

Electronic collection of clinical outcomes

The FDA has approved several new compounds based on efficacy data collected from study subjects via computer. Keith Wenzel and William Fischer of MPH ClinPhone, discuss how, because of time and cost efficiencies, sponsors are increasingly turning to technology to collect this critical efficacy data.

Imagine picking up a drug prescription and, while reviewing the product labelling, you encounter the term IVR. Reading on, you find out the data for the FDA-approved drug you are taking was collected via computer. While you might view this with some scepticism, this scenario is a reality. The product label for Climara PRO, a hormonal transdermal patch treatment for post-menopausal symptoms, includes patient self-report data collected during a one-year clinical trial. These data were collected using interactive voice response (IVR). IVR technology now permits study subjects to enter self-report, clinical trials data using a normal, everyday touch-tone telephone.

Most people are familiar with the use of computers to facilitate the administrative aspects of clinical trials. Clinical trial data management systems help track and manage sites, documentation, budgets, patient recruitment, and overall study progress. IVR systems allow us to efficiently randomise subjects into simple and complex stratifications. IVR systems also track medication inventories to ensure that drug supply material is available, when and where needed. Clearly, there are many success stories with regard to the ability of computers to optimise the operational efficiency for the administrative aspects of clinical trials.

What about the patient data? If computers can help with the administrative aspect of a trial, can they also help identify safe and effective drugs? The safety of drugs is a lively issue in today's media. Can computers help us learn more about the drugs we are studying and the associated side effects? How about treatment effects that occur outside of the office setting? Are there better ways to collect this data so that we know more about the speed of onset? The answer to all of these questions is yes.

What are patient-reported outcomes?

The term patient-reported outcomes (PROs) encompasses both data from diaries and from scientifically validated assessments. A diary is a self-report measure that may or may not have undergone scientific validation; it is often proprietary to a sponsor. Examples include pain, sleep, asthma, IBS and migraine diaries. An assessment (or scale) has typically undergone some formalised validation including publication of the validation data in a peer-reviewed journal. These scales usually have a standardised methodology for interpretation of results and often have a royalty payment to the author.

Importantly, a patient's self-report assessment can be a surrogate for a clinician's assessment.

In the clinical trial setting, validated assessments are used to collect quality-of-life, pharmacoeconomic and symptom severity data. Examples include Jean Endicott's Quality of Life, Enjoyment and Satisfaction and the Endicott Work Productivity and Satisfaction questionnaires; Anita Clayton's Changes in Sexual Functioning Questionnaire (CSFQ); and the Hamilton Depression and Anxiety Rating Scales (HamD and HamA). Not only are these scales used to measure change over time, but they may also be used as inclusion criteria. For example, a patient in an antidepressant trial must meet a minimum level of depression severity to be eligible for study inclusion.

Increasingly, computer assessments are replacing paper with PROs (see Figure 1). There is a growing body of literature exposing the limitations of paper for the collection of patient self-report data. Paper assessments or diaries completed at or away from the study site have data issues such as missing, conflicting, ambiguous or extraneous entries. In addition, the integrity of data collected by completion of paper diaries is suspect due to the unknown time and date of completion. Computers can conveniently and efficiently gather data directly from study subjects. Over the last 15 years, IVR systems have been applied to the collection of PRO data in a wide range of clinical trials for disorders, including asthma, diabetes, migraine, pain and psychiatric disorders. IVR systems are being used in clinical drug trials to collect primary and secondary efficacy data, quality of life data, and work productivity data.

What are the possibilities?

Safety data is vital, for example, when a clinician for a critically important clinical trial, receives safety alerts via voice mail or on his or her PDA. Sponsors and the FDA are under increasing pressure to provide more transparent drug safety reporting. Historically, it has been difficult to receive the right data in a timely manner. Using ePRO data and database (engine) triggers, it is possible to alert sites and sponsors of critical safety data – for example, an increased level of suicidal ideation. With the centralised storage and web-based reporting capability of IVR systems, sponsors and sites can monitor adverse event data, such as sexual

dysfunction data collected via the CSFQ, withdrawal symptoms, and other patient-reported symptoms or side effects.

IVR systems also facilitate the collection of study data between study visits. For compounds with a fast onset-of-action profile, it is critical that data be collected outside of the office setting. At the 2004 American College of Neuropsychopharmacology meeting, Eli Lilly presented IVR-collected data that demonstrated a favourable speed of onset profile for one of its compounds. Specifically, patients started at higher doses of the study drug Cymbalta reported greater improvement by day one in shoulder and back pain when compared with a lower dose of the same drug. Patients also reported reduced pain while awake by day three, improved overall pain by day two, global emotional improvement by day three and global physical improvement by day seven. All results were statistically significant ($p < 0.05$). Similar onset of action effects have been detected through electronic patient self-reports in other clinical trials for other disorders. These IVR data would have been difficult, if not impossible, to collect reliably at the study site or via paper.

