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# Challenges and Tactics of Managing Clinical Programming in Long Term Outcomes Trials

David Wade, GlaxoSmithKline, Collegeville, USA
Joanne Zhou, GlaxoSmithKline, Collegeville, USA
Rakesh Kumar, GlaxoSmithKline, Collegeville, USA

## ABSTRACT

Long term clinical event outcomes trials present a series of unique challenges for managing clinical programming activities. Factors that increases the challenges include the complex and evolving CDISC regulatory environment, and uncertainty of timelines of meeting the targeted number of outcome events. Many components of the CDISC submission processes are designed to work most efficiently for shorter term clinical trials. Some challenges specific to outcome trails are studies spanning multiple CDISC versions, legacy data standards, emerging regulatory tools and processes, drug development funding commitment timelines, and planning for potential primary endpoint futility. In this paper, we describe specific clinical programming learnings from the outcome trial setup and tactics for managing them in the real world.

## INTRODUCTION

Data from long-term outcome trials (e.g., trials that are 5-6 years in duration) are critical in deciding treatment options for patients in therapy areas such as cardiovascular. The nature of cardiovascular diseases requires long term treatment to modify the disease and demonstrate treatment effect in a clinical trial. In trials that are event driven, the difference in incidence rates of the event between trial arms is usually small, either by nature of the event or because of the ever-evolving Standard to Care (SOC) that the patient receives, meaning that the wall to climb (difficulty in demonstrating incremental benefit) has become increasingly higher. This has meant that each trial needs to run for a sufficiently long period (often with very large sample size) to accrue enough event of interest to discern differences between the treatment arms. 'Futility' testing is often employed as a 'gate keeper' in such trials before deciding on committing significant resources to run the full course of the study. Such 'long' term 'gated' trials produce a unique set of challenges for the programming function. Also, many of the outcomes events (safety and efficacy) of interest may be subject to 'assessor' bias because of the complex nature of the outcomes which means that sponsors will likely need to set up an independent centralized clinical endpoint adjudication committee (CEC). Strategies must also be enacted to ensure that none of the events are missed and that all reported events are objectively identified and in an unbiased manner. These factors result in additional programming management challenges in terms of handling and reporting of this data. The objective of this paper therefore, is to discuss some of the key programming management challenges encountered in the conduct of such long-term CV outcome trials (CVOTs) and the tactics to be employed to resolve them. Many of these are challenges and tactics are also applicable to other long term studies.

## 1. LONG DURATION OF THE STUDY – MANAGING PROGRAMMING DELIVERABLES

### EVOLVING DATA STANDARD REQUIREMENTS

The CDISC data standards rules are relatively easy to manage for the more common short term or medium term studies. However, for longer term trials which span over multiple CDISC versions, the rules may pose difficult management challenges for programming for longer term trials. One may find that a currently FDA supported CDISC version may no longer be supported at a future date at which the submission will be submitted.

Currently, most ongoing studies are mandated to use the FDA published CDISC data standards (Study Data Technical Conformance Guide[1] and Data Standards Catalog[2]) in order to be accepted for Agency review. These FDA documents are living documents, and they are updated over time reflecting the evolving data standard needs. FDA periodically

publishes its intent to begin supporting new standards and new versions of current standards in the Data Standards Catalog (FDA[3]). This also applies to the dates at which a version will no longer be supported. For a long term trial, a previously supported CDIISC version may become no longer supported in the Data Standards Catalog.

There are four important tactics for managing these CDISC version challenges. First, always select the most current and best CDISC standards at the inception of the programming planning. Second, establish early and strong communications with the regulatory agency with respect to the selection of data standards. Third, always keep informed of the changing and future version requirements from the Data Standards Catalog. Fourth, engage with the regulator in proactive negotiations for any exemptions which may arise unavoidably from the first three steps or prepare for programming version changes.

#### MANAGING THE QUALITY OF SPONSOR STUDY RECORDS

While widespread implementation of eTMF (Electronic Trial Master File) has made it easy to track sponsor study records, the challenge for CV outcomes trials is that it is often not easy to assess quality of the eTMF records. This is especially true with many of the programming tasks being outsourced. This is further complicated in the case of long term trials as the collective programming team knowledge of the task may wane over time, and it may be very difficult to recall specific technical details after extensive time has passed. The most important tactic to manage this situation is for the programming team to develop and maintain a high quality eTMF periodic review plan. This plan must identify clear responsibilities for each programming eTMF artifact. For studies that are completed by in-house programming staff, a sponsor should have a periodic internal eTMF management audit. This audit should cover presence of artifacts by filing date, and also the quality of the artifacts. For outsourced studies, the CRO partners should provide access to the CRO eTMF system for the sponsor to facilitate this eTMF review. It is also a good practice to develop a common understanding of the required artifacts in the form of the mapping documentation to avoid any unexpected gaps in records.

