protocol. ReX aims to address poor patient adherence by providing safe, reliable and personalized medication therapy management.

The system comprises the following elements:

1. Reusable Drug Dispensing Unit (DDU) (Figure 1(a-1), intended to manage pill administration. The DDU comprises a touch screen, which guides the user through the process of taking a pill, and is used as an e-diary with patient-specific clinical surveys and therapy information. The DDU comprises indicators demonstrating the device’s status, a pill window allowing the pill view, operational sensors and a Bluetooth to App on cellphone, enabling transfer of all information (e.g. pill intake, patient feedback and survey results, drug adherence) to a patient-specific domain on the Dose-E Analytic cloud. The DDU is also used to hold and lock the Disposable Cassette which contains the pills (see point 2 below).

2. Disposable Cassette (Figure 1(a-2), is a locked, tamper-resistant container. It is supplied pre-loaded with bulk pills/capsules located one in each of 16 separated pill compartments. The Cassette is opened only on insertion in the DDU. The Cassette includes an integral part, The Mouthpiece, designed for pill ingestion. The Mouthpiece incorporates an anti-choke mechanism which ensures that the pill falls directly onto the tongue. An integral protective cover keeps the Mouthpiece clean and sealed. Once empty the Cassette is automatically released by the device. Cassette exchange is easily performed by the patient.

3. Cellphone application (App) (Figure 1b), Used to connect between the DDU and the Dose-E Analytic cloud. The App provides reminders to patients and transfers data, stored locally in the DDU, to the Dose-E Analytics cloud.

4. Dose-E Analytics cloud system (Figure 1c) – a browser-based application in which all therapies and patient information are collected and managed. The cloud functions do the following:
   - allows caregivers to track the therapy online and follow patient’s adherence
   - sends alerts to call a center/ contact person when a missed dose is recorded, leading to real-time reminder to the patient.
   - enables the physician or pharmacist to easily setup the therapy regimen, and transfer it to the DDU by the ReX App.
   - collects adherence statistics for analysis over an extended period or user population. Drill down to every pill intake is possible. These features facilitate individual therapy optimization.
Figure 1: ReX system components (a). ReX device, comprising Reusable Drug Dispensing Unit (DDU) (1) and Disposable Cassette (2) (b). Cellphone application (c) Dose-E Analytics cloud system
2.2. Principal operation of ReX:

- Pill intake procedure: the DDU prompts the patient to take a pill at the defined time, by means of sound, light and animations (Figure 2A). The patient requests a pill by pressing on the pill release button (Figure 2B). Then, the patient applies a slight suction into the Mouthpiece and the pill is released onto his tongue (Figure 2C). If the patient presses the button within the pre-defined lock-out period, the device will not release a pill.

- Data management: the device records all pill intake events. This information is transmitted through the cellphone App to the Dose-E Analytics cloud. Therapy data can be relayed in real-time to payers, providers, and care givers.

- Reminders and alerts: the time window in which the user can take a pill is termed the "Tolerance Time" (TT). The TT determines the automatic reminders. These include visual and acoustic alerts as well as text messages to the DDU screen and cellphone App. As the pill intake window progresses, without a pill being taken, the reminders escalate in frequency and intensity. Towards the end of the TT, if a pill has still not been taken, personal reminders are initiated: An email is dispatched to the recognized contact person (PI or a call center). The patient receives a personalized reminder (phone call) reminding him to take his pill and to establish the cause of the delay. This process ensures that reminders are provided only when needed, eliminating diminished responsiveness to unsolicited alerts.

- Surveys and therapy information: Real-time patient surveys and an e-dairy can be filled via the DDU screen (Figure 2d). The patient may use the screen to check his adherence rate, course of treatment and obtain information (Figure 2e).
Figure 2: ReX operation and patient journey. (a) At pill intake time the device alerts the patient to take the pill by means of sound, light and via the App. If a delay is recognized, a personalized phone call reminder is provided. (b) Administration of pill intake by pressing the upper bottom. The pill is transferred to the dispensing compartment by rotation of the carousel in the Cassette. (c) The patient applies a slight suction into the Mouthpiece and the pill is released onto his tongue. (d) The device offers clinical surveys or recording an e-dairy (e) The patient may use the device to check his adherence rate, course of treatment and obtain information.

