



Regulating eDiaries

Secure, private and effective eDiaries deserve the trust of regulators
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When most of the regulations that pertain to handling records for clinical trials were written, diaries (like most records) were completed on paper. Except for a single mention that included 'subjects' diaries' under the definition of source documents (1) provided by the International Conference on Harmonisation (ICH), they were not the focus of regulations. Therapies were approved or rejected based on clinical records, and the direct input from subjects was generally secondary to the medical assessments of their physicians. Paper questionnaires were a trusted source, but in the 1990s many regulators and scientists were sceptical of patient diaries. As eDiaries have entered the mainstream, their regulatory status has become clearer (2), and the signs suggest that regulators are laying the foundation for increasing their reliance for claims and labelling on data supplied directly from subjects in clinical trials (2,3).

BUILDING A CHAIN OF CONFIDENCE FOR ELECTRONIC RECORDS

The FDA sought to encourage "the widest possible use of electronic technology" in 1997 with Part 11 (4, Preamble). The objective was to describe what the FDA would need in order to trust electronic records as much as paper ones and avoid unduly burdensome controls. This 'no worse than paper' principle is embodied in the first sentence of the regulation (11.1(a)): "The regulations in this part set forth the criteria under which the agency considers electronic records ... to be trustworthy, reliable and generally equivalent to paper records..." (4).

From the design of the questionnaire or diary and its implementation on a valid device, to data transmission, storage, access, transfer and archiving, each step in the eDiary lifecycle is subject to regulations and guidelines that apply to both sponsors and sites. The eDiary providers must, therefore, prove to sponsors that their documented processes meet all the requirements for electronic records and that these

standard operating procedures (SOPs) are consistently followed. In this way, the reviewers and regulators will have the information they need to establish a chain of confidence from development to final submission. By documenting compliance with the regulations, eDiary providers help study sponsors make the case that their data – and scientific conclusions – are trustworthy.

This article provides a discussion of the regulatory implications of several specific elements of eDiaries, in which definitions for terms pertaining to the discussion are provided for convenience, drawn from the CDISC Clinical Research Glossary (5).

eSOURCE

Underlying the confidence of regulatory authorities in the results of clinical trials is the notion that the site investigators will provide unbiased data because they have no vested interest in the efficacy or safety of the therapy being tested. The FDA has mandated that an investigator is required to "prepare and

maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation” (6). Diaries, while not explicitly mentioned, are generally considered as part of the case history (source documents) to be maintained by the physician in “files of the institution” (1).

To comply with the letter of the regulations on record keeping, sponsors using eDiaries interpret the provision to mean that the investigators ‘prepare’ the eDiary records by instructing subjects about how to enter diaries and by answering any questions concerning the eDiary data that is actually to be entered directly by the subjects. The investigators ‘maintain’ the eDiary records in files of the institution by reviewing (and clarifying where necessary) the electronic records, and by monitoring compliance with completion schedules, usually via a web application supplied by the eDiary provider (see Figure 1).

The files may be stored many miles from the institution, but the system is configured and validated to permit investigators to access their records at will from their desktop computers – and to prevent access by unauthorised users. Thus, these files can be understood to be files ‘of’ and ‘maintained by’ the investigator.

The latest sign of regulatory acceptance of the idea that investigators can fulfil their record keeping responsibilities via remote access is included in the FDA’s patient-reported outcomes (PRO) Draft Guidance (3), in section V.F. specifically devoted to eDiary systems: “the FDA considers the investigator to have met his or her responsibility when the investigator retains the ability to control and provide access to the records that serve as the electronic source documentation for the purpose of an FDA inspection. The FDA recommends that the study protocol, or a separate document, clearly specify how the electronic PRO source data will be maintained.” This recognition by the FDA that clinical investigators (and regulators) need to know how the system will allow them to meet their regulatory responsibilities is suitably realistic.

USER IDENTITY AND AUTHORISATION AUDIT TRAIL

A core principle of eRecords systems for clinical trials is that they can be used only by duly trained and authorised

individuals. Permission for access, review and editing of eDiary records can be granted to individuals with defined roles in the trial. Thus, an investigator will be able to see private information (initials, birthdates, drug use and so on) that helps them to ensure that the eDiary reports for a particular subject are truly coming from that subject. Other study staff may see less of the data according to their role. The process of authorisation includes identification of investigators and study staff by the sponsor and a formal, documented process to assign eDiaries to particular subjects. Whilst there is no regulation that requires subjects to sign their eDiaries, it is possible to implement signing by linking traditional handwritten signatures, digital signatures (user ID and Password) and voice recognition, for example, to each eDiary report. Such signing could also support the completion of informed consent and other key documents as electronic source documents for clinical trials.

