TriTiCon eCOA White Paper

Data Handling and Change of eCOA data

Author: Anders Mortin

Version 1 – June 22, 2016

Disclaimer:

The views expressed in this White Paper is strictly the opinions of author and does not represent the position of any eCOA vendor, or of any company that the author is affiliated with.

The Paper must not be seen as a reference with regards to authorities' interpretation of regulatory guidelines or laws. No liability or responsibility of any kind (to extent permitted by law), including responsibility for negligence is accepted b

TriTiCon | The 3 Tiers Consulting Company |www.triticon.com

Phone +45 52 19 34 99 |Mail Anders.Mortin@TriTiCon.com

1 Executive Summary

Increased eCOA scope, complexity and site challenges result in data quality issues that require data cleaning and data corrections

Broadened scope of data collection, increased instrument complexity and site challenges in handling the eCOA devices result in a variate of data quality issues. In order to ensure quality data, traditional "CRF data cleaning" of the collected eCOA data needs to be performed. I.e. execution of batch data checks, reconciliations, tracking and handling of identified issues and assessment of residual data issues. These issues also result in situations where querying and update of the patient reported data is both regulatory compliant, business feasible and required, in order to achieve quality data and ensure trial results.

Prevention and proactivity

- Prevent issues by design and minimize issues by proactive, central, monitoring

Device handling issues by sites or patient mistakes, combined with the high frequency data collection that is common for eCOA, quickly result in high number of residual effects if not fully prevented or identified and solved early. Thus, prevention by thorough design considerations and best practices, as well as proactive identification and correction of device handling issues and repeated mistakes, are critical in order to minimize occurrence and impact of issues.

As eCOA often is the data source, and is designed to record the data at the time of collection, missing or incorrect data cannot be recovered. As the data typically is endpoints or safety data, unaddressed issues might have severe impact to the trial validity and results.

Further, the central monitoring paradigm is highly relevant for eCOA data, as this data is sensitive to site performance, collected continuously and with high frequency and thereby a strong indicator for risks and issues.

Different types of issues require different policy and methodology for identification and handling

Device handling, site mistakes, patient mistakes and technical issues causes quite different types of issues. This calls for a structured categorization and differentiated methodology, in order to achieve an efficient and compliant process with high quality.

End to End quality

– Prevent, minimize, address, but also handle the residual issues

Residual issues (issues that cannot be solved) should be documented together with the data, to allow appropriate considerations in the analysis and submission of the data.

TriTiCon | The 3 Tiers Consulting Company |www.triticon.com
Phone +45 52 19 34 99 |Mail Anders.Mortin@TriTiCon.com

2 Table of Contents

3 Introduction

Use of eCOA instruments in clinical trials is increasing both in terms of number of trials and complexity of data and with the inclusion of non-subjective data – for example concomitant medication and symptoms. This drives a need for a central monitoring paradigm to review and analyse data for both quality and completeness and so may result in situations where querying and updating of the patient reported data is both feasible and beneficial.

Data review, cleaning, querying and change (traditional "CRF-data management") performed on patient reported (source) data, and changes claimed by patient/investigator, must be based on a regulatory, scientific and operationally feasible policy. This must identify what data can be challenged, what changes can be made and under what circumstances, and by which participants within the trial process.

This document outlines a suggested end-to-end approach to the challenge of data quality management of eCOA data, including suggested categorisations and handling of different data change claims.

3.1 Regulatory Considerations

Guidelines [Ref 1,2,6] from both the FDA and EMA have clear expectations on the Investigator and Sponsor to actively review the clinical trial data for completeness, consistency and correctness, and for the Sponsor to monitor both site and patient performance to identify potential problems that could result in poor quality or loss of data.

These guidelines do not in any way exclude PRO data. Rather, the FDA PRO guidance [Ref 1] states that the sponsor should avoid

> *"Ability of any entity other than the investigator (and/or site staff designated by the investigator) to modify the source data."*

and

> "*Clinical investigator inability to maintain and confirm electronic PRO data accuracy"*,

Thus, PRO-data *should* be *actively reviewed* by both sponsor and investigator, and actively maintained – *including appropriate changes of the data* – by the investigator.

In addition, there are categories of changes to the PRO data-base that do not require an actual change to the eSource data. These are administrative and structural changes (for example merging data from several devices) and device management activities such as deactivating devices or changing trial stage. These are not source data as they are not subjective data values collected by the patient, they are system data related to the functionality of the device or the conduct of the trial and hence not directly subject to the controls required for eSource.

