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Harmonizing SDTM at the Source: Designing Collection Instruments that Support Sponsor Standards

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ABSTRACT

All too often ensuring that SDTM domains follow sponsor-specific guidelines is reactively based on iterative review of data transfers. As many of the issues that come to light during review can be traced back to differences in the information collected, why not move back a step and ensure that the data as collected are consistent with what the sponsor expects to see in SDTM?

AstraZeneca and Chiltern International have recently formed a partnership to jointly support AZ's Early Clinical Development Program. We will discuss the advantages and challenges this new model brings, using the best practice from both companies, yet still staying within the bounds of sponsor defined standards.

We will also share a few practical ways to design collection instruments (and associated raw data outputs) that support target SDTM standards, including: leveraging sponsor references for atypical forms; reconciliation of collection fields with preferences for inclusion of permissible variables; harmonization of eCRF pick lists with sponsor controlled terminology; and adoption of sponsor defaults for raw data attributes.

The safest, fastest way to build conformant SDTM is to collect what you will submit. Designing collection instruments based on sponsor standards harmonizes SDTM at the source, allowing for efficient generation of sponsor-approved tabulations content as needed to leverage associated ADaM and TFL standards

INTRODUCTION

AstraZeneca (AZ) have recently entered into an agreement with Chiltern International to outsource the Data Management (DM) and Analysis and Reporting (A&R) of their Early Clinical Development (ECD) studies. AZ are looking for a partnership relationship whereby the Chiltern study team representatives work alongside the AZ study team members, to provide effective, seamless management of the Early Clinical Development clinical trials.

Whilst there are many strands to this relationship, this paper focuses on the work done from a standards perspective. Astra Zeneca has a large and detailed library of standards, we are looking at taking the best of the library that AZ has and combine it with Chiltern's technical Electronic Data Capture (EDC) / SDTM expertise, so that we develop a seamless process from collection through to SDTM generation. Our expectation is that by building much of the needs of SDTM at the source, we can automate the generation of the SDTM data structures.

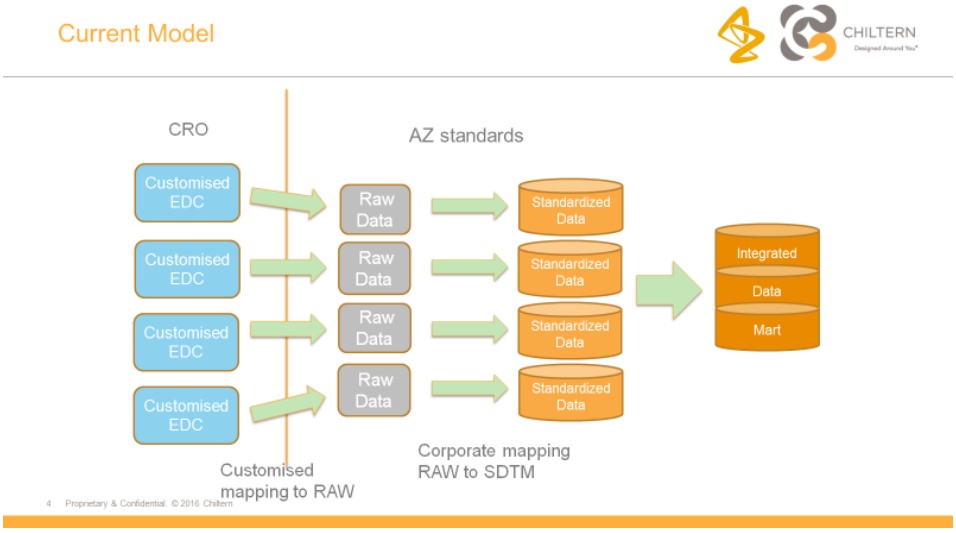
Astra Zeneca's operational goal and strapline is 'Get Closer to the Data', with an overall plan to define best practice for ECD studies.

CURRENT STANDARDS OVERVIEW

AZ have clearly defined standards and a long-standing process for approval of new objects. Each TA has a standards team who manage their individual TA standards, there is a broad, cross-TA standards organization that has responsibility for CORE standards. AZ have implemented an off the shelf product, customized to AZ requirements, to manage library requests, including a submission request workflow. These managed standards in ECD projects, focus on the SDTM end, domains, variables and controlled terminology. The requests are determined to be allowable at the study level, or likely to be reused and therefore promoted to TA or CORE library standards. The approval process can take up to 6 weeks. AZ standards are defined to apply across all phases, all TAs, sometimes these are more focused / applicable to later phases than early development. No rules exist that are specifically focused on ECD type studies, which generally need more flexibility and quicker turnaround times.