2.3. The ReX Usability Study:
This study aimed to evaluate the acceptability and usability of the novel ReX concept. The study was set up to test ReX on uninitiated human subjects, evaluate their capability to use the device and to extract pills. The study also noted reactions to the innovative concept of consuming a pill dispensed directly into the mouth, by sucking through a mouthpiece.

Study objectives:
The study goal was to evaluate the following ReX parameters:
1. Usability of the device (inserting the Cassette, screen menu options, pill extraction).
2. Ease of extracting a pill and acceptance of the pill extraction concept.

The study was “non-clinical” since the pills used were pill-shaped Tic Tac sweets.
2.3.1. Study design:

- All subjects enrolled for the study signed an Informed Consent Form.
- Each subject underwent an in-person training session, including an interactive training tutorial displayed by the device covering Cassette exchange and pill intake.
- Subjects were asked to insert a Cassette and take two pills using the device.
- Subjects filled a questionnaire about their experience with the ReX device.

2.3.2. Study population

The study was carried out with 59 human subjects (29 males, 30 females), aged 18-92. Subjects details recorded were: gender, age, years of formal education and frequency of taking medication (on a daily basis or not). Subjects were divided into 7 age groups. Table 1 shows subjects' demographics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Total # (%)</th>
<th>Gender # (%)</th>
<th>Take pills regularly # (%)</th>
<th>Years of formal education # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>All Subjects</td>
<td>59 (100)</td>
<td>29 (49)</td>
<td>30 (51)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Age 18-30</td>
<td>10 (17)</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td>3 (30)</td>
</tr>
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<td>Age 31-40</td>
<td>7 (12)</td>
<td>6 (86)</td>
<td>1 (14)</td>
<td>2 (29)</td>
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<td>11 (19)</td>
<td>7 (64)</td>
<td>4 (36)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Age 51-60</td>
<td>8 (14)</td>
<td>3 (38)</td>
<td>5 (62)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Age 61-70</td>
<td>10 (17)</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Age 71-80</td>
<td>6 (10)</td>
<td>2 (33)</td>
<td>4 (67)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>7 (12)</td>
<td>3 (43)</td>
<td>4 (57)</td>
<td>5 (71)</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics of human subjects participating in the study

2.3.3. Study measures:

The study evaluated the following parameters:
1. Subjects ability to insert a Cassette.
2. Success rate of pill extraction using the device.
3. Understanding of screen menus.
4. Understanding the concept of lockout and overdose prevention.
5. Overall ease-of-use.
6. General feedback on the whole procedure.

Results were recorded on a questionnaire comprising Likert scale responses. Subjective and non-solicited opinions were noted.
2.4. The ReX “walk around” study:
The study was designed as a self-controlled, “walk around” study with the following objectives:

1. Evaluate the safety, functionality and usability of the ReX system, in a 4 days home use.
2. Assess ReX ability to enhance adherence rate compared to standard of care (taking pills from standard pill container).

Pill-shaped Tic-Tac sweets were used to mimic medication. The study is therefore defined as “non-clinical”.

Human subjects, 18 years and older, were enrolled to the study and signed written informed consent. Each subject participated in the following tests:

1. Control test (n=40) – Subjects took pills from the original package and manually reported for each pill intake or missed dose. At study end, remaining pills were counted.
2. ReX Device test (n= 40) – Subjects took pills using the ReX device. During the study, pill intakes were recorded by the ReX system. Delays in pill intake lead to real-time personalized reminders by a phone call and/or text message. At study end, remaining pills were counted and compared to ReX records. Subjects were also asked to report any safety or functionality problem encountered during the study, and to fill out a questionnaire regarding their experience with ReX.

The study flow chart is shown in Figure 3.

Both tests had the same duration and dose regimen, as follows: 2 pills in the morning, 1 pill in the evening, for 4 days. The specific time of pill intake was programmed in the ReX device to be: 08:00 AM and 18:00 PM. The TT was set as; +/- 1 hr. This implied an intake window for the morning pill of 07:00-09:00 AM and for the evening pill of 17:00-19:00 PM. In case of pill intake delay, after the TT, an email was dispatched prompting the PI to contact the subject via phone call/text message.

Before study start, each subject underwent a short, one-to-one, training session in which he successfully completed 2 pill intakes using the ReX. During the ReX test, real-time adherence data was communicated to Dose-E analytics software in the cloud and made available to the study’s PI.

