The Past, Present and Future of Capturing the Subject's Experience in Clinical Trials

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The goal of clinical research is to evaluate the efficacy and safety of a drug compound or medical device. Historically, most of the clinical data supporting drug evaluation was captured by physicians and nurses extracting blood and other fluids from subjects and/or measuring physiological reactions such as blood pressure and heart rate. A growing trend is to directly ask subjects to report on their experience with the drug (patient reported outcomes; PROs). The primary shortcomings of this approach to clinical research are that most data is captured *only* at the clinical research site, and *only* at a few site visits during the treatment period. In other words, we only obtain a brief snapshot or still photo of the drug's effect on the subject. This brief article discusses how technology will enable clinical research to move beyond the still photo view of drug impact.

We suggest that the ideal evaluation of a drug's or medical device's efficacy and safety is a comprehensive picture of the subject's experience over time – in other words a continuous measurement stream of the patient reported outcomes (PROs)[a] and physiological reactions to the drug. Why? The most accurate PROs information is captured from the subjects in real-time, real-world settings[2]. Moreover, a drug's effect on physiological measures may vary considerably over time, in response to the rising and falling blood levels of the drug over days, and sometimes weeks. In other words, to fully understand a drug's impact, it is necessary to continuously monitor its effects over days, weeks, and maybe months.

Phase I studies of clinical research, where drugs are introduced to humans for the first time, reflect this concern for continuous, accurate PRO and physiological data. In a typical Phase I study, subjects are continuously monitored in the clinic for long enough periods (e.g., one or two days) to ensure the drug is acutely safe, and to begin to determining if the drug is effective. Yet, once the drug moves to later phases of evaluation, where the exposed numbers of subjects exponentially increases, our data collection approach shifts to far fewer measures – the snapshot. We propose that technology will enable the Phase I approach to be expanded to all phases of drug development - subjects will be monitored in real-time, in their real-world settings. Such monitoring would create, metaphorically, a complete 'documentary film' of each subject's experience.

How do we move toward the full subject documentary film? *Technology will enable, but not drive, this advance in clinical research science*. This article discusses how technology, applied with clinical expertise, will enable this more-complete, more-sensitive understanding of subject's experience with a test drug or medical device. We start with the advantages and disadvantages of the historical approach to capturing clinical data. We then describe the current state

[a] Subject reported outcomes, PROs, offer unique insight into subjects' experience with the drug, including: the effectiveness of the drug in many instances (e.g., pain reduction, migraine frequency or intensity reduction); side effects that may have occurred while subjects have been taking the drug; and the overall treatment effect on quality of life.

of the art of technology implementation in collecting clinical data; the silent movies. The remaining sections of the article discuss the requirements for a system that could yield a documentary view of the subject.

The Past: Snapshots

Historically, the subject's experience of a drug's effects has been captured at the time of a visit to the investigator's site. These visits include a pre-drug visit to determine the baseline state of the subjects, a few interim visits during the treatment phase of the study, and an end of treatment visit. The same physiological and PRO measures are typically repeated at each visit. Further, the subject is often asked to recall relevant events that occurred since the last visit, which could be days, weeks, or months ago. By limiting data collection to clinic visits the research and/or healthcare professionals can:

- utilize sophisticated and often expensive measurement tools to evaluate the subject's condition
- have a face-to-face interview with the subject to form a clinical impression
- ensure that all PROs are completed by the subjects

Clinic-only data collection yields significant control over the process, and confidence about when the data was collected.

One disadvantage of collecting data solely at clinic visits is that by definition much of the subject's complete experience with the drug has not been evaluated. The subject's day to day, and even moment by moment effects are not fully captured by taking measures only at site visits. While this may be appropriate for some drugs and conditions that are chronic, or have protracted effects, there are many situations where the impact of the drug would not be fully examined. For example, in a condition such as migraine headaches, the event has an onset, time course, significant variation in pain and other symptoms associate with the migraine. Capturing this after the fact at a site visit will leave out much of the detail of the experience, and the response to any drug taken fro treatment. In turn, both physiological and PRO measures obtained only at site visits will given an incomplete, and potentially inaccurate picture of the drug's effects.