#### CONSIDERATIONS FOR DICTIONARY VERSION UPDATES

The long duration of CV outcomes trials poses a challenge for managing many versions of clinical dictionaries. Very often, study teams are required to track certain groups of adverse events (AEs) of special interest based on previous safety concerns as a part of safety monitoring. To accomplish this a programming team will need a MedDRA terms of interests hit list (TOIs) to identify and flag the events of interest. There may or may not be a Standardized MedDRA Query (SMQ), and therefore the programming team needs to develop a customized list (e.g., a Customized MedDRA Query (CMQ)) of AE terms to run against the study database. There may be many versions of the dictionaries over the long duration of the CV outcomes trials. MedDRA is updated twice a year, with a major release by the end of March of each year and a minor release at the end of September of each year. To keep up with MedDRA version updates the programing team needs to invest resources to make sure that the study specific CMQs are periodically updated coinciding with these releases. The important tactic here is for the team to develop efficient programming tools to isolate additional new terms to be flagged and review by the clinical team and to remove terms that may have become redundant in the newer release. One important area for discussion for long term phase IV follow-up trial should be whether the newer version SMQ's and/or CMQs should be employed on the previous data that was used for the original submission and the impact thereof. For example, the team must consider if the communication strategy is in accordance with good pharmacovigilance practices (GVP) in case a previously rarer or undetected event appears to be occurring at a higher rate because of evolving sensitivity of SMQ.

## 2. SPECIALIZED DATASET REQUIREMENTS FOR CV OUTCOMES TRIALS

One of the most important programming challenges posed by long term CV outcomes trials is that very specialized CDISC datasets are required to support reporting of the trial results and to support a thorough regulatory review. Newly developed CDISC standards for CV outcomes trials data may not be supported by broader sponsor company data collection standards and reporting tools. Thus, making it difficult for programming to implement the new standards. Since these new data standards are still in a provisional state, clinical study teams may not be aware of these newly developed standards or may be unwilling to accept their application.

#### SDTM DATASETS

The first of these programming challenges is posed by the need for specialized SDTM datasets. The most promising programming management tactic to address this challenge is to educate the study team of the availability and utility of the newly TAUG-CV Therapeutic Area Data Standards User Guide for Cardiovascular Studies Version 1.0 (Provisional) (TAUG-CV[4]) as early as possible in the study conduct. This would enable the electronic data capture system to be designed proactively to support TAUG-CV implementation, and it would allow time for sponsor broader data standards and tools to be developed to accommodate the new data structures.

The TAUG-CV introduces a number of new important SDTM variables. The following variables are being requested as additions in the next release of the SDTMIG.

**Approved variables as additions to the Events class**

| Variable Name | Variable Label | Type | Role | Description |
|---|---|---|---|---|
| --EVAL | Evaluator | Char | Record Qualifier | Role of the person who provided an evaluation. Used only for results that are subjective (e.g., assigned by a person or a group). Examples: ADJUDICATION COMMITTEE, INDEPENDENT ASSESSOR, RADIOLOGIST. |
| --EVALID | Evaluator Identifier | Char | Variable Qualifier of --EVAL | Used to distinguish multiple evaluators with the same role recorded in --EVAL. Examples: RADIOLOGIST1, RADIOLOGIST2. |
| --ACPTFL | Accepted Record Flag | Char | Record Qualifier | In cases where more than one assessor provides an evaluation of a result or response, this flag identifies the record that is considered to be the accepted evaluation. Expected values can include Y, N or null. This is not intended to be a statistical censoring flag. |

**ADAM DATASETS**

The second of these programming challenges is posed by the current unavailability specialized of ADaM datasets to represent these long term CV outcomes trial data. The TAUG-CV SDTM standards discussed above are not available for ADaM. A programming tactic to address this challenge is to develop custom ADaM standards to manage these data. The authors developed an ADEVENT dataset in BDS data structure, and along with the use of the available corresponding ADTTE model, to report all of the outcomes event data. Please see the detail in the paper by the authors (Zhou et al, 2017[5]).