Regardless of whether applied to either eSource or operational data, all review, querying, handling and potential changes, must still follow the established guidelines for data handling in clinical trials, especially (but not limited to) regulations on Investigator control of source data, Trusted Independent Third Party roles and data integrity and transparency [Ref 3,4,5].

TriTiCon | The 3 Tiers Consulting Company |www.triticon.com
Phone +45 52 19 34 99 |Mail Anders.Mortin@TriTiCon.com

3.2 Sponsor Considerations

Due to its nature with numerous data reporters and devices, eCOA data is challenging to collect and requires robust and active monitoring and management to identify and resolve issues as early as possible, and to implement corrective actions to prevent repeated issues.

It is unlikely that a single incorrect data point can impact patient safety or the overall finding of a study, but with high volumes and frequencies of data collection a simple issue can rapidly multiply into a significant problem. Without efficient procedures and suitable tools in place, a problem such as this can not only create a significant workload in data clarifications and corrections, it can also have a severe impact on the quality of the final data and therefore the results of the study.

Issues in data capture are not the only potential source of data problems within an eCOA study. Incorrect handling of devices and mechanical failures can also introduce complications into the data set which will also result in an additional administrative workload to correct.

If not identified and resolved in a timely manner the systemic build-up of data issues can result in protocol deviations, unmet study timelines and, potentially, insufficient data for analysis.

In addition, Sponsors must consider the drivers from the change initiator and ensure an unbiased review and change handling process in order to ensure that no bias or imbalance is introduced into the data and that it remains a true and accurate reflection of the study.

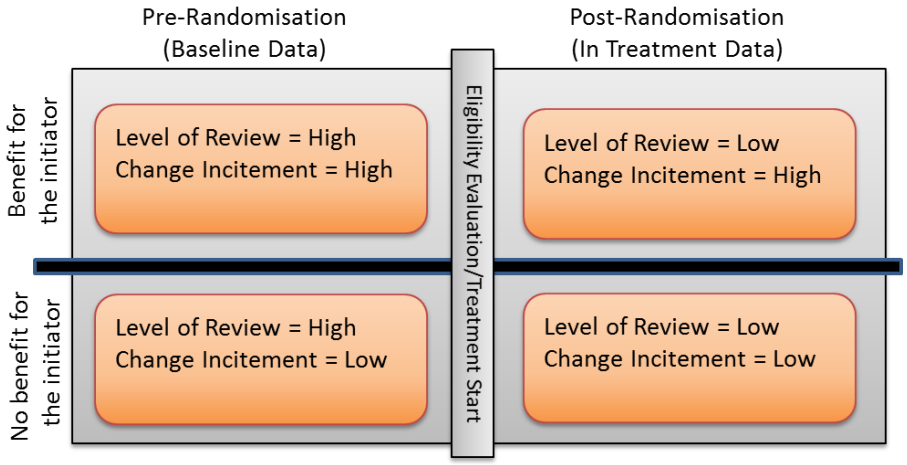

Figure 1: Typical Data Review Levels and Change incitement.

3.3 eCOA Vendor Considerations

In eCOA trials, the Vendor is typically assuming two key roles, acting as an independent third party for hosting the source data, and as a Sponsor delegate to manage handling and review of the eCOA data.

In their role as independent third party, the eCOA Vendor must ensure full control of the data by the Investigator, and prevent exclusive control by the Sponsor. In this role the eCOA Vendor can implement approved changes on behalf of the Investigator, but never on behalf of or under direction from the Sponsor.

As Sponsor delegate the eCOA Vendor can also undertake data review and performance monitoring on behalf of the Sponsor, to identify and address issues in usage and data.

As long as the Investigator has complete control and the Sponsor never has exclusive control, a Vendor can be both a CRO and maintain the system. However, it is important that the responsibilities are clearly defined in contracts etc.

4 Data Handling Policy

4.1 General Considerations

In order to ensure data quality:

- Data must be reviewed for completeness, correctness and consistency – *data issue identification*.
- Corrections of the data should, under right circumstances, be made to eliminate the issue – *data issue resolution*.
- Issues that cannot, or should not, be resolved must be documented and the residual consequence of the issue should be handled with regards to potential impact on analysis and reporting – *handling of residual issues*.

Collection of quality data from patients presents a significant challenge. Instruments must be designed to encourage good data entry policies without imposing burdensome restrictions on the patient. Typically, this need for flexibility in data input can result in structural or operational issues that need to be addressed in the database. It is important to differentiate changes to operational data from changes to subjective data provided by the patient, and to ensure that the appropriate policies and processes are applied for the different categories of change.

