

Disaster Can Be Avoided: Building Integrated ADaM datasets for Regulatory Responses from an Internal SDTM CDISC-compliant Repository

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Dominic, age 8, living with epilepsy



Objectives

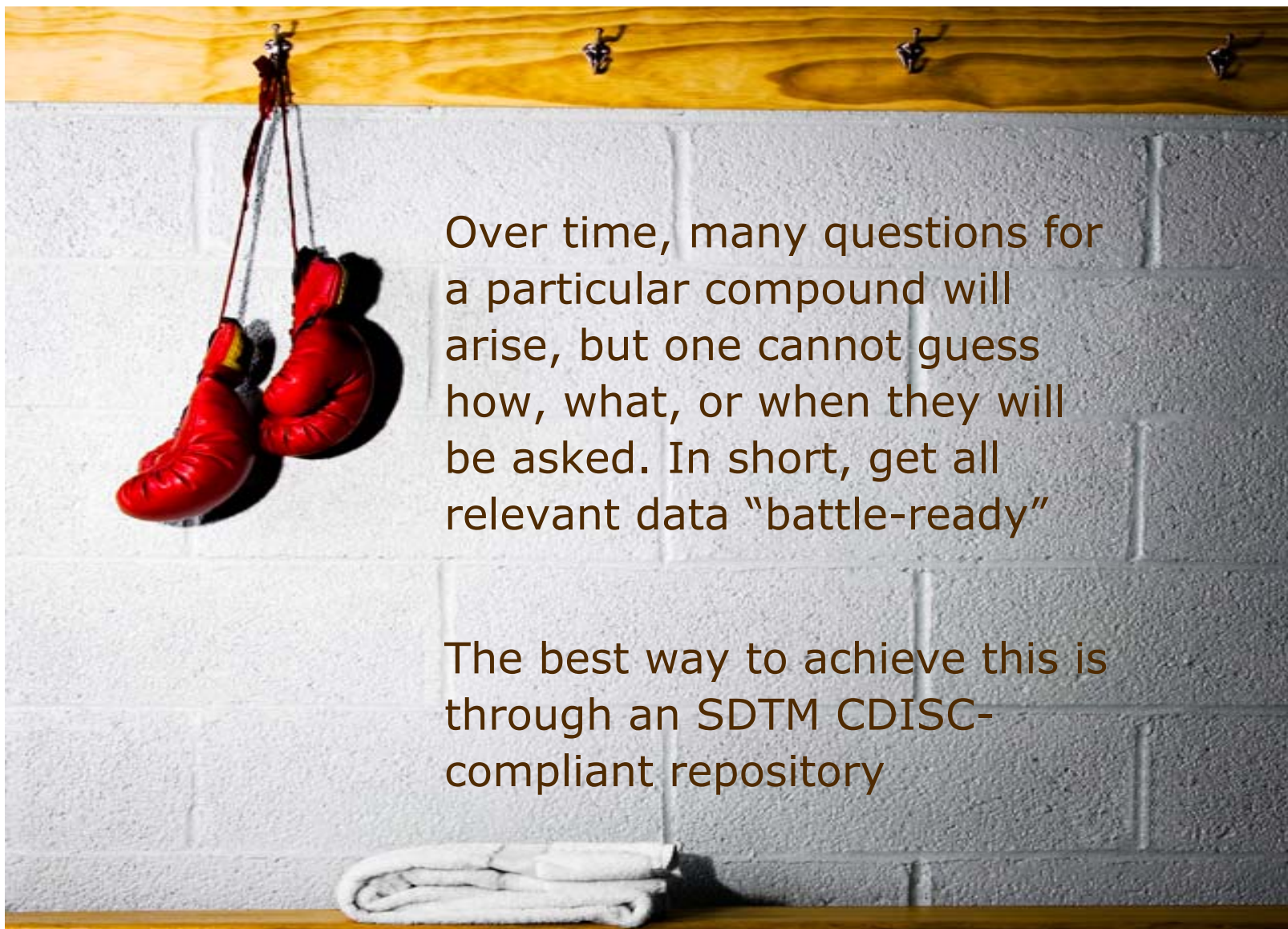
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- At the end of presentation you should understand:
 - Importance of remapping and integrating legacy studies along with current studies that use SDTM standards
 - Methodologies and considerations that should be addressed with legacy and SDTM CDISC-compliance data
 - Developing focused ADaM datasets in response to regulatory requests from the integrated SDTM CDISC-compliant repository
 - Impact of programming efficiencies for focused analyses



Is there a real need for an SDTM repository?