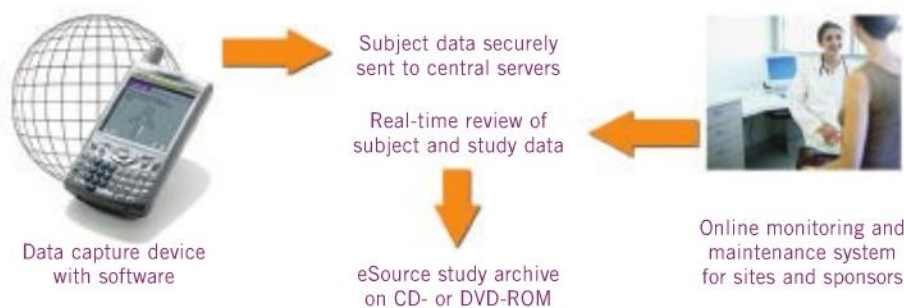
For paediatric trials and those involving disabled subjects, it is useful to enable reports to be completed by particular caregivers, who may observe the subject. Access codes, passwords and handwritten signatures are often an element of the Part 11 controls that eDiary systems will typically implement in order to ensure attribution of such actions on electronic records in a way that the responsible parties cannot easily disavow at a later stage.

PRIVACY

Several intriguing studies have shown that subjects are more willing to reveal sensitive personal data (for example, ratings of sexual performance by a partner) when an eDiary is used that will not allow an outsider (or a spouse) to see the ratings. In order to honour the willingness of subjects to make accurate disclosures of their personal health state, eDiary systems must successfully protect privacy. This need has been enshrined in regulations worldwide (7-10). The eDiary systems implement various physical, cryptographic, administrative and technical safeguards to ensure that subject data is protected from disclosure and loss. These security provisions must be properly developed, tested, documented and validated.

Observations indicate that the privacy controls on eDiaries have been effective, but this effectiveness for privacy brings up a question. How is it then possible for the user’s identity

Figure 1: Typical ePRO system



to be held private as well as be traceable with certainty under regulatory inspection and audit? Given the relative ease with which paper diary documents can be read if acquired, it would seem difficult to address these contradictory requirements with paper technology. However, with eDiaries, the site staff and investigator can view initials, names, signatures, *ad hoc* comments, or other personal data that may be captured, and the system can restrict such data so that neither the sponsor nor sponsor agents can access private information. With proper privacy statements in consent forms or waivers, subjects can be informed of the extent of planned disclosure of their health information, so that the system provider can fulfil corresponding requirements for permissions and role restrictions. Such restrictions can then be validated to operate as intended. The result is that the technology enables devices to capture the sort of personal identity information that makes it easy for site staff to see the data pertaining to each particular patient they oversee. Sponsor trial managers working from the same repository can see information on trial management but not patient names or codes. Data analysts can review data sets that have been planned from the outset to ensure anonymity.

A final point on privacy deals with the opportunity for increased safety monitoring of individual subjects. With eDiaries, self ratings on symptoms and behaviours that are signals of impending problems can be captured daily. Algorithms for alerts based on such data can then run locally on devices or at the system level when the data are transmitted, thus making it possible for automated review to help physicians intervene on behalf of trial subjects in a timely manner. The regulatory context for such a capability is the underlying objective of regulatory authorities to protect the subjects who volunteer for clinical studies. Remotely reviewing what patients convey daily about their health state is a more immediate and more sensitive way than adverse event forms to know when a patient takes a turn for the worse. Thus ePRO records can serve as a helpful adjunct to the AE process, allowing close management of subjects to improve safety.

ARCHIVE

The requirements for archiving (and retaining) trial data (1,2,6,9) are directed at ensuring that the original data can be audited years later. Such inspectors will want to 'reconstruct' the trial in order to understand exactly how it was conducted. The data cannot easily be understood on its own, so the full context of the trial (protocol, objectives, processes and monitoring) needs to be part of the archive in order to support reconstruction. Longevity of access to the eDiary data can be achieved by rendering the archive in XML, ideally according to a standard such as the CDISC ODM in combination with the SDTM and a dictionary of standard data elements.

