**Subject Compliance as an Electronic Patient-reported Outcome –**
**How Much Compliance is Enough?**

**Abstract**
Subject non-compliance with clinical trial requirements can lead to invalid data, false-negative results, and inaccurate dosage recommendations. Investigators and subjects generate barriers to compliance, and the reasons usually involve poor comprehension, communication, and/or follow-up. As mobile electronic devices have become ubiquitous, they have led to significant changes in individual behavior, including the expectation of constant communication and an increased comfort in sharing personal behavioral information. The use and integration of these same technologies in clinical trials provide the opportunity for recording and assessing subject compliance as it is happening rather than retrospectively. The result will be the establishment of subject compliance as an electronic patient-reported outcome.
**Disclosure** The author is CEO of Medicus Research LLC and Systemedicus Inc.
**Correspondence:** jay.udani@medicusresearch.com

Patient compliance is the degree to which a patient correctly follows medical advice within a given timeframe, and patient adherence is the persistence in staying with a particular regimen. Outside the scope of a clinical trial, if a patient does not adhere to a specific regimen (and the World Health Organization estimates that the adherence rate for long-term therapy in developed countries is at best 50 %),1 the results can be medically negative for that individual. In clinical trials, subjects are given a particular regimen to follow and the degree to which they do (or do not) comply with it is recorded as their compliance rate. If these subjects are not compliant, the negative impact can be felt far beyond their individual health status. Reduced subject compliance and adherence can lead to a false-negative conclusion, they can diminish the ability to compare the data to previous studies, and dosage recommendations may be inaccurate, leading to higher rates of adverse events when the medication is actually taken as directed.

The current paradigm for assessing compliance during clinical trials is to wait until the subject returns to the clinic for their next visit, at which point the actual number of pills in the bottle is compared to the expected number of pills based on the dispensed quantity, the prescribed frequency of consumption, and the length of time between dispensing and returning. The standard of practice involves the study coordinator manually counting the pills and calculating the compliance ratio (taking into account whether or not the last visit counted as the first day of treatment, and whether or not the subject actually took their pill on the day of the visit). This is fraught with potential errors in many ways, because there is no documentation of when the pills were actually taken (date and/or time of day), who took them, or whether the pills were actually taken or just dumped in the garbage.

Even when daily paper diaries are required from subjects, a careful analysis of the individual diaries shows that these documents are often filled out in the waiting room just before the visit. The reasons for this non-compliance are rarely malicious. Usually subjects are too busy with the rest of their lives (work, children, household chores, education, entertainment, etc.) to be full-

time research subjects. While this is not surprising, it is often our own health that takes a backseat relative to the countless demands of the day.

**Improving Compliance and Adherence**

The AIDES method for improving medication compliance and adherence includes five evidence-based solutions (see *Table 1*).[2] Assessment and individualization are less relevant to subjects participating in clinical trials, but providing written documentation, providing tailored education, and providing continued supervision are certainly valuable solutions. This is where compliance technologies can emerge as a valuable asset.

**Compliance as an Electronic Patient-Reported Outcome**

Electronic patient-reported outcomes (ePROs) on mobile devices have become widely adopted in clinical trials. Mobile devices have the advantages of convenience, portability, simplicity, and accessibility and, as smartphone usage becomes ever-present (according to some estimates, 63.2 million Americans and 72.6 million Europeans were using smartphones at the end of December 2010), familiarity with these devices is growing rapidly.[3] Their primary use in clinical trials has been for the recording of subjective data (scales, questionnaires) as ePROs. Secondary use has included appointment reminders, education, and motivation, in concordance with the documentation and education recommendations of the AIDES method.

What remains absent from the solution is ongoing supervision. When one considers that, during a clinical trial, a subject spends most of his/her time spends outside the clinic, where there is no direct supervision, it is easy to understand why compliance and adherence are difficult to maintain. There have been clinical trials in developing countries in which the study medication was delivered daily to the subject's house and its consumption directly observed by the delivery personnel. This solution is not viable in most locations, nor is it scalable. Mobile devices, many of which are already in use in clinical trials, can bridge this gap. These devices can be grouped as follows:

- devices that automatically record an activity (opening the cap on a bottle sends a signal to a mobile device or directly to a remote server);
- devices on which the subject records an activity (the subject logs their activity on a mobile electronic device or through a web browser on any connected device or computer); and
- devices that record the subject performing an activity (the subject is recorded while consuming their study medication).

The first type of devices will record the time and date of an event, but they cannot authenticate the user. It is also limited in that the opening and closing of the cap of a bottle does not ensure that the correct number of pills (if any) have been removed from the bottle, and cannot confirm that the pills have been consumed (rather than discarded). The second type of devices is currently in use and, while their eDiary features allow for time/date stamps, they too cannot authenticate the user or confirm whether the study drug has actually been consumed by the subject. It is the third type of devices that heralds the progress of compliance assessment in healthcare. The actual video recording of the subject while he/she is taking the study medication (in conjunction with the reminder systems and time/date stamps inherent in the second type of devices) will provide a dramatic departure from the current guesswork. The identity of the subject can be validated through biometric authentication, the identity of the study medication can be validated through barcode or radio frequency identification, and the recordings will be stored on the mobile device for review at the next clinic visit or transmitted wirelessly to the clinic for review.

Compliance is now calculated automatically based on valid realtime data encounters. Alerts for non-compliance can be auto-generated and sent to study coordinators so that they can invervene earlier. All of the features and benefits readily ascribed to ePROs are now available for compliance. In this way, the realtime recording and validation of the consumption of the study medication becomes a reliable ePRO rather than the product of retrospective speculation.