For the Control test, subjects were asked to self-record each pill intake. Missed pills were not recorded. No reminders were performed during this test since the adherence data was not available to the study’s PI.
2.4.1. Study population:
The study comprised 40 human subjects, aged 18-90, male and female. Subjects details recorded were: gender, age, and frequency of taking medication (on a daily basis or not). Subjects were divided into 3 age groups; 18-40, 41-70, 71-90, in order to test the performance and adherence of different age groups while using the ReX for pill intake. Subjects details are shown in Table 2.
<table>
<thead>
<tr>
<th>Group</th>
<th>Total # (%)</th>
<th>Average Age (Years)</th>
<th>Gender</th>
<th>Take pills regularly # (%)</th>
</tr>
</thead>
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<tr>
<td>All Subjects</td>
<td>40 (100)</td>
<td>48.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males # (%)</td>
<td>21 (52.5)</td>
<td></td>
<td>Females # (%)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Females # (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 18-40</td>
<td>13 (32.5)</td>
<td>27.5</td>
<td>6 (15)</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Age 41-70</td>
<td>18 (45)</td>
<td>53.7</td>
<td>10 (25)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Age 71-90</td>
<td>9 (22.5)</td>
<td>79.4</td>
<td>5 (12.5)</td>
<td>4 (10)</td>
</tr>
</tbody>
</table>

Table 2: Demographic characteristics of human subjects participating in the study

Inclusion criteria:
- Age 18-90,
- Ability to extract pills by the ReX device.

Exclusion criteria:
- Significant physical disability of hands or head or mental disorder,
- Failure to extract 2 pills after 3 attempts during ReX training.

2.4.2. Study objectives:
- Safety – to assess safety events including; (a) pill overdose; (b) pill malformation; (c) safe dispensing into the mouth.
- Functionality – to evaluate ReX capability of (a) providing pills according to the dose regimen; (b) management of reminders and adherence rate.
- Adherence efficacy – to compare user’s adherence in the ReX test and the Control test.
- Usability – to assess ease of use and subjects’ acceptance of novel ReX technology during 4-day home use.

2.4.3. Statistical analysis:
Paired differences were calculated for adherence rate and % of missed doses between ReX test and Control test, for all subjects and by age categories. Paired differences were calculated for % of doses taken between before and after reminder, only for ReX test.

The Paired T-test and Non-parametric Signed-rank test for two means (paired observations) were applied for analyzing the paired differences.

Statistical power was calculated for the paired differences.
All tests were two-tailed, and a p-value of 5% or less was considered statistically significant.

The data was analyzed using the SAS * version 9.3 (SAS Institute, Cary North Carolina).
3. Results:

3.1. Evaluation of ReX in a usability study:

The ReX system is based on the innovative concept of dispensing solid medication, in pill or capsule form, directly into the patient’s mouth. This novel approach of sucking solid matter through a plastic mouthpiece requires patients’ acceptance and willingness to use. The first feasibility study aimed to evaluate usability, acceptability and ease of use of the ReX device for oral medication provision. 59 subjects, aged 18-92, participated in the study.

All subjects successfully inserted the Cassette into the ReX dispensing unit, following a short tutorial, and defined this process as "Easy" (data not shown).

Usability of ReX for pill extraction was measured by success rate of 2 pill intakes. All subjects managed two successful attempts of pill intake as required and 81% of subjects required 1-2 attempts to extract pills. A learning effect was evident in taking pills: subjects were more successful in taking their second pill compared to the first.

All subjects easily grasped the concept and functionality of the ReX's screen displays. After two successful attempts at pill intake, 100% of subjects understood the concept of lockout and overdose prevention, as shown on the screen following a third attempt at pill intake. The overall impression was very positive. 97% of subjects expressed confidence in using ReX by themselves, without assistance.

Figure 4 demonstrates subjects' response regarding overall ReX ease of use: 81% of all subjects, rated the ReX device as easy to use. This rating did not appeared to be influenced by years of formal education, but was influenced by age. Usability analysis by age group demonstrated that 28.5% of subjects above 80 years old reported that ReX use was difficult. Opinions as to "ease of use" slightly decreased with age. Still 94% of subjects aged 18-40, and > 80% of subjects aged up to 80 defined the ReX as "easy to use."
3.2. Evaluation of ReX system in a “Walk around” human study
Following validation of ReX usability and ease of pill extraction by most subjects, we aimed to evaluate ReX's capability to monitor and enhance patient’s adherence. ReX system was evaluated in a self-controlled, “walk around”, study, in which pill intake using ReX was compared to intake from a standard pill container as control. The same dose regimen was used for both methods: 4 days, twice a day, 2 pills in the morning and one pill at the evening. 40 subjects were enrolled with age range 18-90.