Inspection of eDiary data also occurs following submission, as regulatory authorities review the analysis and the conclusions drawn from the trials. Here, the requirements include formatting (for example 12-point type, 2.5cm margins), rather than longevity or reconstruction. The burden

on eDiary providers and sponsors to prepare a submission may not be fulfilled by the preparation of a compliant archive. This contradiction seems unnecessary; ideally, the archive and the submission could be identical, and the inspectors would be granted restricted review permissions on the appropriate subset of the full archive. The full archive would include all the information needed to reconstruct and audit the conduct of a trial, including the private and identifying information for each subject, which now resides with each site. A regulatory inspector would have access to such information only with the knowledge, and possibly the assistance, of the site investigator. It is hoped that the present distinction between the archive and submission will ultimately disappear, and the submission will represent a planned subset of the archive content and format.

DATA INTEGRITY AND QUALITY

Many of the regulations are directed at protecting data against loss and ensuring that no tampering or fraud occurs (data integrity). eDiary systems support such safeguards with subject- and site-use access codes on each device, role-based permissions for reviewing data, and advanced encryption and security technologies for transmitting and storing data. In addition, integrated eSource measurement devices can be implemented to eliminate manual entry of fake data by automatically transferring scores from measurement devices used by subjects into their eDiary. This assures investigators, sponsors and regulatory authorities that subjects have used the measurement device appropriately and in a timely manner. In the EU, there has been some regulatory encouragement for use of eDiaries to increase data integrity:

- ◆ Guidance on endpoints in asthma says: "If home recording equipment is used, reproducibility is particularly important and an electronic diary record should be considered to validate the timing of measurements" (11)
- ◆ Guidance on efficacy for steroid contraceptive states that: "The separate calculation of the Pearl Index for method failure requires reliable methods for recording of compliance (for example electronic patient diaries) not to include non-compliers in the denominator" (12)

Fraud was anticipated by the Agency as a risk of electronic methodologies. But, in our experience, fraud has not been a significant factor with eDiaries. Some sites have attempted to complete daily diaries on behalf of subjects, but this has proven both burdensome to sites and detectable from various clues in the data (13). It seems that the controls established by Part 11 have proven to be effective.

Data quality has recently been the object of regulatory guidance (2). Common problems with data quality on paper (incomplete forms, illegible fields, illogical values, improperly formatted dates, ambiguous selections and so on) are all preventable by controls in eDiaries. Data quality is enhanced

dramatically by such controls, and eDiaries yield more data suitable for evaluation per subject than paper ones.

SENSITIVITY OF SELF ASSESSMENTS AND SCIENTIFIC POWER

A few studies using eDiaries have demonstrated the power of an electronic system to reduce data variance as compared to paper. By utilising restricted time-response windows, completeness rules, formatted response options, edit checks and screen sequence controls, eDiaries increase data quality. Depending on the trial, the enforced timeliness of data entry by patients may also make it easier for them to be more aware of their symptoms and thus more precise in their self assessments. The end result is a trial that can be conclusive at the same power with smaller sample sizes than would have been necessary in a paper-based trial. Getting more information from each subject is a hugely important practical benefit. But the regulatory context concerns the potential for reducing risk to patients. By using more sensitive eDiary methods, it should in principle be possible to reduce the number of subjects exposed to investigational therapies whose potential harmful effects are not known.

CONCLUSION

Modern eDiary records have so far proven to be more secure, more private, more sensitive and of higher quality than paper diary records. They deserve the trust of regulators and, as submissions for market approval based on eDiary data undergo regulatory review, the willingness of regulatory authorities to rely on such data for decisions is becoming increasingly apparent. This article has mentioned some key areas where regulations pertain to eDiary systems, and noted some of the ways eDiary providers and sponsors approach conformance. The most satisfying aspect of the co-operation among providers, sponsors and regulatory authorities worldwide is that the increasing use of eDiaries is enhancing the participation of subjects in documenting the effects of therapies. If this trend continues, the industry can reasonably expect information from subjects about what happens to them as they try a medication or device to be available in product labels and clinical advisories. Subjects who are prescribed therapies will then have greater insight into what they are likely to experience. ♦

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