The utilization of mobile phones for clinical outcome trials in the scope of regulatory compliance and trial duration

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Introduction

Clinical trial design is basically determined by the clinical endpoints used for statistical analysis and by the medical data necessary to support an objective interpretation of the diagnosis or progress of treatment, respectively. Study data are mostly collected by physicians – accurate and objective reporters with high level education. Certainly, for the acquisition of clinical data such as medical diagnosis, laboratory parameters, results from imaging methods, etc. this is a matter of course. However, especially for the evaluation of new drug candidates clinically meaningful endpoints for many trials are data about the progress of treatment and the patient's outcome. Typical outcome data are observations that the patient makes during every day live e.g. about the frequency of occurrence and severity of headaches, episodes of dizziness or nausea, etc. The progress of treatment can be monitored best by periodic, standardized measurements of health data like blood pressure, blood glucose level, etc. Both, symptomatic parameters as well as quantitative values are usually collected at periodic, scheduled clinic visits by physicians. Although the usage of written diaries helps to get more accurate data, the results of several comparative clinical trials show, that subjects are often noncompliant with the required protocol when using paper diaries [1, 2]. Patients are repeatedly careless when collecting data into paper diaries and the data are usually of insufficient quality to be used as primary clinical endpoint. The aim of our work was to elaborate the utilization of mobile phone based electronic patient reported outcome (ePRO) technology for clinical outcome trials in the scope of regulatory compliance and duration.

electronic Patient Reported Outcome (ePRO) technology

Functionality and utility of ePRO technologies differ widely. For a specific group of subjects a web based solution using personnel, tablet or touch-screen computers might be appropriate. Personal digital assistants (PDA) with proprietary trial software might be issued to patients entering a study. These devices have a small screen to display questions, and a number of buttons to control navigation through questions and to assign a response to a question. Data are normally stored locally and transmitted to a remote clinical trial centre e.g. via a modem link. Since the ubiquitous availability of the broadband mobile telephone network data entry and transfer via mobile phones become more and more the method of choice.

Regulatory issues according to GCP and FDA guidance

The Guideline on Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH) provides an unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. In section 1.52 of the Guideline on GCP the term "subjects' diaries" is especially expressed as an example of "Source Documents" [3]. This definition classifies both paper and electronic diaries using ePRO technology as source documents. Being a source document differentiates the subject's diary from the case report form (CRF), which is a collection of data derived from many source documents in a medical file. The investigator is responsible for retaining all original source documents whereas the sponsor is responsible for keeping the original of the CRFs. Moreover the Guideline on GCP (section 2.10) makes the following statement regarding data: "All clinical information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification." In section 4.9.1 the guideline also requires that the "investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and all required reports".

In parallel to GCP the U.S. Food and Drug Administration (FDA) refers to the "21 Code of Federal Regulations Part 11" (21 CFR 11) which applies to electronic subject diaries and electronic signatures [4]. This law does not apply to paper diaries unless they are scanned into electronic form and archived as electronic records. No matter if a paper or an electronic diary is used, it must yield high data quality and integrity. The FDA makes the following statements in the Guidance for Industry: Computerised Systems Used in Clinical Trials: "FDA's acceptance of data from clinical trials for decision-making purposes is dependent upon its ability to verify the quality and integrity of such data during onsite inspections and audits. To be acceptable the data should meet certain fundamental elements of quality whether collected or recorded electronically or on paper. Data should be Accurate, Legible, Contemporaneous, Original, and Attributable" accordingly labelled ALCOA principle of data quality and integrity [5]. Additionally to the ICH GCP concerns mentioned above FDA 21 CFR 11 adds:

- time-stamping to the audit trail so that local time can be established for any edits or changes and
- the use of "operational system checks to enforce permitted sequencing of steps and events, as appropriate."

These two additional components are crucial for subject diaries and demonstrate the advantage of ePRO technology. A combination of alarms, prompts, and lockouts can enforce protocol requirements for subject responses to be made in a specified sequence and at prescribed times. Timely or contemporaneous recording of the subject's experiences, or condition, is one of the key components of the ALCOA principle. If subjects wait to record the relevant information, the impact of other life experiences will affect the accuracy of their recording. Paper diaries can be filled in at any time, and this fact leads to the questionable accuracy of their data. Therefore, 21 CFR 11 compliant ePRO solutions include mandatory times in the protocol which allow to enter the data only at specific times, by preventing subjects from entering data out of sequence, and time-stamping of subject entries.

Issues of trial duration

The main assumptions utilised in the comparison of paper vs. ePRO workflows are shown in Figure 1 [6]. The top part refers to the progressive step-by-step workflow involved in the paper process. The bottom part is the comparable workflow utilising an appropriate ePRO technology. The black arrows within each section depict the workflow involved in that process. The difference becomes clear: the first eight sections during the classic paper workflow could be processed mostly in parallel. Analysing of paper diary data usually occurs long after the investigator has processed the data in a trial (visit, assessment, enter of diary data). ePRO data, however, reach the investigator for diagnostic processing in the shortest possible time, even though it might be first received on the server of a CRO. Incomplete data sets or misinterpretation of protocol procedures are recognised immediately and therefore, correction measures such as automatic reminders could be taken very early. Thus, electronic methods can yield high rates of subject compliance with protocol procedures. This higher compliance will be followed by more reliable and potentially more accurate data, which makes electronic diary methods compliant with ICH data quality guidelines and the ALCOA principle.

Discussion

The analysis of the appropriate regulatory guidelines shows that accurately developed ePRO technologies fulfil the requirements for regulatory compliance. Although the pharmaceutical industry is somehow conservative in using new technologies in the course of clinical trials the obvious advantages over traditional paper diaries should lead to a remarkably reduction of trial duration which finally should result in positive return on investments.

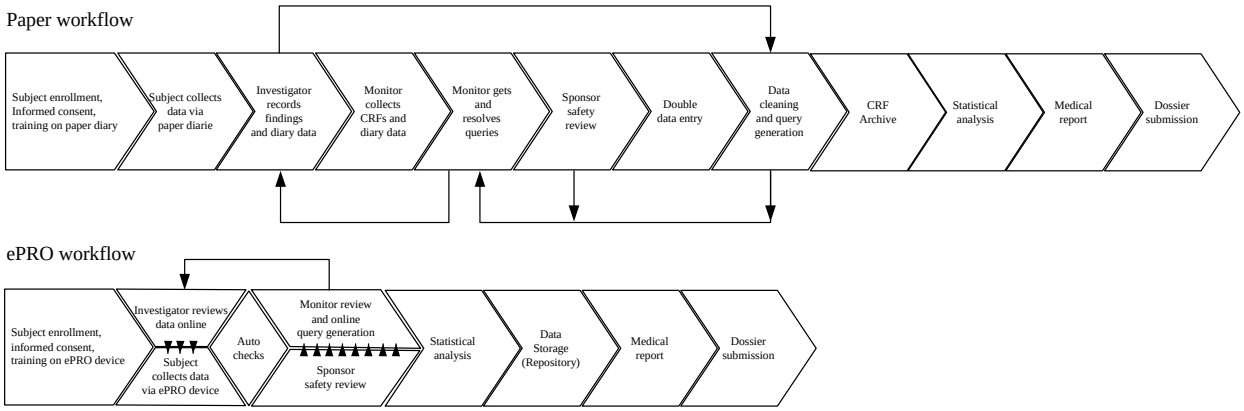

Figure 0: Comparison of the workflow of paper based trials to the utilization of ePRO technology.

References

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