Whilst there are a few scenarios where a patient reported value may be changed, the majority of changes actually requested are structural, relating to operation issues, rather than data relating to patient reported values.

Regardless of the reason for change, the review, querying, change and handling of residual issues must be based on adequate considerations and policies, and using a systematic process, documentation and technology framework. It should be noted that as the patient reported data are, in many cases, the source, there are additional tracking and management requirements that must be met [Ref 3,4,5].

4.2 Data Issue Categorizations and Handling

As outlined above there are different categories of issue associated with eCOA data, these categories and their associated handling policies are described in the table below.

Issue Category	Handling Policy
Non-modifying	
Administrative: e.g. Close out devices, merge data from different collection units, correct identifiers.	These are corrections of device management and handling issues that may be performed without the need for multiple approvals. Therefore, these may be performed by the Investigator without additional approvals from the Sponsor[1]. Further, this category of change may be executed by the Vendor on behalf of the Investigator provided that a clear and unambiguous change request is either raised or approved by the Investigator.
Structural: e.g. Change trial stage of the data, move data to other visit, split or consolidation of reported events.	As these changes are corrections of structure (i.e. not actually changing the patient reported values, but correcting data provided by the investigator), they may be performed by the Investigator without Sponsor approval or executed by the Vendor on behalf of the Investigator. Which data that should be collected in different trial stages or at different visits might differ and therefore changes in these parameters must be evaluated for missing or additional data compared to protocol, and any issues handled as missing/additional data.
Modifying	
Objective/Evidenced: e.g. AM/PM. Mix up of rescue medication and IMP. Wrong visit date. Redundant data.	Issues in patient reported data values that can be clearly identified by comparing to other data sources or references. The policy for if and how to address these issues should be set by the Sponsor in order to ensure a consistent and balanced approach to handling of the issue and a quality and efficient process. For clearly defined and frequent issues, post processing might be the most consistent and efficient approach, see Data Change Policy section below.
Subjective/No evidence: e.g. *Change of subjective assessment. Change of time-point. Missing entries.*	For subjective data as reported by the patient – often source data – it is difficult to identify issues or claim a different value to be more correct. Hence this data should in general not be changed. Even with the Investigator in control of the data any data change must be based on evidence which, by definition, is not available and hence changes would violate this data change principle. There will be a certain level of error in the reported data. This is expected and should be handled by the trial design and statistical analysis, as long as bias is not introduced by unbalanced review and data-change.
Technical	
System	Issues in system generated data[2] or caused by issues in internal post-processing, should be corrected, or documented as residual issues, by the system vendor. As this is not data provided by the Investigator, it should not be regarded as Investigator controlled source data. However, of course, any issues in system generated data must be investigated, accounted for and any change agreed with the Sponsor, communicated to the investigator and adequately documented.

Table 1: Data issue/change categorization.

[1]Whilst data changes must not be limited by sponsor approval (as the investigator must have full control of the data), QC processes might be required to ensure consistency and correctness. However, not all changes are appropriate, and data changes are subjected to Sponsor oversight of investigator performance and compliance, in the same way as all other investigator responsibilities.

[2] Special attention should be given to issues in the electronic record attributes (user id, timestamps etc.) that are required to demonstrate that records comply with the ALCOA principle [Ref 3,4]

4.3 Data Change Policy

Clinical data is under the ownership of the Investigator, should be kept under the Investigator's control and must only be changed by the Investigator. [Ref 3,4]. The eCOA vendor may, following approval by Investigator, implement data changes on the Investigator's behalf.
The Sponsor (or sponsor delegate) should assume a leading role in monitoring the use of instruments and reviewing the data to identifying issues, and initiate resolution/clarification. This responsibility can be delegated to the eCOA vendor.

4.3.1 Methodology Policy

4.3.1.1 Single approval for multi-record changes

A single investigator approval (such as confirmation of a visit id correction) can be defined to cover a set of records, and the resulting data changes to the full set of data records (e.g. change of visit id for all data records for that visit) can be implemented based on the single approval. Individual approvals/signatures for each data record are not required. However, this of course requires that the scope and impact of the approval must be fully described and clear to the Investigator at the time of approval.

4.3.1.2 Changes driven by Master systems or derived from Master data

If a defined master source for the patient status or data exists (for example in an IRT/IVRS or EDC system), a validated process (fully automated *or* with manual intervention) can be used to implement the correction.

For example, device deactivation without direct approval by the Investigator. The deactivation of the diary is seen as a direct effect of deactivating the patient (following completion or withdrawal) in the same way that addition of CRF data post completion is prevented.

Changes made in this manner require that the process is clearly defined, documented and validated.

4.3.1.3 Post-processing changes

As an alternative, systematic issues may be addressed in post processing steps, and not necessarily changed in the original database, preferably using a structured, computer-aided (i.e. programmed) methodology. This approach ensures a consistent and well defined implementation, which is less subjective, easier to document, easier to ensure data integrity and transparency and more efficient.

4.3.2 Issue Category Policy

4.3.2.1 Changes of Structural, administrative and technical issues:

The Sponsor can and should have an active role in identifying issues and suggesting resolutions and, following approval by the Investigator, implementing changes. These changes should generally always be implemented, as they will most often have a direct impact on the data collected and how it is analysed. However, proper design of instrument and database structure will limit the amount of issues in this respect.

4.3.2.2 Changes of Objective data issues:

These should be implemented if they add value or impact the results. Therefore, it is important to understand how the data is going to be used and analysed. It is also important to consider actual value and potentially biasing impact of addressing a subset of data issues.

Post-processing can be an option to ensure balanced and consistent implementation.

4.3.2.3 Changes of Subjective issues:

In general, neither the Sponsor, nor the Investigator should initiate any challenge of the subjective patient or assessor reported data, and even though the Investigator owns and controls the data, the Sponsor should consider data change policies with regards to risk for unbalanced drivers for change. (See section 3.2).

4.4 Data Change Policy – Approach to common cases

Case	Approach
Close out Device	*Identify and perform change as soon as possible.*
Proactively identify devices that should be closed out, using external data sources (such as EDC) and internal calculations (such as comparing to completed questionnaires). Prompt Investigator for confirmation of devices that should be deactivated. Preferably deactivation is promptly performed by the Investigator, but can also be implemented by the eCOA Vendor (on approval) on behalf of the Investigator. Policy for *Changes driven by master system or derived from master data* can be applied.	
Merge Device Data	*Identify and perform change as soon as possible.*
Proactively identify devices that should be merged using internal checks. Prompt Investigator for confirmation of data that should be merged. Preferably merging is promptly performed by the Investigator, but can also be implemented by the eCOA Vendor (on approval) on behalf of the Investigator. Policy for *Single approval for multi-record changes* can be applied.	
Change Trial Stage	*Identify and perform change as soon as possible.*
See approach for deactivation above. In addition, try to avoid using trial stages in the data collection, if this is not required to drive the diary behaviour. Policies for *Single approval for multi-record changes* and *Changes driven by master system or derived from master data* can be applied.	
False events **(Example: Based on false glucose result)**	*Pre-define rules. Batch approve and batch delete (with audit-trail). Consider post processing.*
By identifying potential scenarios and issues up front, or by identifying the issue through active trend monitoring, rules for how to handle these issues can be defined. For the example of obviously false glucose readings: valid ranges can be defined and a) implemented in the diary set up to prevent registration in the first place and/or b) post-registration identification and handling. Obviously such ranges and rules must be defined together with medical experts, and be implemented with adequate instructions, training, check messages etc. Policy for *Single approval for multi-record changes* can be applied. Policy for *Post processing changes* can be discussed.	
Add events **(Example Voids)**	*Generally, do not add subjective data. Specially consider change implications such as eligibility and protocol violations.*
In general, this kind of missing data should not be added. Lack of source makes these changes inadequate from a validity aspect. Adding data from other sources, introduces mixed mode and handling problems. The frequency of and trends in missing data should be continuously monitored. Limited missing data should be handled by analysis / design robustness. Extensive missing data should be identified by monitoring and the root cause and collection concept re-assessed. Special considerations should be made regarding changes that have implications on factors such as eligibility and protocol compliance. (See section 3.2)	

4.5 Handling of Residual Data Issues

Data issues that cannot be resolved and changes requested that are not approved/implemented must be documented as residual effects in the data and identified in the database documentation at delivery/handover of the data for analysis. This can be performed by the Sponsor internally or by the eCOA Vendor. The issues should be assessed for impact with regards to protocol compliance and data validity, to determine the classification of the patients/data in analysis populations, and for reference in analysis and reporting.

5 References

#	Reference
1	FDA: Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims (December 2009)
2	FDA: Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (August 2013)
3	FDA: Guidance for Industry Electronic Source Data in Clinical Investigations (September 2013)
4	EMA: Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (09 June 2010)
5	FDA: Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application (August 2003)
6	EMA: Reflection paper on risk based quality management in clinical trials (18 November 2013)