A second disadvantage to solely clinic-based measures is that we often rely heavily on retrospective recall of information from subjects. Specifically, PROs often require subjects to recall and summarize information over the days, weeks, or months since the last clinic visit. Unfortunately, a large body of data on the workings of autobiographical memory (recall of one's own experience) indicates that such recall is inherently inaccurate and subject to a number of biases that distort research data collected in this way[3].

Collecting data only at site visits represents a snapshot of the subject that is a limited, and most likely a distorted, view of the drug's impact on subjects.

The Present: Silent Movies

There is a growing realization that a more complete picture can be obtained by collecting clinical data from subjects outside of the context of the clinic. This is reflected in the development and implementation of field-based instruments for physiological and PRO measures. For example, a number of small ambulatory instruments can measure and digitally record blood pressure and heart rate on a regular basis throughout the day. For PROs, subjects complete diaries while in their real-world settings. In some studies, the measures are combined for collecting physiological and PRO data. Today, the current technology and practices yield a clinical data stream that more closely resembles silent movies than still photos, but still falls short of the full feature documentary film of the subject.

Small, mobile instruments are now available for some of the traditional measures of the physiological impact of a drug. As just mentioned, ambulatory blood pressure/heart rate devices can be worn by subjects throughout day-to-day life. Some of these devices can be programmed to automatically take blood pressure and heart rate measures at various times of the day. For studies with a diabetic population, or where blood glucose is an important measure of the drug, glucose devices are now available that passively measure blood glucose without the subject needing the stick themselves with a pin and place their blood into a measurement device; these newer instruments can measure blood glucose many times throughout the subject's day and digitally record the data for later use. Moreover, such devices can audibly alert subjects if blood glucose drops to a dangerous level. Another common use of mobile instrumentation is measurement of respiratory capacity using small peak flow meters. Some of these peak flow meters digitally record the data, and also have the capacity to enter information about their condition-related symptoms (e.g., difficulty breathing). These instruments allow much greater flexibility and capacity for capturing physiological data from subjects in their day-to-day life.

Recent advances in technology have really begun to extend the limits of capturing physiological data from subjects in the field. For example, at least one company has developed a shirt that continuously monitors subject's heart rate, blood pressure, cardiac activity, and other measures. The vast amounts of data recorded by this shirt is all locally stored and then transferred to a computer at a later time. Even more recently, some companies are employing wireless technologies that permit instruments to 'speak to each other.' These advances, still relatively early in their development and adoption, establish the found for continuous monitoring of subject physiological data.

There have been concurrent breakthroughs in the measurement of field-based PROs data as well. The traditional approach to measuring PROs in the field has been paper dairies where subjects record their experience. The problem is that

subjects do not complete these paper diaries in a timely manner, often filling them out after the fact and in batches[4]. These diaries are thus effectively like the PROs completed at clinic sites because subjects are retrospectively reporting about themselves; as such paper diaries suffer the same recall bias problems with clinic-based PROs. In response to these problems with paper systems used to capture field-based PROs, a number of companies have developed technical alternatives. One alternative is the capture of PROs via interactive voice response systems (IVRS). These systems are often phone-based. The subject call into a computer system that administers questions asks the subject's experience with the drug; the subject responds to these questions by using the key pad on the telephone. These systems have been used in a number of settings, especially if there are a number of question to ask subjects on a weekly, or monthly basis.

Another alternative to paper diaries for field-based PRO data is the use of a hand held computer, or personal digital assistant (PDA) to record information. Since the PDA date and time stamps the data, any retrospective recording can be detected and eliminated. PDAs have also been successfully used to actively prompt subjects to complete PRO information as dictated by the study protocol. In some studies, such active prompting yields over 90% compliance with the protocol procedures[5]. With the many advances in PDAs, such as integration with cell phone and other wireless technologies, these may be a solid foundation for collecting and communicating continuous data from subjects.

We have clearly moved beyond clinic-only data collection. Moreover, a number of technologies permit the frequent evaluation of physiological and PRO data from subjects in while in the real-world settings. However, to form the complete picture of subject, we will need to move beyond individual instruments collecting and storing data to an integration of these various data streams.

The Future: Documentary Film

Clinical research is clearly advancing and there is movement toward the documentary film version of the capturing the subject's experience with a drug. This film would reflect the impact of the drug on a subject in their real world, in real-time over the period of time the subject was under treatment (and possibly beyond to observe after-effects of the drug during the washout period). Ideally, the measurements from the subject should not artificially create findings – that is, there should be no measurement reactivity. Such a subject recording system would literally yield a stream of continuous information that when summarized would clearly show the efficacy *and* safety profile of the drug or medical device under study.