Inevitable changes

In principle, the possible benefits of using computers to collect patient data are clear, but for a professional in the field of clinical drug research what is logical and what is accepted by regulatory authorities do not always go hand in hand. The question arises if the Climara PRO example above an anomaly and what the position of regulatory authorities with respect to acceptance of patient-rated data is.

The FDA has already approved many new medical entities where the primary efficacy data was reported directly by study subjects. For example, Paxil for social anxiety disorder, sertraline for premenstrual dysphoric disorder, Topamax for migraine/headache, and Sontata for sleep disorders were all approved using data collected via self report from study subjects.

The FDA has also approved compounds based on electronically collected PRO data. Two examples include Estottra for insomnia and ACULAR LS for ocular pain. The insomnia example included weekly IVR sleep diaries completed in studies of up to six months in duration; these patient self reports were the primary endpoints.

On 4 August 2004, the FDA issued guidance with regard to the use of self reports as efficacy measures for compounds being studied for depression. Specifically, the FDA indicated, 'we would accept self-report in general as an approach to assessing symptom severity in drug trials focusing on major depressive disorder in outpatients. This is true, whether that approach involves IVR technology, paper and pencil, or other means.' The HamD, the Inventory for Depressive Symptomatology (IDS) and the Quick Inventory for Depressive Symptomatology (QIDS) were all mentioned as acceptable means assessing symptom severity. For the HamD, IDS and QIDS, the FDA indicated to sponsors, 'if they intend to use one of these assessments, they should submit protocols that include their preferred assessment.'

A further indication of the FDA's activity with regard to PROs is demonstrated by a notice that is soon to be published in the Federal Register asking for public comment about the use of PROs to support medical product claims in both labelling and advertising.

The European Medicines Agency has issued regulatory guidance for the use of health-related quality-of-life measures. It includes the statement, 'The

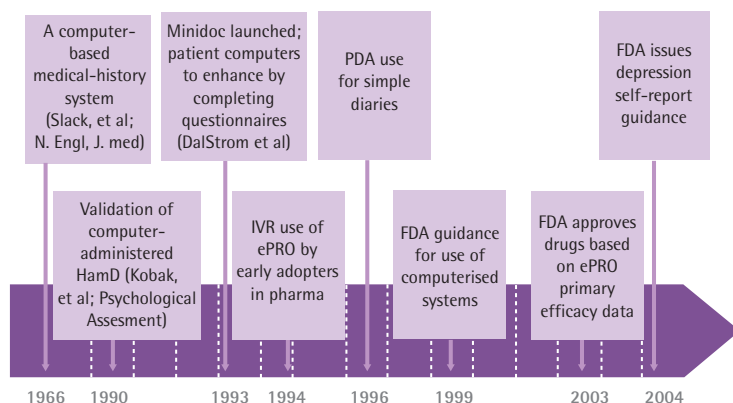


Figure 1. Electronic patient-reported outcome timeline

role of patient-assessed measures in randomised clinical trials in general is well established and needs no special position statement.'

The message for sponsors is clear: PROs are already being used as part of the approval data for new compounds. The information above shows that the regulatory authorities are receptive and have provided PRO-related guidance.

Current clue

While not all sponsors are using ePRO, adoption is growing very quickly. DataMonitor reports that 25–30 per cent of all clinical trials use diaries to collect patient self-report data. The patient diary market was estimated to be worth \$800m for 2003 and is predicted to grow to an estimated \$3bn by the end of 2005.

Several new compounds have recently been approved based on primary efficacy data collected electronically from study subjects. The FDA has been active in providing guidance for industry, including the recently released guidance with respect to electronic self-report measures for depression and the soon to be released notice in the Federal Register asking for public comment on the use of PROs to support medical product claims in both labelling and advertising.

The expanded use of patient-reported outcomes provides many opportunities for increased clinical trial efficiency. Subject screening has been facilitated by using electronically collected self-report data to assess subjects; unnecessary study procedures can be eliminated by early identification subjects not meeting inclusion criteria. In fact, such screeners have been used during patient recruitment campaigns to ensure that only qualified patients arrive at study sites. Because of built-in data checks and time/date stamping, sponsors are able to show measured improvements in data quality and integrity compared with PRO data collected on paper. In instances where the sponsor wishes to collect onset of action data or supplemental pharmacoeconomic or quality of life data, technology efficiently facilitates data collection between study visits.

As a result, industry use of electronic PROs is growing. IVR-collected self-report data is being used not only for primary and secondary efficacy data, but also for pharmacoeconomic and quality of life data. Future technology improvements should provide additional efficiencies and increased data integrity for clinical trial sponsors. ■