Correction of ePRO data

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ePRO solutions allow patients to report clinical trial information directly from mobile devices into electronic CRFs. This eliminates both the need for data entry by site staff and potential transcription errors, as data are collected directly from the source and stored in the ePRO system's or EDC system's database. Hence, the source data are the data stored in the central database. Source data should be accurate, which means that a procedure should be in place to address the situation when a study subject realizes that he/she has made a mistake and wants to correct the submitted data. This suggests that ePRO systems need to offer support for correcting ePRO data. Yet such functionality should be built in a way that helps finding the optimal balance between data authenticity and data quality, while at the same time preserving data integrity. Such a balance can be achieved by not allowing for excessive rethinking of answers by subjects, but instead providing a built-in threshold that serves as a filter for those changes that really lead to an improved accuracy of the data, and by recording all changes in an audit trail that is accessible for both investigators and sponsor users.

Objective

During the last few years, the regulatory authorities have given critical findings related to handling of electronic patient reported outcome (ePRO) data. Among those is a critical finding given to a commercial ePRO vendor due to processes related to data integrity of ePRO data [1]. One of the identified issues was that incorrect data in the ePRO could not be changed and were included in the analysis. Requests to change the incorrect data had been submitted by the investigators but were rejected as it was explained that changes to the data could not be made and the investigator would need to document the response in the source.

This raises the question whether the traditional view that ePRO data should not be changed needs reevaluation, and whether we should consider ePRO systems to allow correction of subject-submitted data if necessary. Since data changes should ideally be made in the source, some of the concerns arising with this question are which data are considered source data, and who should be allowed to make the changes, and when? How should the ePRO system allow for the possibility to correct patient-submitted data? The objective of this paper is to discuss these issues, and to present the way we have chosen to address the possibility to correct ePRO data when using Viedoc.

ePRO source data

An ePRO system is an electronic Patient Reported Outcome system that is used to collect data directly from patients in a clinical trial. Using a data collection device, which can be a hand-held device supplied by the ePRO vendor or the patient's own computer, tablet or mobile phone, patients can record events such as drug administration, level of pain, side effects or adverse events. The information is uploaded electronically, either directly to the database of the EDC system, or first to the database of the ePRO system, and then synchronized with the EDC database at a later time. ePRO systems replace the original pen and paper, and offer a set of advantages over the use of paper diaries [2]:

- Improved compliance through the use of alarms, reminders, and date and time stamps
- Improved data quality through the use of electronic data collection and inbuilt data checks
- Reduced trial times due to quick access to data without requiring data transcription

Yet, while in the original pen-and-paper world it was undisputed what the source data is – the paper questionnaire that the patient had filled in – it is a lot more debatable to define the source data when ePRO data is involved. Especially when the patient's answers are temporarily stored on the device itself, as opposed to remotely and continuously synchronized with the ePRO vendor's database or even directly with the EDC database.

According to GCP guidelines [3], source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. This must be the first record made by the appropriate person, for example an ePRO record produced by the subject, or the first acceptable result from scans or laboratory tests. Source data are contained in source documents. Source documents, in turn, are defined as original documents, data, and records, among which are for example subjects' diaries or evaluation checklists. Regarding electronic source data, it is currently accepted that the earliest durable record is considered as the location of the source data and therefore the source document. Thus, the data in the EDC system's or ePRO system's database can be considered source data, even if the data have been temporarily stored on the patient's ePRO device before transfer to the central database [5].

If original data records are captured in one system (such as a device supplied by the ePRO vendor), and then transferred electronically to another repository (such as the clinical data management or the statistical analysis data sets), a concern is to provide the assurance that the record today contains exactly the same information as it did at the time it was first recorded. Since the subsequent copies are the ones used for data analysis, the record must be protected as it moves between systems. One approach is to create certified copies, copies that are created according to a validated method of copying that certifies that the copy is complete and accurate, and that it includes the relevant metadata, such as date, context, layout, electronic signature and the full audit trail. ePRO solutions that directly interface the central database without first storing the data on an ePRO device do not face the challenge of having to copy source data, but instead require subjects to have an online connection (internet or cellular) with the central database in order for data collection to be possible.