**REVIEWER LEVEL DATASET**

The third of these programming challenges is posed by the need for specialized diagnostic datasets beyond CDISC to support a thorough regulatory review that is still not completely covered under TAUG-CV. The tactic to address this challenge is to communicate early with the regulatory reviewers to plan for submission products to support this need.

One potential tactic is to discuss with the regulator review team the design and submission of diagnostic datasets to address the following non-binding recommendations regarding of potential “red flags” that were presented by an individual staff member of the FDA.

NDA Submissions: Red Flags for FDA (Hicks, 2015[6])

- Investigator-Reported Results and CEC-Adjudicated Results go in opposite directions for the primary endpoint and major secondary endpoints
- Investigator Description of Event is different from the CEC description of Event OR there is disagreement about an event amongst CEC reviewers
- Original Verbatim Term is mapped to a completely different final adverse event or endpoint.

In order to provide diagnostic datasets to clearly answer FDA questions, the authors developed a dataset structure which can facilitate the FDA review of the data.

| Subjid | Re-adj.? | Reason for re-adj. | Unique event number | AE reference ID | Event type | Event trigger | Investigator -CEC concordance | Event sweep type | Adjudicator | Adj. Results | Adj. Event Date | Adj. Date |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | N | | 101 | 2.003 | MI | CEC | No | Troponin/ CKMB | Dr. Stewart | MI | 1-Nov-13 | 1-Jan-14 |
| 2 | N | | 101 | 2.003 | MI | CEC | Yes | Troponin/ CKMB | Dr. Johns | not MI | 1-Nov-13 | 1-Jan-14 |
| 2 | N | | 101 | 2.003 | MI | CEC | No | Troponin/ CKMB | Dr. Stewart Dr. Johns | MI | 1-Nov-13 | 1-Jan-14 |
| 3 | N | | 102 | 3.001 | MI | Investigator | Yes | none | Dr. Stewart | MI | 2-Dec-13 | 1-Jan-14 |
| 3 | N | | 102 | 3.001 | MI | Investigator | No | none | Dr. Johnson | not MI | 2-Dec-13 | 1-Jan-14 |
| 3 | N | | 102 | 3.001 | MI | Investigator | No | none | Dr. Stewart Dr. Johns | not MI | 2-Dec-13 | 1-Jan-14 |
| 3 | Y | Additional information | 102 | 3.001 | MI | Investigator | Yes | none | Dr. Johnson | MI | 2-Dec-13 | 10-Jan-14 |
| 3 | Y | Additional information | 102 | 3.001 | MI | Investigator | Yes | none | Dr. Stewart | MI | 2-Dec-13 | 10-Jan-14 |
| 3 | Y | Additional information | 102 | 3.001 | MI | Investigator | Yes | none | Dr. Stewart Dr. Johnson | MI | 2-Dec-13 | 12-Jan-14 |

Note: adj. = adjudication.

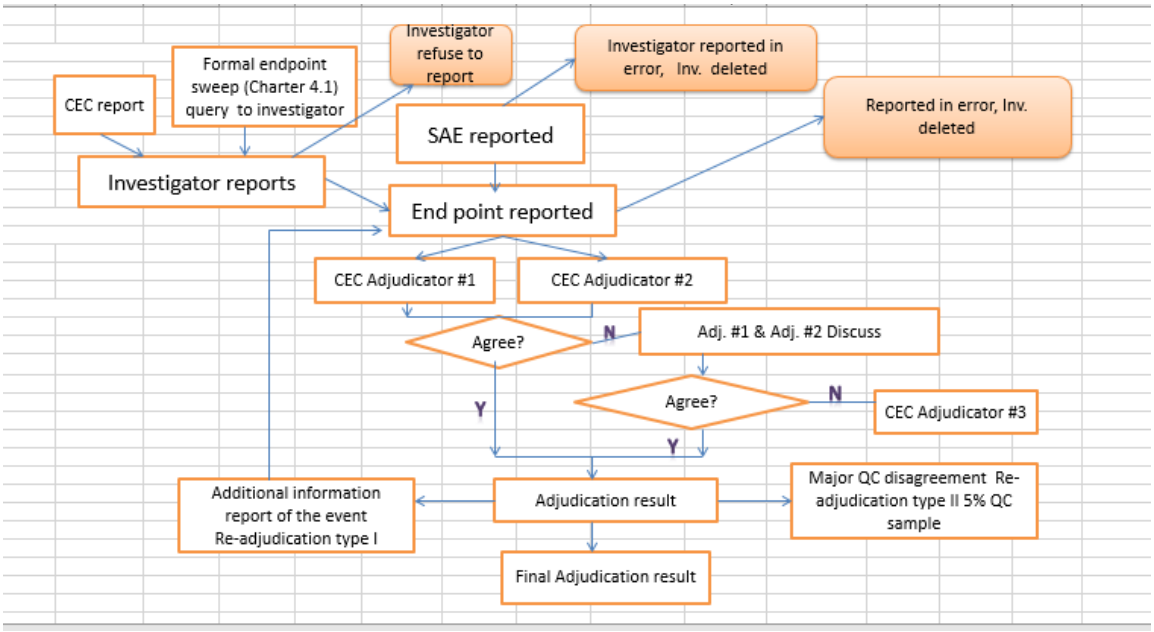
The following control terminology was developed in conjunction with this data structure:

Event sweep type:
1 AE
2 Procedures/Hospitalizations
3 Troponin/CKMB
4 ECG
5 SAE narrative
6 TIMI and MM review SAE in real time
7 Source data R/V

Reason for Re-adjudiacation
1 Additional information
2 Due to findings from QC (in the 5% QC sample)

Event trigger
1 Investigator Initiates
2 CEC initiates

The following flowchart describes the typical event collection and adjudication process, and this process corresponds to the data structure for the dataset described above. Electronic data must be maintained for all portions of this flow chart in order to conduct a sound trial and to support a thorough regulatory review.



## 3. TEAM RESILIENCY

Team resiliency may be particularly challenging for long term CV outcomes trials that cover long periods of intensive work pressure, and a team's use of selective tactics for boosting resiliency will increase the likelihood of delivering a high-quality set of study deliverables. Useful programming management tactics to mitigate these challenges include health and stress resiliency programs, proactive career management, succession planning, lattice resourcing, and avoidance of resource recording bias.

Health and stress resiliency programs provide a key means of addressing the human scale challenges of conducting long term CV outcomes trials. CV outcomes trials by nature often have very large databases collected from a large number of subjects over a long duration of time. In this situation, rare and unexpected combinations of data will tend to reveal themselves. It is often the case that complex algorithms are needed to cover these unexpected combinations of data, and the complexity increases in a non-linear rate as a function of the number of data points collected. For example, a team may need to work on an algorithm to select a baseline measurement for a blood chemistry parameter to make the algorithm properly function for one or two rare cases out of thousands of subjects encountered in a long-term CV outcomes trial. Similarly, a team may need to expand the same algorithm to for a set of repeated vitals measurements for one or two rare cases of the collection of those data. The complexity of the algorithms for either of these cases alone may increase in a roughly linear pattern with the number of subjects. However, the interaction in complexity across multiple algorithms may result in the complexity of all algorithms to increase in a non-linear fashion. It is a human trait that we tend to extrapolate linear increase in complexity of programming work based on our past experiences, and the non-linear exponential increase of complexity is often a difficult to imagine part of resource planning. Teams must ensure that they are engaged with reasonable working hours, recognition rewards, rest, stress reduction, and team building activities to manage this increase in complexity.

Teams should employ proactive career management over the course of long term CV outcomes trials. In a shorter-term clinical trial, an individual programming team member may complete a study leadership role or a contributing team programmer role, and then the person may be ready for a promotion or increase in responsibilities upon delivery of the study. The study team members will then be ready to move on to successively more challenging assignments. On longer term CV outcomes trials, the programmers may be needed to work on the trials for 4 to 6 years of time, and the team may be at a loss if the key programmer is promoted out of the technical role they serve. This may disadvantage the career progression for the programmer. An important tactic of a proactive career management strategy to address this challenge is to implement a classic matrix management model where team members can take on multiple roles in an organization. Under this model, a programmer may simultaneously be a lead programmer for a trial, and a contributing line programmer for another trial. A second programmer's roles could be flipped on the same two trials, so that each programmer has an opportunity to lead and contribute technically simultaneously. Also, a key programmer may be promoted to have management responsibilities while at the same time also retaining a portion of the key technical responsibilities for studies over the long-time duration. This classic matrix management may also serve to increase morale amongst the team members as traditional roles of hierarchy are reduced and the team focuses on the shared goals for the development program.