The study aimed to evaluate the safety, functionality and usability of the ReX system, by comparing adherence rates between the Control test and the ReX test. The adherence rate was recorded by the ReX system (ReX Test) or by subject’s self-reporting (Control test). Delays in pill intake in the ReX test lead to real-time personalized reminders to subject. At the study end, remaining pills were counted and compared to ReX records.

3.2.1. ReX device safety:
Safety of the ReX system was evaluated by questionnaires filled in by subjects and confirmed by data recorded in the Dose-E cloud. No incidence occurred of pill overdose dispensed and no pill malformation was reported. Furthermore, no severe adverse events, such as pill inhalation, occurred. The results indicated that the ReX system may be safely used to provide pills at home.

3.2.2. ReX Device Functionality and Adherence Efficacy:
Functionality of the ReX system was measured by the success rate of pill intakes. All subjects (100%) successfully obtained pills by the ReX device, according to their dose regimen. Over 80% of subjects and PIs did not encounter any technical difficulties during device use, such as problems involving the touch screen; pills extraction on time; and data transfer, monitoring and management by the Dose-E Analytics cloud system.

3.2.2.1. Comparison of adherence rates:
The study aimed to compare two processes of pill administration; use of the ReX system (ReX Test) or use of a standard pill container (Control test). Subject’s adherence rate was compared during the study, and measured by remaining pill count at study end. Table 3 lists the data obtained for all subjects and by age groups. Figure 5 demonstrates the mean adherence rate for all subjects and for the 3 different age groups; 18-40, 41-70 and 71-90, as well as their general frequency of pill intakes (users were asked if they take pills on a daily basis). Results show that adherence rate of all subjects in the Control test was 76.3%, while adherence rate in the ReX Test was 97.6%. This implied an elevation of 21% in the adherence rate when using ReX system. This difference was found to be statistically significant, P<0.0001, power>95%. Analysis by age group demonstrated similar results: adherence rates in the ReX Test were stable and reached 97-98% for all age groups with very low variations (up to 5.8%). By contrast, adherence rates in the Control test varied significantly between age groups and were subject to high standard deviations (up to 27.8%). Most young subjects (age 18-40) do not take pills on a daily basis. Their adherence in the Control test was relatively low – 64.9%. However, use of ReX increased the
adherence of this age group to 98.1%. All subjects aged 71-90 take pills on a daily basis. Their adherence rates in the Control test were relatively high, reaching 86.2%. Nevertheless, this improved to 98.6% by using ReX. 55.5% of subjects aged 41-70 reported that they take pills on a daily basis. Their adherence rates in the Control test were moderate (79.4%). This increased to 96.8% by using ReX. Differences in adherence rate between ReX and Control were found to be statistically significant ($P < 0.05$) in all age groups.

<table>
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<tr>
<th>Adherence Rate</th>
<th>N</th>
<th>Mean</th>
<th>Std</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>$P$-value (Paired T-test)</th>
<th>$P$-value (Signed-Rank test)</th>
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<tr>
<td>ReX</td>
<td>40</td>
<td>97.6</td>
<td>5.2</td>
<td>83.3</td>
<td>100.0</td>
<td>100.0</td>
<td>95.9</td>
<td>99.3</td>
<td>&lt;.0001</td>
<td>&lt;.0001 (power&gt;95%)</td>
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<td>40</td>
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<tr>
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<td>9</td>
<td>98.6</td>
<td>5.8</td>
<td>83.3</td>
<td>100.0</td>
<td>100.0</td>
<td>93.9</td>
<td>101.2</td>
<td>0.0206</td>
<td>0.0313 (Power=69%)</td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>86.2</td>
<td>13.4</td>
<td>66.7</td>
<td>87.9</td>
<td>77.0</td>
<td>77.0</td>
<td>94.0</td>
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*Table 3: Adherence rate statistical analysis for all users and by age group. Std- Standard deviation, CI - Confidence Interval
Figure 5: Adherence rate (%) of subjects to dose regimen and the frequency (%) of subjects taking pills regularly. Adherence rate was calculated based on remaining pill count at study end as well as ReX system records (in ReX Test) and subject’s self-report (in Control test). (a). Adherence rate (%) of the Control test and the ReX Test, for all subjects and at different age groups. (b). Frequency of regular pill intakes by subjects at different age groups.