The ECD studies cross many therapeutic areas and therefore touch many of the TA standards, the types of studies can cover a broad spectrum, including complex Oncology studies, sometimes including new/novel data to be collected. Protocol design can be complex and timelines can often be challenging.

CURRENT MODEL

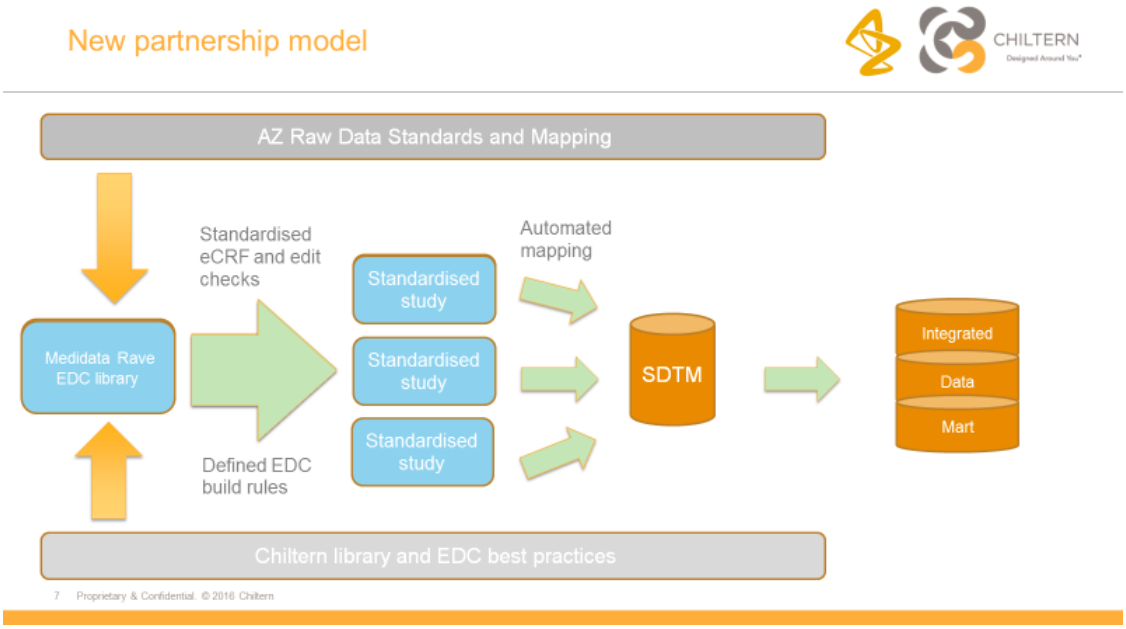


This model is used for all late phase studies, known as Global Medicines Development (GMD) studies. Standards are defined at both the RAW and SDTM mapping level, there is also standardised mapping between the RAW and SDTM definitions. This ensures consistency for TFL generation and reporting and forms the basis for ADaM generation. The standards are comprehensive and should include all data required to be collected per the protocol. Derived data is kept to a minimum. These standards are shared with the CRO. The CRO is required to submit the data compliant to the RAW data standard definitions.

As the GMD CRO is required to provide RAW compliant datasets, this allows for some flexibility at the EDC level, with respect to naming conventions, visit definition, folder, forms, variables and codelists. Whilst the RAW definitions can be used as a basis for definition by the CRO, depending on their internal setup this may not necessarily be done. The eCRFs are annotated to the RAW data standards and the annotations are approved by the AZ data management representative, who also acts as the contact point for any standards requests that are needed.

For ECD studies, the model implemented is slightly different and the CRO can work outside the RAW Data Standards, only providing data mapped to the AZ SDTM model. This gives the CRO an increased amount of flexibility around the eCRF design phase, needing a higher level of review than should normally be required if standards were implemented fully. Whilst this has allowed flexibility to enable the CROs to respond to challenging timelines and novel/exploratory study design, it has ultimately led to a significant level of differences of implementation at the EDC level. Therefore, much of the benefit that highly defined standards provide in consistency of front end design and setup, has been lost. Increased variability from study to study, ultimately can slow down the review process and any gains from following a more flexible model may be lost.

THE NEW MODEL



DEFINING THE END TO END PROCESS

Working alongside the AZ ECD team, a new process is being defined. The process is now more end to end than the previous model. The team felt that this model would support the overall AZ goal of 'Getting closer to the data'. As part of earlier workshops, the decision had already been taken to use Medidata RAVE™ as the EDC system, and build out all studies within a new URL. The AZ management were also keen to make sure that we make best use of the EDC functionality.

Whilst the AZ RAW data standards form an important part, they are no longer directly part of the study setup process. Along with the SDTM standards, the RAW standards are used as a point of reference, during eCRF development (mainly for anything not currently available within the EDC library). The long-term intention is to expand the EDC library to include Therapeutic Area Standards, but for now the roll out is limited to safety standards – see the next section for more information.

