TriTiCon eCOA White Paper

Data Handling and Change of eCOA data

- Addendum 1: Change categorization examples and additional considerations

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1.1 Data Issue/Change Examples and, categorization and comments.

It is recognized that the suggested approaches below might not be possible with platforms/process/services provided by any or all eCOA vendors today. However, the rationales and recommendations are intended to describe an optimised approach, and to illustrate principles in the main white paper.

Example	**Rationale / handling** **Recommended actions/proactive management**
Close out a device.	Responsibilities and approvals Closing (or deactivating) devices is an investigator responsibility. If not performed on the device as expected (e.g. due to investigator error or lost device), the correction (deactivation in retrospect, not using the device) should still be done by the investigator and without any further approvals. In designs and setups where the conclusion that a device should be closed out can be made based on available, confirmed data (such as end of trial data in PRO or EDC database) a validated process (fully automated *or* with manual intervention) can be implemented to perform the deactivation on behalf of the investigator. Method To ensure quality and efficiency close out should be performed with a process (and if possible a system) that clearly prompts for required information, verifies the validity of the information (for example vs other active device(s) for the patient) and obtains the appropriate confirmation of the intended actions and consequences. Proactive Management Instructions, training and technical design (such as natural investigator workflow step to close out the device(s) in connection to completion of final visit data collection or diary return) should be used to minimize the investigator errors in not closing out devices. In addition, daily reconciliation between device status and ePRO + EDC databases regarding patient status should be part of ePRO Data Management process, both to take immediate actions on individual cases (identify and close out individual devices – *minimize the consequence of the issue*) and to identify and act on trends on investigators, users, CRA, country level – *minimize the number of issues.*

Merge data from different devices	<u>Responsibilities and approvals</u> As for the close out of devices issue, this is an administrational change, not changing the actual data, and can be implemented by the investigator without further approvals. Further, on a single Investigator approval the resulting set of changes can be implemented. <u>Method</u> The need to merge data from two devices is normally a consequence of an administrative issue. Whilst the merge process will address the problem it is key to understand the root cause of the problem in order to ensure proper implementation of the change (for example ensuring the reporting days are in sync with the study days such as day on treatment), and to handle any subsequent issues (such as redundant or missing records). To ensure the merge is done correctly and as intended, and that subsequent issues are handled, it should be performed with a process (and if possible a system), clearly prompting for required information, verifying the validity of the provided information (for example comparing the data in the two devices) and with required confirmation of intended action and consequences. As merging of device data is complex, the method must be more robust and should handle more scenarios then at present and must be supported by a rigorous system module or subjected to a sponsor/CDM QC/support. <u>Proactive Management</u> As the need to merge devices typically arises from problems such as lost devices or device failure, all efforts should be made to understand the root cause and try to resolve it. To do this, ensure reason for the required merge is clear and tracked, and identify and act on trends on investigators, users, CRA, country level – *minimize the number of issues.*

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Change subject id	<u>Responsibilities and approvals</u> Whilst the subject identifier is critical to ensure that the data is associated to the correct patient, it is not a *patient reported value* but an assignment of a placeholder to the data and hence is categorized as a structural change. However, ensuring the validity of the linking of patient data to identifier is a key source record attribute and patient knowledge that lies solely with the Investigator. Hence a change in subject identifier must only be performed by Investigator and should be permitted without further approvals. The Sponsor can identify issues or inconsistencies in patient identifiers and present these to the Investigator for resolution. (By continuous reconciliation within ePRO database (for example home based diary device versus questionnaires) and between ePRO, IVRS and EDC databases). <u>Method</u> Subject management module allowing change of the identifier, with standard requirements to audit trail etc., and also with edit checks such as comparing identifiers to other ePRO internal data points (for example checking that the new subject id is not already used) and confirmation of intended action and consequence. <u>Proactive Management</u> Monitoring of frequency per investigator as an indication of overall performance / quality.

Addition of patient reported data values	<u>Responsibilities and approvals</u> Addition of data (objective as well as subjective) must only be performed by the Investigator. The Investigator must have – and be allowed to execute – full control of the data, and therefore be allowed to add data without further approvals. However, addition of data is also regulated by the other aspects of data and source data. This strongly limits the real cases where compliant addition of data is possible, as it would require an existing trustworthy source for the data, and that this source includes all the required attributes and is handled as per other source documents. If such records exist as a natural source, the whole concept of patient reporting this data is unfeasible as it is not meaningful from a quality, patient burden or operational perspective to have the patient enter data that exists in another source. Allowing patients to create and submit the data by other sources (such as paper notes) raises a series of additional problems (such as mixed mode complications) and generally should be avoided. <u>Method</u> As a general policy patient data should not be added. Missing (and incorrect, see below) data is expected for patient reported data, should be accepted (to a defined level) and handled in the analysis stage. However, it must be controlled and limited to an acceptable level and key principles for handling of missing data should be defined in the trial protocol and statistical analysis plan. Missing data (low reporting compliance) is a protocol deviation and should be handed as such. Preferably the protocol eligibility criteria should include requirements on patient capability to manage the instrument correctly and in a compliant manner. Patients that do not meet these criteria should not be included. If addition of data is still allowed, it should be performed using an entry screen mimicking the patient instrument, requiring entry of all the attributes required for source records and have the same checks and logic applied as if the data were registered by the patient as intended. Further, the policy and requirements source for data handling could be presented for confirmation / acceptance. The Sponsor should follow up and identify the root cause for each case of data addition, and continuously evaluate the causes and frequency of the problem and, if required, make study level decisions on how to address the problem. <u>Proactive Management</u> As addition of data indicates a failure of the concept of patients reporting data directly as source, the most important proactive management of the problem is to ensure a feasible and adequate trial design and set up.