3.2.2.2. Effect of personalized reminders:
Following a 1-hour delay in pill intake, recorded by the ReX system (1-hour delay was defined as beyond the Tolerance Time), subjects doing the ReX test received a personalized reminder. This personalized communication aimed to prompt them to take their delayed dose and to understand the cause of the delay. Table 4 showes analysis of difference in % dose taken before personalized reminders were
provided and following personalized reminders, only for ReX test, as well as in % of missed doses in both ReX test and Control test. Both differences were found to be statistically significant, $p < 0.0001$, power>95%.

Figure 6 demonstrates the mean of % of doses taken by subjects, before and following personalized reminders (only for ReX test), and the % of missed doses in both tests. The reminders were provided personally, by a phone call made by the study’s PI, once a delay was recorded by the ReX system. In the Control test, personalized reminders were not applied, therefore only % of doses taken before reminders or missed doses are shown.

Results demonstrate that the mean % dose taken with no personalized reminders was 79% in the ReX Test and 70% in the Control test. % of dose taken after personalized reminders was 18% in the ReX Test. Only 3% of doses were completely missed in the ReX Test, while 30% of doses were missed in the Control test. These results demonstrated that real-time, in-person, phone call reminders can significantly enhance adherence rate to therapy.

<table>
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<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value (Paired T-test)*</th>
<th>P-value (Signed-Rank test)*</th>
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<td><strong>ReX test</strong></td>
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<td>% of dose taken before personalized reminders</td>
<td>40</td>
<td>78.9</td>
<td>19.6</td>
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<td>79.2</td>
<td>100.0</td>
<td>72.9</td>
<td>84.9</td>
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<td>&lt;.0001 Power&gt;95%</td>
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<tr>
<td>% of dose taken after personalized reminders</td>
<td>40</td>
<td>18.0</td>
<td>16.7</td>
<td>0.0</td>
<td>12.5</td>
<td>75.0</td>
<td>12.9</td>
<td>23.2</td>
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<td><strong>ReX test</strong></td>
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<td>% of missed doses</td>
<td>40</td>
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<td>0.0</td>
<td>0.0</td>
<td>25.0</td>
<td>1.0</td>
<td>5.2</td>
<td>&lt;.0001</td>
<td>&lt;.0001 Power&gt;95%</td>
</tr>
<tr>
<td><strong>Control test</strong></td>
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<tr>
<td>% of missed doses</td>
<td>40</td>
<td>30.1</td>
<td>31.8</td>
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<td>25.0</td>
<td>100.0</td>
<td>20.8</td>
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</table>

Table 4: Analysis of % dose taken before and following personalized reminders (only for ReX test), and % missed doses in both tests.
Figure 6: Effect of real-time, personalized reminders on % dose taken. Doses taken were recorded by pill count at study end and by ReX, or by self-reporting in the Control test. Only in the ReX Test, did a 1-hour delay in pill intake lead to an email dispatched prompting the PI to call the ReX user who missed his scheduled dose. Graph shows % of dose taken before personalized reminders in both tests, after personalized reminders only in the ReX Test (personalized reminders are not applicable in the Control test). % of missed doses was recorded in both tests.

3.2.3. ReX device usability:
Usability and ease of use of the ReX system were evaluated by questionnaires completed by subjects. Figure 7 demonstrates ease of use and acceptance of the ReX device by subjects. 87% of subjects found the ReX system easy to use and almost 90% of subjects mentioned that they felt comfortable using ReX for their medications. Moreover, over 90% of subjects described the ReX device as:
1. a preferred tool to run an e-dairy during their medication therapy.
2. more effective in reminder provision and error prevention compared to standard of care (data not shown).

These results demonstrated high usability and acceptability of the ReX system, incorporating pill ingestion by sucking as a means of medication provision during home treatment.
Figure 7: Usability of ReX system. Results were extracted from questionnaires filled by subjects at study end. (a) Subjects were asked if they feel comfortable to use ReX system for their medication. (b) Subjects were asked to rate ease of using ReX.