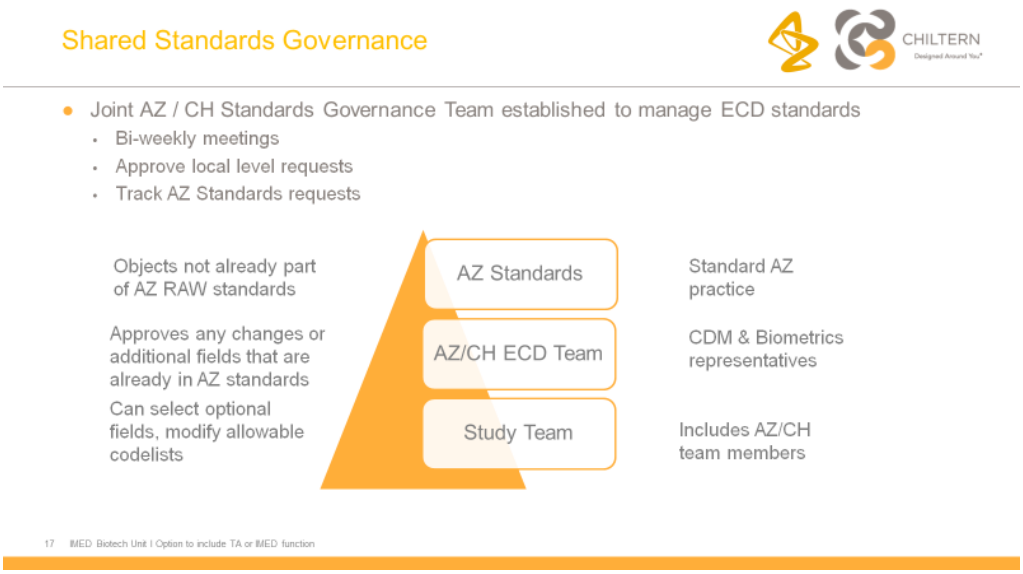
The library is used as the copy source for the study build, in the usual way the EDC programmer/designer is responsible for interpreting the protocol and defining requirements in the EDC specifications. The intention here is that the allowable modifications are clearly defined and controlled, the designer and study team are required to remain within the bounds of the standards. Any new requirements or exceptions need discussion and approval.

Having planned for a 'standards led' build, it is important to ensure compliance to those standards. This is one area where automation in theory is possible. By identifying Highly Recommended/ Recommended/Conditional fields in the metadata, then compliance to the library can be automatically confirmed. Changed field attributes can also be highlighted, so that any changes can be confirmed as allowable. It can sometimes be challenging to find what at first glance can be a minor textual change, but that can completely change the meaning of a form / field.

Medidata RAVE™ is a flexible tool that allows different ways to build out a study. Requiring RAVE™ Copywizard to be used, is an easy way to copy from libraries, retaining the copysource metadata and supporting automated checks back to that library source.

By ensuring the EDC front end is compliant to our standards and rules, then the mapping to SDTM should also be compliant. The metadata can be extracted to be analyzed and build out the required mapping. This approach supports our goal of end to end consistency across all ECD studies.

STANDARDS GOVERNANCE



An important part of this whole process is Standards Governance. This is a shared responsibility between the two companies and a joint ECD Governance Team has been established. This team has responsibility for managing the ECD specific standards and review of ECD study build to confirm compliance. Any requirements not covered by the current AZ standards still need to be go through the current AZ standards approval processes. Part of the study team responsibilities is to define the new requirements and with the support of the Governance Team, submit for approval.

PROGRESS SO FAR

DEFINING THE STANDARDS LIBRARY

Where to start? The clock is ticking – there is an initial list of studies with planned FSI (First Subject In) timelines looming. We needed to rapidly move ahead, but agreed it was important to establish a library, no matter how small, from the start. Establishing new standards from scratch is a huge and time-consuming project. We could use 'off the shelf' CDASH libraries, however both organizations already have defined standards that have been developed with CDASH terminology in mind. Chiltern's standards are focused very much around the Medidata RAVE™ EDC system, on safety data collection and are not as extensive as the AZ standards from a TA perspective. Whilst the AZ standards are at the RAW and SDTM level, there are EDC forms defined as well and available for consideration. We wanted to use the wealth of information that we already had, but make rapid progress.

We established a small EDC Standards Working Party with representatives from both organizations. The team chose to do a comparison between the Chiltern EDC and the AZ RAW definitions. We determined the list of AZ CORE mandatory datasets and set about the task of review.