The path to this documentary film is technology. However, technology will only *enable* the development of this new system for monitoring subjects – the

predominant *driver* will be the expertise and creativity of the clinical scientists. Only the scientists can delineate what is to be recorded, when it is to be recorded, and most important, how to interpret the data. The technology will support meeting these goals.

So, where do we begin? All technology-based systems begin with a clear set of requirements delineating the purpose of the system and the needs of its users. These requirements are the technical equivalent of a clinical protocol. We delineate below a list of the user requirements by extrapolating from the current use of technology in collecting field-based measures of a subject's experience with a drug. These requirements are subsumed under three major questions for the technology-based system:

- What are the right platforms or devices for clinical data?
- How does the system fit into the subjects day-to-day life?
- How are data integrated to become meaningful?

<u>What are the right platforms or devices for clinical data?</u>

When choosing hardware platforms or devices for use in field-based clinical research, there are a number of factors to consider:

- Portability and durability
- Interface modalities
- Programmability
- Device Integration
- Connectivity
- Platform stability

Let's consider each of these factors in turn.

Portability and Durability. First and foremost, the hardware platform must be, to borrow Jeff Hawkins' phrase, "unconsciously portable" (Mr. Hawkins is the founder of Palm Computing, and the inventor of the PalmPilot handheld computer). Subjects need to be available for brief assessments throughout the day, in real time, in their real world. If the data collection devices are cumbersome, heavy, or inconvenient, subjects will be disinclined to carry the device with them at all times, and subject compliance will fall, in turn jeopardizing the reliability of the study results. An obvious result of that portability is that the devices must be durable; in the real world, people drop things. These requirements of course eliminate laptop computers and devices of similar bulk and fragility. For PROs, some of the PDAs used today begin to meet these requirements. The instruments for physiological instruments tend to be a bulkier and more difficult to carry, but the introduction of the shirt that can be worn by the subject is a step in the right direction.

Interface Modalities. In clinical studies, researchers deal with a cross-section of the population, covering many demographics. The devices we develop to conduct this research must be usable by this broad demographic—whether young or old, technically savvy or naïve, in the U.S. or worldwide. Even with the explosion of technology, a majority of people get through each day without directly, consciously interacting with a computer. Taking this into account, today's handheld computing platforms provide a very simple and literal "point-to-select" interface modality which greatly facilitate capturing of PROs. Even better would be devices that require no action on the part of the subject; for example, the automatic recording of the physiological measures at the appropriate times. Finally, some devices may respond to the subjects voice to activate or record PRO or physiological information.

Programmability. Programmability may seem to be a given, but it's worth exploring, if only to look at some emerging technologies. Field-based studies rely on protocol designs that engage and interact with the subject. In many cases, these interactions change based on when, where, and how the subjects respond to the interview questions. For example, consider a clinical trial designed to measure the time taken for a drug to relieve an acute condition. In such a study, when subjects record that they have taken a medication, the device should repeatedly sample the subjects' perceived relief during the critical time window to ensure a sensitive test of when they first experience symptom relief. Only programmable devices allow researchers to change sampling schedules so that certain data types and time windows for data collection are built into the diary protocol.

Device Integration. Hardware devices will need to communicate at the time of data collection. One could imagine that a subject's recording of increased pain or discomfort automatically generates a number of physiological readings with no additional action from the subject. Alternatively, the detection of an change in a physiological reading could generate a PRO measurement for the subject's perception of the change. This type of integration is facilitated by wireless personal area networks (using blue tooth technology, for example) that facilitate communication of devices in close proximity to each other.

Connectivity. Its pretty simple, we need to be able to connect and transmit any and all times. Data cannot be lost if a connection cannot be made. The system may communicate data to a central data repository on a daily basis for review by study managers. However, if a finding emerges that calls into question the safety of the drug under study, an message can be sent immediately to the medical monitor managing the trial. In return, the medical monitor could send a message, or possibly call the subject if wireless telephony is being used in the trial.

Platform Stability. Given the nature of clinical research—long lead times (for the technology world) and study durations, broad constituencies, and the need for

peer and regulatory approval—it's only natural that the industry be concerned about the long-term viability of any computing platform they use. It's important for anyone pursuing field-based research to consider this and to choose a computing platform that is going to be around not just when the study is run, but also when the results are reviewed by regulatory bodies.