4. Discussion:
Reliable monitoring and collecting drug adherence data is a major challenge. Successful adherence measurement allows for better interpretation of therapy outcome, while enhancement of adherence leads to improved clinical outcome and significant cost savings for healthcare systems and pharmaceutical companies [1, 16].

ReX is an innovative system designed to directly monitor patient adherence during therapy, allowing 100% confidence in the resulted adherence rate. ReX incorporates “tracking to the mouth”, which is based on a patented technology of safe ingestion of solid pills into the patient’s mouth and digitally tracking this action to provide accurate, reliable and real-time adherence data to stakeholders.

Most common methods of adherence monitoring involve patient’s self-report and remaining pills counts. However, these appear to be the least reliable methods for collecting adherence data. There is extensive evidence that such methods greatly over-estimate medication adherence, when compared to plasma drug level and electronic devices measurements [10-12]. These methods may also suffer from intentional non-adherence, including removing and discarding pills from a blister card or bottle, to create false record while reporting good adherence [12]. The ReX approach eliminates false measurements since each pill is tracked directly during ingestion. The adherence rate is obtained in an unbiased way, without the patient involvement.

Another known approach is medication packaging/organizers with memory chips. A memory chip embedded in bottle caps or blister packs tracks medication adherence electronically. The most extensively used product is the MEMS cap [17] (AARADEX Group, SA) which records the date and time of
each opening. However, if a subject takes too many (or no) pills when the cap is opened, or removes pills and takes them later, a false record of dosing is created [12].

There is a vast pool of medication adherence cellphone apps available to help patients manage their medication regimen [18]. One such idea is photo- or video-assisted direct observation (AiCure, LLC, NY, US). This approach is based on patients using camera/video capable cellphones to transmit images of capsules before ingestion in their mouth or videos of ingestion [19]. This application shares with ReX the recognition that a pill located in the patient’s mouth mostly implies intake. However, photo or video apps add burden on subjects to record and send images/videos each time they take a pill. This action may be missed at the time of pill intake. Other patients may refuse to cooperate in sending their images/videos for cultural and privacy reasons. By contrast, ReX is based on “all in one” methodology, in which each pill intake is monitored during actual ingestion. No pill can be taken without monitoring. This approach is simple to operate and does not burden the patient. The ReX methodology is accurate and unbiased by patient’s involvement. Drug overdose is eliminated since each pill intake is tracked separately.

Other new technologies are based on incorporating chemicals (2-Butanol, Xhale, Inc. US) [20] or ingestible sensors (Proteus Digital Health, Inc.) [21], that can be detected following ingestion, by a body-worn patch that collects physiological and behavioral metrics, and transfers this information to a mobile device. Although these methods indeed track the pills after ingestion in the patient's body, they cannot eliminate overdose nor prevent abuse by confirming the patient’s identity. Moreover, this approach requires heavy regulation for each specific drug, leading to very costly products. ReX offers a cost-effective solution for adherence monitoring, while safeguarding patient identity and dose regimen.

An initial usability study was conducted to evaluate basic usability parameters of the ReX device and acceptability of the pill extraction concept. Results demonstrate that all subjects could successfully use the device for pill intake, and > 80% only required 1-2 attempts for successful pill intake and defined the device as easy to use. Only mature users, aged > 80, reported more difficulty although they all could manage and extract pills by the device. These results demonstrate the feasibility of the ReX novel technology.

Following this, we designed a “walk around” study to evaluated ReX safety, functionality and usability, in 4 days home use. Adherence rate by ReX was compared to standard of care. The ReX device was found to be safe. Pill inhalation did not lead to any adverse events, overdoses or pill malformation. The safety of pill ingestion by sucking was previously confirmed in a clinical study evaluating the same technology for pain analgesics medication provision to post-operative patients in the hospital setting [22].