We also established some guidelines for the review and defined overall design rules:

- Focus on mandatory/Highly Recommended fields on mandatory forms, optional (Recommended/Conditional) fields were considered if they were likely to be required for ECD studies.
- Refer to CDASH guidelines as required as reference point to ensure consistency and compliance.
- Design the screen with the end user in mind, ensure the collection flows, the screens are not too cluttered. Chiltern general EDC design rules were applied too.
- Wherever possible include the CT codes in the codelists.
- The codelists were a subset containing terminology that we considered was relevant to the initial ECD studies, with the option to expand as required.
- Where the two companies differed between implementation, such as normalized vs, denormalized structure, we decided to go with the design we felt best suited entry.
- Where a denormalized structure was chosen, test codes were used wherever possible as the variable name.
- Help text, instructions are to be included later, but will also ultimately form part of the library
- A decision log that details out the discussion, was maintained, this has proved useful as we move forward with the implementation.
- The Chiltern specification templates were used, as these are designed for Medidata RAVE™ definitions.

We reviewed a core set of forms that we considered formed the basis of safety. Consolidated specifications were created for around 25 eCRFs and these were then reviewed by a broader team and classed as 'Initially Approved' by AZ.

We were ready to build!

From an EDC perspective, the decision was taken to delay the formal definition of a Global Library until after the initial round of studies had been built. These initially approved standards would be used as the basis for each study, but would undergo a final review and approval prior to being defined as a library. Current plans have the library published early 2018.

STANDARDS AND BEYOND – ITS NOT JUST ABOUT THE ECRFS

Having defined eCRFs, we have begun looking at other areas that could be improved, if standardized:

- Visit Naming Numbering
- Mandatory forms
- Placement of Key forms
- Visit Scheduling / Mandatory Visits
- Handling of unscheduled visits
- Handling of screen failures and pre-screening visits
- EDC dynamics (AE/CM links, visit visibility rules)

- Standard Edit Checks
- Other areas for consideration: integrations IVR/IXR, eCOA, Safety Reporting, Centralized coding

The work on many of these, at this time, is ongoing, an initial proposal for standardizing visit numbering / naming has been defined. However, this list may need to be revised, based on integration requirements. For example, IVR and SAE have specific requirements that are yet to be fully determined.

At the time of writing, a similar activity for edit checks is ongoing, an assessment of both companies' standard checks has been made and a consolidated set is under review. The plan is to have a core set of standard edit checks, plus a base set of data management guidelines for any new eCRFs.

AUTOMATING THE PROCESS

Work has begun on the automations, this is the area where we anticipate much can be gained. It is important that boundaries for eCRF design fit within the concept of automating mapping generation, including field and form naming conventions and visit / time point definitions.

TIPS AND HINTS

Below is a list of some additional items for consideration that as a partnership, we have felt important during the early stages:

Training	Define training material as you go, do not leave it to the end.
	Define common training, so that all team members receive the same information.
	Train by study team.
	Chiltern and AZ trained side-by-side.
	Detailed process training provided / repeated.
Documentation	Provide Quick Reference Guides to broadly cover all aspects of the new process.
	Single page documents – support for new staff or act as refreshers
	Support process rollout and embed
	Facilitate consistency across studies from both AZ and Chiltern
Hypercare	Implement a model where the teams feel supported, especially those 'first in'
	Ensure change leadership is engaged at the study level
	Provide rapid feedback to resolve any roadblocks the study teams may face
Standards	Include standards representatives in meetings and trainings
	Avoid the 'Ivory Tower' Standards Model, ensure representatives are engaged and accountable for standards related issues

NEXT STEPS

As mentioned previously, the standard library will be revised following the initial 'early adopter' studies and then more formally defined and implemented. The ongoing activities should be completed and rolled out at the same time.

Plans are being developed to extend the library beyond those safety standards. Priorities will be decided based on the portfolio of studies. To really ensure standards are followed and to gain those efficiencies, the library needs to be comprehensive and cover 80%+ of a study's needs.

We have a firm grounding to now develop the process and the libraries further. It is important to ensure that compliance to the standards is embedded and becomes second nature to the study teams. Study team education and Standards Governance needs to reduce those requests for 'nice to have' data fields, yet not clearly defined within the protocol.

CONCLUSION

This is a different approach to outsourcing. Partnership relationships are not new, however, often standards are an afterthought and an add-on. Developing a set of standards is a large effort of work, a costly exercise where the benefit is difficult to quantify – at least in the early stages of a relationship. The 'Let's get the first studies through and then we can go back and look at standards' kind of approach is often the norm. What is refreshing about this partnership, is that standards were the first thing we established. Also, standards were not enforced from the sponsor, AZ wanted to gain experience/ knowledge from Chiltern. We have a shared set of standards, shared governance, with a shared goal with advantages to both organizations.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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