	This includes trial design and instrument design, but also data and activity design, and instrument implementation and to ensure that the collection of data is feasible with regards to actual data sources, patient burden and capability, investigator and patient workflow and behaviour etc. In the trial maintenance phase, reporting compliance should be closely monitored and borderline patients as well as trends on investigator and CRA trends should be identified early and promptly acted on. Indications of general issues (trial level) should be evaluated (sooner rather than later) with regards to feasibility in design and set up, and corrective actions assessed.
Modification of patient reported data values.	The modification of patient reported values follows, in principle, the same rationale as Addition of patient reported data values (See above). In addition: <u>Method</u> For objective data issues, up-front rules can *in some cases* be defined and changes implemented on behalf of the Investigator based on a general approval. Any such upfront definition must of course be fully clear and unambiguous, precisely defined and fully data driven. The rule, approval as well as the execution of the changes must be fully documented. Further, some issues can be handled by post-processing (i.e. not changed in the source data, but handled in a post processing step before data is delivered to the next process). This could include for example handling of redundant records, false events etc. (See also section 2 for objective data modifications). These methods, used correctly, can be a more efficient, systematic and controlled way of handling data issues, thus decreasing manual workload and the risk of human errors and yielding higher consistency and being easier to document and ensure data maintenance transparency and traceability. <u>Proactive Management</u> Data structure, rules and relations should be defined in the set up stage. Associated edit checks should be implemented in the collection instrument, and backend checks continuously applied to the database to identify issues (violations of rules). Issues should be continuously monitored to identify and act on trends on investigators, users, CRA, country and trial level – *minimize the number of issues.* Actions can also include changes to the setup.

Change device phase	<u>Responsibilities and approvals</u> Ensuring that the device is in the right phase is an investigator responsibility, and hence the correction of device phase should still be performed by the investigator and without any further approvals. In designs and setups where the conclusion on correct device phase can be made based on available, confirmed data (such as end of trial data in PRO or EDC databases), it can be agreed upfront that the sponsor (or sponsor delegate) can perform such phase change on behalf of the investigator. <u>Method</u> Because the device phase often drives the logic of the diary (i.e. which questions that are being presented to the patient and when, alerts etc.) there is often a residual effect in too little/too much data if the device is used in the wrong phase. The residual effect must be identified and handled to ensure consistent and appropriate data structures in order not to impact downstream. In practice this can be performed by including such checks in batch checks of data structure (rules defined as part of the set up), and handle the issues identified by corrections (potentially remove or add data/null records) or documentation as residual issues (recommended). To ensure quality and efficiency, change in state should preferably be performed in a device management module, that clearly prompts for the information required, verifies the validity of the information (for example vs other data such as randomisation or completed visit based questionnaires) and with required confirmation of intended action and consequences. <u>Proactive Management</u> *Effects from device being in the wrong phase can be critical as the result can be missing key data that might partly or fully disqualify the patient from analysis, so substantial efforts should be made to ensure that devices are in the right phase.* As far as possible device phases should be avoided in the instrument implementation, and only be used to control the behaviour and logic of the device where this is required. If a device phase is specifically required, it should be a transient property of the device only and not stored in the database. Instructions, training and technical design should be used to minimize the potential for investigator errors in not deactivating devices. Changing the phase of the device is a responsibility that should not be delegated to the patient. In addition, daily reconciliation between device status and ePRO + EDC databases regarding patient status should be part of ePRO Trial Management, both to take immediate actions on individual cases (identify and deactivate individual devices that should be changed – *minimize the consequence of the issue*) and to identify trends on investigators, users, CRA, country level – *minimize the number of issues.*

	Assignment of the data to the correct trial stage is better performed as a post-processing derivation (part of the creation of analysis datasets) and the device phase should not be stored at record level unless there are specific reasons to do so. (A general design rule is to only collect and store data in the database that is needed for the analysis or another specific purpose. Any additional data only constitutes an overhead in handling and processing).

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