

ENSURING DATA RELIABILITY WITH eDIARIES CAPTURED ON PORTABLE DEVICES

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Abstract

Predicate rules and guidelines were written with the intent of ensuring that clinical research data is trustworthy and that clinical practices for trial design, conduct, execution and statistical analysis meet a quality standard so that decisions concerning efficacy and safety by regulatory bodies can be made with confidence to justify public trust. Do current practices with eSource data on mobile appliances meet that test? Are they as trustworthy as paper records?

This presentation focuses on detailed issues of data reliability, and specific methods in current practice that ensure accuracy of electronic data.

Accuracy: Provisions that impact accuracy include the validation of data capture elements, device operation controls, and edit checks. Process and programmatic controls, also validated, ensure that devices are operated in a validated power regime.

Protection against loss/corruption: Accuracy depends on protection of captured data and security from tampering or undetected alteration. This presentation will describe use of non-volatile memory on the device for temporary storage in case of program failure, "resets", loss of power, etc. as well as controls that prevent access or alteration.

Transmission fidelity: Provisions include validated operation capability to deal with loss or transient interruption of transmission channels, encryption to prevent snooping, and checks to ensure faithful receipt of captured data. This presentation will describe use of a 3 phase commit process to ensure all captured data that is transmitted is retained in a secure central store.

Timestamp accuracy: Device clocks are relied upon to provide accurate time and date stamps in local time. This requires qualification of the device clock, repeated and regular synchronization to external clocks of proven accuracy, ongoing monitoring of time disparities to detect and disqualify any inaccurate devices.

In practice the standard of trustworthiness of data accuracy on paper seems to be exceeded by electronic data and this presentation will compare error rates.

Introduction

Reliability means the extent to which an experiment, test, or measuring procedure yields the same results on repeated trials.

ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) With paper diaries, it's very hard to know

- Whether a subject is recording his/her experience when the protocol requires
- What to do with incomplete, illegible fields
- What to do when all boxes are checked and there are extensive marginalia
- How to avoid well-known problems with retrospective data
- Uncertainty about authenticity: on paper momentary data is known to be filled in retrospectively

Known problems with paper diaries make reviewers skeptical of results obtained.

eDiary Data Quality/Reliability

There are already a number of published accounts where eDiary data quality/reliability is at least as high, and often higher, than that for data gathered using traditional paper diaries:

- Adult asthmatics using paper diaries reported higher compliance with inhaled medication use than was actually completed. [1]
- Subjects aged 17-81 with GI disorders preferred an electronic diary over paper. Data quality and data handling were improved with the electronic diary. [3]
- Data quality in electronic diary for IBS was high and subjects liked using it. [4]
- Subjects preferred electronic diaries. Data quality and compliance were better with electronic diaries. [5]
- Subjects with chronic back pain used electronic and paper diaries for 1 year. High compliance, attributed in part to two-way messaging thru the eDiary. EPD obtained valid data. [7]
- Women using an electronic diary and a paper diary to record menstrual bleeding preferred the EPD. Data quality higher with the EPD. [8]
- Childrens' compliance with inhaled asthma medications is lower than reported in paper diaries. [9]
- Peak flow paper diaries in childhood asthma are unreliable. [10]
- Electronic patient diary was used successfully in an ambulatory setting. Data quality comparable to that obtained with paper diary, and patients liked using it. [11]
- Children reported compliance with inhaler use was 95.4% in paper diaries, but was actually only 58.4%, as recorded by an electronic monitor in the inhaler. [12]
- Women, ages 20-84, using an electronic incontinence diary preferred it to paper. Data quality was higher with the electronic diary. [13]
- According to an electronic monitor that records pill bottle openings, subjects' compliance with medication regime for ischemic heart disease was 55%. Subjects' compliance reported on paper diaries was significantly higher (71%). [15]
- Electronic diaries were used in two pulmonary studies. Subjects liked the electronic diaries, data quality was higher, data handling was easier. [16]
- An electronic diary was effective in measuring subtle changes in headache pain due to high quality data and compliance. [17]
- The subjects invented 22% of peak flow values when they completed their paper diaries. [18]

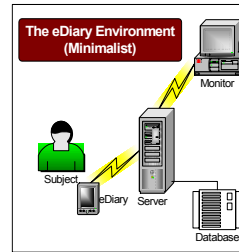
Additionally, lack of controls on paper diaries allow for retrospective entries. Such entries reduce data reliability:

- Retrospective report of alcohol consumption is not as accurate as daily paper diaries or electronic diaries. [2]
- Retrospective data entry and errors in entries in paper diaries may be as high as 24%. [6]
- Specially designed paper diaries that recorded the date/time the diary was opened were used to 'timestamp' the paper diary. Subjects completed 90% of the paper diaries by the end of the trial, but only 11% of the diaries were completed on time. [14]

Validation at PHT

To a great extent, reliability of the data collected in a clinical trial depends on the trial's design, which is embodied in the protocol. Data reliability further depends on validating all of the components of the eDiary environment:

- eDiary device
- eDiary study software
- Telecommunications
- Clinical databases
- Technology requirements
- Programmability in a non-proprietary language
- Software development tools available
- Study application (re-loadable over communication medium for in-field updates)
- Time synchronization capability
- Uses a stylus for data entry by screen touch
- Allows the graphical capture of free-hand characters
- Gives application developers the ability to invoke server-stored procedures from the handheld
- Multiple language and multi-byte language support
- Usability
- Employs a standard O/S to ensure that the same application will run on different devices while requiring minimal code changes.
- Easy to use. (Intuitive interface that minimizes requirements of subject memory, attention span, physical limitations, etc.)



Definitions:

- Validation is the "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through the software can be consistently fulfilled." [19]
- Validation: "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes." [20]
- FDA considers software validation to be "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled." [21]

Each of these components, along with their supporting processes, needs to be validated across the following factors:

- General requirements
- Security [22]
- Data safety

eDiary Device Validation

General Requirements:

- Technical requirements (sounds, screen resolution, accurate internal timekeeping, etc.)
- Sound(s): audible alarms, scheduled alarms
- Screen resolution for legibility
- Screen dimensions:
- Screen color:
- Weight
- Writeable, non-volatile memory [sufficient for one month of stored reports]
- Available memory for applications and reports
- Accurate internal timekeeping: $\leq \pm 10$ seconds per 24 hours, operating at a battery life of 20-100%, with 6 or more calendar days between data transmission and/or time synchronization
- ...
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Security:

- Supports encryption
- Ability to lock out native applications to prevent the user from leaving the study application and from running non-study applications

Data Safety:

- Device is robust and dependable
- Battery life
- The eDiary must not lose data. If a report is completed it should stay on the device safely and reliably until it is transmitted to the central database. Persistent (no data lost if the eDiary is turned off) - non-volatile memory

eDiary Study Software Validation

General Requirements:

- Built-in logic checks
- Screen flow, invisibly replacing complex diary branching
- Automatic time stamping
- Numerous collection elements - VAS, body diagram, multiple choice, etc.
- Alarms/reminders
- Data specificity
- Programmed selections
- Spinners
- Data scales
- Supports data checks
- Support for messaging from site
- Creates an accurate and complete audit trail
- Mid-study change support

Security:

- Identity of assignee certified by the site
- Initial registration and assignment of eDiary to a specific subject at a specific site for a specific study.
- Screen access code to access eDiary screens.
- Attribution of data entry actions to the subject.
- Secure eDiary access to server/database.
- Committed records cannot be edited.

Data Safety:

- Reports should be removed from the eDiary only if the transmission of the report to the clinical database has been successful and the database has been backed up.

Telecommunications Validation

General Requirements:

- Data checks to ensure faithful receipt of captured data.
- Assurance that eDiary can transmit in subject's locale.

Security:

- Data encryption to prevent snooping.

Data Safety:

- Transmission of the diary data should never fail in such a way as to cause data loss or the entry of corrupted data into the clinical database. (Transmission reliability)

Clinical Database Validation

General Requirements:

- Accurate storage of eDiary data.
- Audit trail information is linked to its data record

Security:

- See the HIPAA Security Rule (21 CFR Part 164), ISO 17799, and many others, for guidance

Data Safety:

- Backed up
- Redundant

Conclusion

The eDiary can be a valuable tool in ensuring clinical trial data reliability because:

- It minimizes errors that effect data reliability, including:
 - Missing data
 - Data errors (multiple responses, unreadable responses)
- The data is timely, gathered at the point of experience
- It provides for improved patient compliance through reminders and compliance monitoring reports.
- It provides privacy when reporting sensitive data.
- It is flexible, allowing for automatic downloading of protocol amendments
- It provides for real-time monitoring of diary data, enrollment, compliance, etc.

If the study protocol and study environment requirements are accurate and comprehensive, and the validation of each of the components of the eDiary study's environment, including clear evidence of such validation, is complete and thorough, then one can be confident that the reliability of the data gathered using an eDiary will exceed that gathered using traditional paper methods.

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- [22] See also the HIPAA Security Rule (21 CFR Part 164), ISO 17799, and many others, for guidance.