How does the system fit into the subjects day-to-day life?

While the choice of platform is interesting, the point of the platform choice is to deliver a compelling user interface. Going back to first principles, any field-based clinical research must concern itself with engaging the subject in the study, both deeply and continuously. The subject must feel respected, valued, and supported throughout the study process. The result: a user interface that is extremely easy-to-use, consistent, succinct, and reasonable.

First and foremost, successful field-based clinical research requires ease-of-use in the interface, almost literally to the point of instant usability. Subjects are really the key, the linchpin, to clinical research. As such, they carry a heavy burden of responsibility. The appropriate study design, properly applied in the user interface, can actually encourage, support, and engage the subject, driving higher subject compliance with the study protocol[5]. Conversely, complicated user interfaces that require extended time and effort discourage participation and undermine compliance.

As a consequence, in a field-based clinical trial simple is better. For PROs, use of a small number of well-known interface widgets with good real-world analogues (sliding scales, check-boxes, number spinners, and so on) on a PDA really works to facilitate subject's engagement in the trial[4,5]. For physiological data, devices that require little or not action from the subjects will be ideal. If subject action is required, simple button pushes will increase the likelihood the subject complies. The result: higher subject performance, better subject compliance.

Finally, the interface must be reasonable and respectful at all times. The data collection device must fit into the subjects' daily lives, both in terms of its form factor (see our previous discussion of portability) and with respect to user interface. Well-designed device interfaces include many "livability" features — e.g., a bedtime setting, and protocol suspension — that are designed to accommodate the varied patterns of subjects' daily lives. Let's discuss protocol suspension as an example. There are times during almost every day when a subject simply can't be interrupted to respond to a protocol requirement. Devices need to respect that, and provide a mechanism for the subjects to remain compliant while suspending their participation for limited amounts of time.

Data Integration and Interpretation

The next step, after measuring the subject's physiological and subjective reactions to the drug, is to integrate, analyze, and interpret the subject's data. The challenge with a extremely dense set of data from multiple sources is the integration of the information into a meaningful summary. It will be important to summarize the information for each type of data, and then to look across various types of data to form a picture of what has or is occurring with the subject. For example, heart rate changes measured over the course of a day may be graphically summarized, and significant changes may be mapped to PRO measures captured at those times during the day. The system might be sophisticated enough that only those overlapping occasions that are meaningful to evaluating the efficacy and/or safety of the drug would be presented to trial managers. Moreover, safety results might be shown to the medical monitor for the study, while efficacy results would be directed to the data management group. The goal is to not overwhelm any single person managing the trial with too much information – this makes the system user-friendly for the subjects *and* the people conducting the study.

The implementation of a sophisticated data integration and interpretation component of the system will largely rely on the clinical scientists, data managers, and statisticians to provide the algorithms for summarizing the data. Statistical, graphic, and reporting software packages available today most likely contain the infrastructure to support the type of work need to summarize intense field-data. In terms of the hardware, high-speed computer processors are needed so that data can be quickly summarized, and large amounts of data storage capacity are also required. Again, today's computing hardware most likely meets these needs. Data integration and interpretation for the continuous data stream from the patient will largely rely on the scientists conducting clinical research.

Summary

We suggested at the outset of this article that the ideal evaluation of a drug's or medical device's efficacy and safety is a comprehensive picture of the subject's experience over time –a continuous measurement stream of the patient reported outcomes (PROs) and physiological reactions to the drug. Historically, the impact of a drug or medical device was only captured at the time of a visit to the investigator's site, representing a snapshot of the subject. This is a limited, and most likely a distorted, view of the drug's effect on a subject. We have clearly moved beyond clinic-only data collection with the development and implementation of a number of technologies that permit the frequent evaluation of physiological and PRO data from subjects in their real-world settings. However, to form the complete picture of subject, we need to move beyond individual

instruments collecting and storing data to an integration of these various data streams. We need a full length documentary film of the subject.

The path to this documentary film is technology. However, technology will only *enable* the development of this new system for monitoring subjects – the predominant *driver* will be the expertise and creativity of the clinical scientists. Only the scientists can delineate what is to be recorded, when it is to be recorded, and most important, how to interpret the data. The technology will support meeting these goals.

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