Correction of ePRO data: to do, or not to do?

Source data should be accurate, which means that a procedure should be in place to address the situation when a study subject or other operator capturing data realizes that he/she has made a mistake and want to correct the recorded data. This is the accepted standard for regular CRF data, and all EDC systems provide functionality that allows raising queries on data, and correction of data a query is raised on. Yet for a long time, changing ePRO data was not considered acceptable. One of the main reasons is that one would like to catch the patient's initial, momentary response ('The pain is unbearable!') and not his/her cognitions and considerations a few hours after the moment of interest ('It wasn't so bad after all'), when other factors such as pain medication or the environmental context start to attenuate the initial experience. The intensity of pain is easily forgotten. In general, FDA PRO Guidance states that more accurate PRO data is obtained when using questionnaires that ask patients to describe their current state, rather than to ask them to compare their current state with an earlier period or to attempt to average their experiences over a period of time [6]. Problems with recall are:

- Recall is often inaccurate, especially for details, routine matters and timing. Human memory imposes limitations on what and how much can be recalled.
- Recall is often biased; the content of memories is often influenced by external factors, such as environmental context. The accessibility of information at the time of testing influences how questions are answered.
- The patient's mood at the time of testing can affect the response; negative events are better remembered when a patient is in a negative state.
- Expectations or beliefs can influence recall. Patients may find it threatening to report a certain answer if they think this is not the socially acceptable answer and might be prone to changing the original answer into a more desirable one.

Momentary assessment – assessing phenomena at the moment they occur – reduces recall bias. This is an argument for not allowing a patient to change their answers once submitted. The value of diary data depends on timely completion in the natural environment. Yet, this argument primarily regards questions about subjective experiences, such as how a patient perceives his/her well-being or pain level. When questions are asked about more specific events, for example the number of pills that were taken, the risk of recall bias when allowing changes to ePRO data might outweigh the negative consequences of including incorrect information in the analysis. A patient might have misunderstood the questions or the scale to select his/her answers from, for example because he/she missed a negator in the sentence and structurally answered the questions incorrectly, leading to incorrect data being included in the analysis. Such circumstances opt for the possibility to allow changes to be made to ePRO data. Similar occurrences might have caused the British MHRA inspectors to give a critical finding to the sponsor for Data Management for, among others, the inclusion of incorrect ePRO data in the analysis, and the denial of requests of investigators to change the incorrect entries.

Considerations regarding ePRO data changes

In light of the above discussion, it is important to mention the critical finding for data integrity that was given by the British MHRA a few years earlier [7]. During the inspection, it was found that several hundred changes had been made to ePRO data across a number of trials, and that these changes had been requested by the sponsor's data management team in conjunction with investigator site staff. These data changes were then subsequently accepted in the study databases without adequate support from source data: there was no contemporaneous source record of the discussion between the investigator site staff and the subject or caregiver documenting the reason for the changes. There was no source data to support either why the changes were needed, or to confirm patient approval of the changes.

With regard to changes in ePRO data, there is a thin line between correcting incorrect data, and preserving data integrity. When is it legitimate to change ePRO data? The following considerations should be taken into account when changing ePRO data or designing systems that allow for EDC and ePRO data changes.