Functionality analysis revealed that all subjects, aged 18-90, could successfully use the ReX device for pill intake and that adherence data were available for the study’s PIs in real time. Study results showed statistically significant difference of 21.3% in adherence rate between the ReX Test and the Control test. It is possible that low adherence rates in the Control test (76.3%) occurred because subjects took Tic-Tac sweets and not real medication, making it less important to them. However, the same subject group achieved an average adherence rate of 97.6% in the ReX Test. Such high adherence was due to stringent monitoring of each subject by the study’s PI and timely reminders to subjects in any case of delayed dose. This created effective communication and reinforcement to take the missed dose.
The adherence rate of the Control test varied between the 3 different age groups; 18-40, 41-70 and 71-90. Only 8% of the young subjects (age 18-40) take pills regularly, and are therefore not used to taking pills. Their adherence in the Control test was consequently relatively low, 64.9%. However, use of ReX increased their adherence rate to 98.1%. Mature subjects (age 71-90) demonstrated higher adherence in the Control test (86.2%). This may be because all subjects of this age group take pills on a daily basis. However, using ReX enhanced adherence rate in all age groups. All differences in adherence rate between ReX test and Control test were statistically significant. Notably, the variation of adherence rate between subjects was substantially higher in the Control test (up to 30%) relative to the ReX Test (up to 5.5%). ReX achieved maximal adherence for subjects of all ages.

Personalized reminders were shown to add 18% of doses taken. This explains the major difference in adherence rate between ReX Test and the Control test. Notably, adherence rates in the ReX Test were 8% higher compared to the Control test before any personalized reminder. This may be due to the non-personalized alerts, visual and acoustic, provided by ReX. The interest of subjects in the novel technology and their intention to succeed in using it may have contributed to the higher adherence rate in the ReX Test compared to the Control test, before personalized reminders. % missed doses in the Control test was 10-fold higher than in ReX Test. This observation clearly demonstrates the benefit of using ReX system to monitor and enhance adherence.

Electronic monitoring devices have been shown to provide good quality information on adherence rates [12] and hold promise for improving adherence, as demonstrated in multiple clinical trials [17, 20, 21]. Methods which involve reinforcement interventions were successful in improving patient’s cooperation and adherence behaviors. Clear and effective communication between caregivers and their patients is essential in improving patient’s adherence [23]. ReX was designed to provide a timely personalized reminder to patients only in case of missed dose. This direct and relevant communication enables PIs to understand the reasons for non-adherence, increases patient’s engagement with the therapy and reinforces it in real time.

The usability of ReX was tested by questionnaires filled by the subjects participating in both ReX and Control tests. ReX device is based on a novel approach of solid pill ingestion, Nevertheless, almost 90% of subjects reported, after 4 days of use and 12 pill intakes, that they felt comfortable taking their medication via ReX and that it is easy to use. Moreover, over 90% of subjects believe that ReX provides effective reminders, is highly effective in error prevention and is most suitable to be used as an e-dairy to record symptoms during therapy. These results are in agreement with the high usability and well acceptance demonstrated in a previous clinical study [22].

5. Conclusions:

Two feasibility studies confirmed the safety, functionality and usability of the ReX system. All objectives were achieved;
1. ReX safety: The ReX system is safe under the study conditions; no severe adverse events, no pill provision during the lockout interval, no overdose and no pill malformation were found.
2. ReX functionality: All subjects successfully used ReX to take the pills according to their dose regimen. The data were available to the Study's PI in real time and personalized reminders were provided in any case of 1-hour delay in pill intake. Adherence rate in the ReX Test was significantly higher compared to the Control test. Only 3% of doses were completely missed, compared to 30% of doses in the Control test. 18% of doses in the ReX Test were taken after personalized reminders by phone call, indicating the effectiveness of real time personalized reminders.

3. ReX usability: ReX technology was well accepted by subjects participating in the studies. Above 80% of participants described it as easy to use and mentioned that they feel comfortable to use it for their medications.

Study limitations:

Limitations of the study included the heterogeneous small groups size, and the use of candies and not real drugs. Adherence rate was based on self-reporting and remaining pill counts in the Control test. These are known to be non-reliable methods. ReX records are more reliable in the ReX Test. The study design ensured that half of the subjects completed the Control test before the ReX test, and vice versa for the other half.

Conflict of interest:

The authors declares that they all are DosentRx employees.

Contributorship:

Designed & developed the ReX system: SC, KS, RaS, EhM, EnM, HE, AP. Designed & performed the feasibility studies: RS, SE, HE. Analyzed the data: RS, HE. Wrote the manuscript: RS. Reviewed and edited the manuscript: HE.

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Acknowledgements:

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Abbreviations:

App – Application,
DDU - Drug Dispensing Unit,
LED – Light Emitting Diode
TT- Tolerance Time
MEMS – Medication Event Monitoring System
6. References:


