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In the next issue of
EDC Today:

Metrics

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eClinical and Patient Diaries

EDC TodayTM is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

Many biopharmas are exploring EDC and many are still supporting both EDC processes and paper processes. Our nineteenth issue explores patient diaries. In particular, we will discuss why they are important to many clinical trials and why the move to electronic patient diaries promises a lot of benefits with seemingly little downside.

Introduction

With the relatively recent emphasis in clinical trials on proving that a study compound improves a person's quality of life (QOL), many larger (Phase II and III) studies now have extensive Case Report Form (CRF) "real estate" dedicated to collecting a number of hard-to-quantify measurements. These measurements are generally subjective assessments on the part of the study subject; such as a response to the question, "How much pain do you feel today?"

Unfortunately, a lot of studies have shown that paper CRFs work poorly in capturing this sort of information. Paper patient diaries have no mechanisms for reminding subjects to complete the forms, and they have no date and time stamp mechanisms for recording completion of diary pages.

Electronic Patient Diaries (ePDs) seem to offer solutions to some of the shortcomings of paper patient diaries. With suitable programming, ePDs can be configured so that subjects complete the diaries in a timely manner.¹ Finally, whether or not either a paper patient diary or an ePD can provide data suitable for analysis rigorous enough to prove or disprove a study hypothesis is yet to be determined.



What Are Patient Diaries?

Data that cannot be measured electronically or mechanically (typically pain, mood, attitude to illness or treatment, and perceived quality of life) is often collected using a “patient diary”. Sometimes a drug dosing record is kept using a patient diary in therapies that require pills to be taken daily for a certain period of time. Other common areas where patient diaries are used are shown in Chart A.

- Chart A. Common Uses for Patient Diaries¹**
- Depression/Mood Chart
 - Tobacco or Alcohol Craving/Use
 - Sleep Log
 - Asthma or Ease of Breathing Log
 - Side Effect Monitoring
 - Headache Severity
 - Hypertension
 - Muscle Tremors/Spasms
 - Interstitial Cystitis² (Pain)

Paper patient diaries with scales, typically labeled “None” at one end and “Lots” at the other end (see Figure A) and/or a log with rows and columns of dates and numeric ratings (see Figure B) are probably familiar to most readers.

Today's Date: ____ - ____ - _____ Time: ____ : ____ AM PM

The amount of pain I experienced this morning was:

|-----X-----|-----|-----|
 None Some Lots

Figure A. Diary Scale

Pain Experienced (Please rate on scale of 1 to 10 with 1 being low and 10 high):

Date	Time (AM/PM)	Pain Level
09/29/2003	10:00 AM	6

Figure B. Diary Log

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According to Laurie Burke, Division of Drug Marketing, Advertising and Communications at the FDA, in “Importance of patient self reports as measures of effectiveness in drug labels”, January 22, 2003, paper-based patient diaries are used in about 30% of all phase II and phase III trials.³

Given the extensive use of patient diaries, it is alarming to learn that the data collected is often considered unreliable and inconsistent. Worse yet, studies indicate that as much as 79% of patient diary entries are falsified.⁴ Understandably, subjects tend to fabricate the data if they haven’t completed the diary entries at the requested times and fill them in long after the fact, usually just before the study visit.

Equally surprising is that forward filling of diaries also takes place. Subjects that know they will be too busy to complete their forms in the next couple of days often fill out the diary a couple days ahead. This data is not only biased, as in the case of data that is completed late, but is in fact completely fictional.

Given the “technology” of paper and pen, it can be very difficult to detect non-compliance. The paper lacks a date and time-stamping mechanism.

Another problem is the use of scales, such as the one shown in Figure A. They require generating a numeric value that corresponds to the mark made by the patient. We have actually seen a Clinical Research Assistant leaning over reams and reams of paper diaries with a ruler and annotating the scale with a rough measurement. Once a value has been assigned to the scale position, a data entry clerk enters the data into the clinical trials database, a process open to transcription error.

Even when subjects do make an effort to comply and make timely diary entries, external factors influence the subjective self-evaluation. One might suspect a diary recording subject’s mood might show the influence of a nice romantic dinner with someone special or the influence of getting a flat tire on a dark rainy night, but are the patient diary recordings taking such factors in account? A patient diary log, with date, time, and numeric value, obviously doesn’t record such externalities. Even less significant external factors could bias the patient’s self-assessment of the level of “annoyance” they are experiencing. For example, a child having a nighttime bed-wetting episode might cause a person to exaggerate their “headache pain level” (of course, the elevated level may well be “real” but how is the researcher to know?)

Lastly, when one considers the effect of extreme physical conditions on a patient attempting to comply with diary recording expectations, it is very reasonable to doubt that diary entries will (or even can) be recorded when they are requested. Consider someone with a “massive” migraine headache; making an entry into their diary is most likely not a priority, and in fact may not be physically possible. Yet, this is the critical juncture in the patient’s experience and a time where the diary information could show with clarity any perceived efficacy of the study agent.

What Are ePatient Diaries?

ePatient Diaries (ePDs) are electronic data collection programs designed to allow study subjects to record diary information from wherever they are. They are designed so that subjects can take the recording device with them, or if the ePD is an IVR system, the subject can call into a central computer from a telephone.

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ePDs have been created in a number of different forms including interactive voice response (Telephone IVR) systems, electronic devices such as pill dispensers, lung function testers (spirometers), and often handheld computing devices (such as Personal Digital Assistants and Pocket PCs). These handheld computers are programmed to capture Self-Observation (e.g., pain onset, shortness of breath, coughing), Subjective Symptoms (e.g., distress, anxiety, headache), and/or Quality of Life data (e.g., how I felt when I woke up this morning, readiness to face the world).

ePDs record the data entered by the patient either directly into a central computer in the case of an IVR system or in the electronic device or handheld computer. Various means are employed for uploading data from electronic devices to the sponsor central database, including hardware docks or cradles with built-in modems to tone generators so that one places the device next to the mouthpiece of the telephone to send in data.

Let's consider the advantages and disadvantages of ePDs versus paper patient diaries.

Some Advantages of ePatient Diaries

Clearly for an ePD to provide compelling reason for biopharmas to use them, they must solve at least some of the shortcomings of paper diaries. The two major shortcomings are non-compliance (diaries not being filled out at the appropriate times) and poor data quality (data is entered incorrectly, data is affected by poor memory recall, and/or data is affected by poor transcription from the paper form to the sponsor database).

ePDs can improve the quality of data. With the convenience of either using a phone or a portable handheld, data can be quickly entered with instant feedback. Structured data entry with built-in validity checks can prompt users for what data to enter, and thereby avoid incorrectly entered data and inconsistent data. In addition, reminder alarms substantially increase the likelihood that subjects enter complete and correct data at the specified time.¹

ePDs can increase adherence or protocol compliance. Subjects are made aware that the date and time of their entries will be recorded, and since entries are date and time stamped, adherence cannot be faked (electronic diaries cannot be filled out retrospectively). This awareness, coupled with alerts prompting users for data entry, has been shown to improve compliance. According to Healthcare Technology Systems website, ePDs have shown better than 90% compliance rates compared to only 20 to 50% with paper diaries.⁵

In addition to alerts, programming time windows can further control the timing of subject entries. So not only do subjects know when they have to make an entry, they cannot enter more than they are expected to enter at any given time.

Other advantages of ePDs include the elimination of data transcription errors, since data is entered directly in electronic form, and is transferred to the sponsor database electronically. Thus the data is also available to the sponsors more quickly. Additionally, the data can be subject to complex logical tests and involved scoring of subject assessments.

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Some Disadvantages of ePDs

The disadvantages of ePDs depend upon the particular implementation of the diaries. If the ePD is implemented using handheld devices, then the disadvantages deal with the device to be purchased, programmed, distributed, maintained, carried around, etc.

With handheld and electronic devices, recent advances in technology have overcome some of their previous problems, such as short battery life, the ability to change the device's clock, data loss due to power loss, and the hurdle of connectivity. Still, the requirement for uploading the data still presents some activity that the user needs to perform and they may not do it on a daily basis as requested.

A patient may need to remember to “carry” an ePD device with them throughout their day. The patient may lose the device, forget to carry it one day, or simply drop and break it. Furthermore, some patients may have techno-phobia.

If the ePD is implemented using IVR, then it may be more difficult, if not impossible, to implement alerts to remind subjects to call in and enter their data unless the IVR system calls the subjects. With an IVR system, a patient may have a hard time getting to a phone at the appointed time to make the appropriate data entries. Hard of hearing patients may find the IVR menus difficult to traverse. Some patients may have a hard time with listening and responding to the menu prompts.

From the sponsor's point of view, some of the disadvantages with ePDs are that purchasing and distributing devices is more costly, and they involve more logistics and raise training issues beyond those where the investigators simply handout and possibly collect paper booklets. The IVR may have less logistic problems, but publishing and distributing instruction cards and subject training will still be required.

Further, sponsors will have to deal with source document issues and 21 CFR 11. Data entered into the handheld or into the IVR will be considered source documents, and will have to be preserved as source documentation.

In addition, some problems are not specific to ePDs. Problems such as those encountered with getting compliant patient diary entries during extreme physical conditions will likely always exist. There is no getting around the situation where a person with a serious headache won't want to deal with making a diary entry.

Direct Measuring Devices

If a measurable quantity could be found that is analogous to the self-assessed quantity, even if not completely “accurate”, it might provide “better” data than subjective self-assessed data. That is, using some quantity (e.g., fatuously, eye color brightness) for which measurements correspond “level by level” to the (not measurable) perceived values (e.g., “headache pain”) might provide data that is less troublesome to capture and may, in actuality, be more meaningful statistically.

Wearable measuring devices are available on the market. These devices can directly measure such things as activity levels, heart rates, pulse rates, and other meaningful quantities. These objective measures may be used more in the future if the data collected proves to be of good quality.

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Regulations and ePDs

In an eyeforpharma interview with Timo Ahopelto, co-founder and Worldwide Vice President of CRF Box, in May 2003, Ahopelto suggests ePD usage will soon be required by regulation:

“The improvement in patient data quality [due to ePD use] has lead regulators to not only accept, but endorse the use of e-patient diaries. ‘The FDA is most probably going to mandate and even drive the change from paper to electronic technologies during the next three to four months even’ Ahopelto predicted.”⁵

Certainly the FDA has a reason to be concerned about the reported poor quality of paper diaries.

What Is Available

Several companies market ePD products. A partial list includes:

Vendor	Product(s)	Platform
CRF Limited	eDiary Patient Edition, eDiary Site Edition	PDA
HealthCare Technology Systems	Custom Clinical IVR systems	IVR
Micro Direct ⁶	MicroDL Spirometer	Proprietary
PHT Corporation	LogPad, SitePad	PDA
Symfo ⁷	Symfo [®] Electronic Diary	Proprietary

Conclusions

With the relatively recent emphasis on proving that a study compound improves a person’s quality of life (QOL), many larger (Phase II and III) studies now have extensive CRF “real estate” dedicated to collecting hard to quantify measurements. Unfortunately, a lot of studies have shown that paper patient diaries work poorly in capturing this sort of information.

ePDs seem to promise solutions to some of the shortcomings of paper patient diaries. In particular, ePDs can improve compliance and data quality. However, issues with patients carrying electronic devices or having to call into an IVR system are still real and need to be considered. Furthermore, sponsors will have to consider whether the benefits of ePDs are worth their added cost.

References

¹ <http://www.healthtechsys.com/ivr/ivrdiaries.html>.

² <http://www.ic-network.com/handbook/scale.html>

³ The Gantry Group, LLC. “ROI Value Driver Study for Palm Mobile Solutions: Clinical Trials. White Paper: Fulfilling the Promise of Clinical Trial Diary Research.” May 2003.

⁴ Arthur A. Stone, Saul Shiffman, Joseph E. Swartz, John E. Broderick, and Michael R. Hufford. “Information in practice: Patient non-compliance with paper diaries”, *BMJ*, May 18, 2002, pages 1193-1194.

⁵ <http://www.eyeforpharma.com/index.asp?news=36628>

⁶ <http://www.micro-direct.com/microdl.htm>.

⁷ <http://www.symfo.com>



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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