Succession planning is another important tactic to employ over the course of long term CV outcomes trials. It is particularly important in the setting of these longer-term trials to encourage the growth of more junior team members into increasingly more challenging technical and leadership roles. Well placed career development plans will enhance the likelihood of success of the team and provide incentives for individual contributions. The most effective way of implementing succession planning is to ensure widespread awareness across the team of the career pathways of the disadvantages of bias. The bias often arises when team members view a teammate based on the more limited role the teammate had when they joined team. This effect is often lessened on shorter term clinical trials where team members may have the opportunity to change to different teams frequently. Long term CV outcomes trial teams should be aware of this phenomenon and the succession management process may be need to be enhanced to counter-balance this effect.

Lattice resourcing is a tactic to assign more than one person to each key role of a study. This follows the pattern of classical statistical lattice sampling design. It typically involves assigning two people to cover each role (e.g., a lead and a co-lead). It is a key tactic for managing teams under the risk of losing key team members. Lattice resourcing is similar to the matrix management model discussed above, but it differs in that it focuses on key tasks/roles to be filled and planning for contingencies in the event that key individuals are lost from the team. The ultimate objective of lattice resourcing is to increase the resiliency of the team without significantly increasing the overall human resource budget. To this end, teams must be diligent in managing that individuals are working cooperatively together on tasks and not simply double covering tasks to be completed. By its very nature of pairs of people having to work closely together, lattice resourcing may also be expected to yield increased levels of communication and morale across teams.

A final important management tactic is the avoidance of effort reporting bias for long duration CV outcomes trials. A tendency of teams and individuals in working on large complex studies is to be over-optimistic in estimating the amount of time required to develop complex algorithms under the challenge of very large datasets. It has been the authors' experience that we tend to estimate the amount of future work to be done from linear extrapolation of past work for smaller studies or initial smaller blinded test datasets from the longer outcomes trials. Coupled with this tendency is the tendency for each person to under-report the amount of time they spend in light of the fact they had previously estimated less time. Teams must openly communicate and stress the importance to report all resources expended on parts of the work to deliver the study results, so that accurate resource forecasting can be applied to the remainder of the work.

## 4. STRATEGY FOR APPLYING RESOURCES IN RESPONSE TO INTERIMS AND FUTILITY ANALYSES

Staging the programming resource spending during a long-term CV outcomes trials is an important tactic to manage risks and efficiently apply resources across the larger corporate portfolio. The end goal is to have in place sufficient team resources, quality data, and ready-to-execute computer code to very quickly deliver submission deliverables upon unblinding. The risk posed by the possibility of future negative study results, future introduction of new regulations, and future introduction of new company-wide standards may be managed during the long duration of the outcomes trials by carefully timing the spending of resources in proportion to the risks discharged during the development program. This is of course a constant challenge for all clinical trial programs, but it is particularly needed for long term CV outcomes trials which may use very large amounts of a sponsor's resources and extend over very large periods of time in which risks may arise.

In long term CV outcomes trials, carefully timing the spending of programming and submission preparation development resources may manage these risks and efficiently apply team resources. The most common tactic is to spend the programming budget in pulses in response to milestones that reduce risks (e.g., interim analysis results, futility analysis milestones). Plans must be made to re-allocate the programming resources to other development projects in the event of the project failure at one of these milestones. This is important for team morale, maintaining technical skills, and efficiently allocating resources.

## CONCLUSION

Long term clinical event outcomes trials present a series of unique challenges for managing clinical programming activities. The tactics presented in this paper represent a diverse set of technical and management actions that exceeds the traditional clinical programming practice focused solely on coding. The clinical programmer must be engaged with all members of the study team, proactively plan for long range management of challenges, remain in close communication with regulatory reviewers, and keep abreast with the changing regulatory environment.

References

[1]FDA. "*Study Data Technical Conformance Guide*"
[http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm]

[2]FDA. "*Data Standards Catalog*"
[http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm]

[3]FDA. "*Study Data Standards: What You Need to Know*."
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511237.pdf

[4]CFAST Cardiovascular Team. *"Therapeutic Area Data Standards User Guide for Cardiovascular Studies Version 1.0 (Provisional)" CDISC web site October 17 2014*. Available at:
https://www.cdisc.org/sites/default/files/members/standard/ta/cardiovascular/taug-cvv1.pdf

[5]Joanne Z, Rakesh K, David W. *Developing ADaM Dataset for Cardiovascular Outcome Studies.* 2017. Available at:
https://www.lexjansen.com/pharmasug/2017/PO/PharmaSUG-2017-PO13.pdf

[6]Karen A. Hicks, M.D., *Medical Officer Considerations for Endpoint Adjudication Committees –Regulatory Perspective.* 2015.
Available at: https://www.ethicalclinical.com/media/313108/hicks_karen_pres.pdf