- It is important that original electronic entries are visible, and all changes are traceable, for example by implementing an automated audit trail that records changes as they are made by the system users, whether this is the subject, the investigator, or any other user with data edit permissions (ICH GCP 4.9.3 and 5.5.4). Such an automated audit trail provides a digital alternative for the single-line cross-out, initial, and dating that is done for corrections to paper documents.
- No individuals other than the subject or the investigator should be allowed to change ePRO data. EDC systems should be designed to protect against this possibility.
- Essential is that the initiative should come from the patient, or from the patient and the caregiver or doctor together. Source data should only be modified with the knowledge or approval of the investigator (ICH GCP 4.9.3, 4.9.4, Chapter 8).
- The investigator shall maintain the original source document or a certified copy (ICH GCP 2.11, 5.15.1). This however is difficult to achieve in those cases the ePRO data are continuously synchronized to the ePRO vendor's or EDC system's database and only a single copy is stored on a central server.
- The sponsor should not have exclusive control of a source document. (ICH GCP 8.3.13). Sponsors should provide guidance to investigators on making corrections to ePRO data. There should be written procedures to assure that corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the corrections (ICH GCP 4.9.3).

The Viedoc approach

For collection of patient eDiary data, Viedoc offers ViedocMe, our web-based ePRO solution and an integrated part of our EDC platform. It allows patients to report clinical trial information directly from their mobile devices into the eCRFs available in Viedoc. This eliminates both the need for data entry by site staff and potential transcription errors, as data are collected directly from the source and stored in the EDC system's database. No data is ever stored locally on the subject's device, which means that the source data are the data stored on Viedoc servers.

From Viedoc release 4.48 in February 2019 onwards, Viedoc introduces the possibility to change data submitted by subjects through ViedocMe. This is accomplished by the option, set in Viedoc Admin, to allow roles with lock data permission to unlock forms submitted through ViedocMe. When this option is activated, users with lock permission, typically monitors, can unlock forms submitted by subjects

through ViedocMe, so that the forms are open for data edit by the investigator. We have activated this option as default for all studies starting after Viedoc release 4.48 in February 2019, but it can be inactivated if considered not relevant for the study in question. For studies started earlier, this option is by default set to inactive, but can be activated manually.

A generally raised question is whether it is desirable to let patients change their submitted data themselves. The answer to this question lies in a fine balance between data authenticity and data quality. It is not desirable if we prioritize data authenticity and would like to avoid patients changing their original answers to a questionnaire into a 'on second thought'-answer. It is desirable, if we value data quality and would like to offer patients the possibility to correct a mistake ("I took two tablets instead of one" or "I systematically interpreted the questions in a wrong way"). In Viedoc, this balance is achieved through the fact that the patient him-/herself cannot change the ePRO data. The data can be changed by the investigator, but only after the investigator has requested the monitor to unlock the form. This way, Viedoc has a built-in threshold for ePRO data correction, that involves at least two people in addition to the subject, and that might serve as a filter for those ePRO changes that really are a correction of incorrect data, rather than a change of opinion after time.

Like changes to regular CRF data, all corrections of ViedocMe data are automatically recorded in the audit trail, which means that the old data never disappear, they are only marked as 'obsolete', while the corrected data are instead added as 'current'. Every time a data point is entered and saved, Viedoc creates a PDF of the form. Every time an existing data point in the form is edited and saved, a new PDF is generated. These PDFs serve as a contemporaneous, independent and certified copy for the investigator. Through the automatic generation of these PDFs, Viedoc meets the requirement that the investigator maintains the original source document or a certified copy. Moreover, no system users other than those with data edit permissions, typically the investigator, have the possibility to edit ePRO data. Since both regular CRF data and ViedocMe data are always visible or accessible for the investigator, and the data are stored on servers hosted by Viedoc as independent third party, the sponsor can never have exclusive control of clinical trial data when Viedoc is used for administrating the study.

In conclusion

There is a clear trend towards an increased use of ePRO as a vital component for data collection in clinical trials. At Viedoc we believe that the critical finding mentioned in the beginning of this paper undoubtedly suggests that there is a need for ePRO systems to offer support for correcting ePRO data. Yet this functionality should be built in a way that does not allow for excessive rethinking of answers by subjects, but in a way that by design helps to filter for those changes that improve the correctness of the data and as such the quality of the analysis. A way that helps finding the optimal balance between data authenticity and data quality. And a way that preserves data integrity by keeping track of the full change history of any ePRO data element. The Viedoc way.

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