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Over time, many questions for a particular compound will arise, but one cannot guess how, what, or when they will be asked. In short, get all relevant data “battle-ready”

The best way to achieve this is through an SDTM CDISC-compliant repository

Why have an SDTM CDISC-compliant repository?

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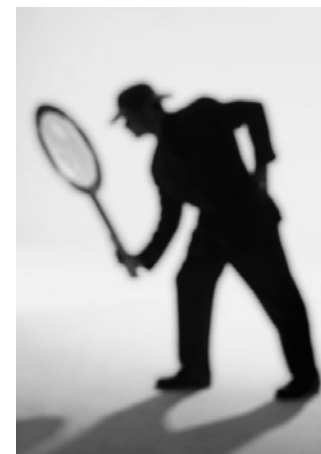
- Regulatory Authorities wanted specific adverse events from all randomized, double-blind, placebo-controlled, parallel and cross-over, phase 2-4 studies who received at least one dose of study medication.
- This translated to roughly 95 studies over a 20 year period for a focused analysis.
- As with most regulatory responses, there was a very tight timeline to complete this monumental task.



Where to start?

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- If there is no complete pooled SDTM CDISC-compliant repository, where does one begin?
 - Find all relevant source data
 - Search for any documentation for the studies
 - Must make quick decisions concerning source data that does not have any documentation
- In this case, finding studies that dated back to the late 1990's proved very difficult and time-consuming. Often, proper documentation was lacking and the "best-guess" approach was taken.



Start the Process Early

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- ▶ If nothing else was learned from this difficult task, one must start as early as possible to build an SDTM CDISC-compliant repository. Do not wait for regulatory inquiries!
- ▶ Develop a plan of action:
 - Retrospective SDTM mapping of legacy studies.
 - Validate all of those mappings. Treat them the same current studies.
 - Combine the current SDTM studies to the SDTM remapped legacy studies
 - Update medical coding that harmonizes with current SDTM studies
 - Use the repository as the source data for the focused analyses.



Retrospective SDTM Mapping

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▶ Retrospective Mapping

- Re-mapping projects partially or fully with a specific focus on the general safety domains into the SDTM framework where the reporting has already been completed or is currently ongoing.
- “Best case” data: Usually the OC source data is preferred. If that is unavailable nor feasible then the analysis data is used as a last resort.
- Clearly document all decisions and actions!



Retrospective SDTM Mapping

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➤ Advantages:

- Can be done at any point after the completion of a study.
- Will have a reduced impact of upstream standard versions.
- Supports early adoption.

➤ Disadvantages:

- Back engineering.
- Heavily involved programming and validation needed to properly map.
- Analysis datasets that may be submitted have the strong possibility of not matching the remapped SDTM data.
- Documentation is indirect and often times lacking; therefore, more time is needed for investigating the proper interpretations to SDTM.



Communicate

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- Retrospective remapping of source data into SDTM compliant domains consist of a broad spectrum of communication.
- Get as many issues communicated as soon as possible. Otherwise, it can snowball into massive failure if it is not caught in time.
- Clearly document every discovery, decision, and data issue when remapping in order to readily explain if necessary.



Validate

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- ▶ Please take validation of an SDTM-compliant repository seriously.
- ▶ Double program every domain to confirm data source, documentation, and algorithm needed.
- ▶ As an extra step of confidence, it would be wise to use a validation tool to ensure SDTM compliance (OpenCDSIC, WebSDM).



Coded Dictionaries

- ▶ In order for an SDTM CDISC-compliant repository to become truly effective, then coded dictionaries need to be updated properly to harmonize all of the included studies.
- ▶ Develop and validate a formal process for the updates.
- ▶ Determine a schedule to periodically update the entire repository. Calculate the timing it takes to complete the task of updating. With our example, coding 11,598 unique adverse event terms took slightly over 2 months to complete.



Building ADaM from the ISAP

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- Once you feel confident with combining the SDTM CDISC-compliant retrospective studies to the newer/current ones, it's time to explore how to fully utilize the repository for the integrated statistical analysis plan.
- In our example, the analytical algorithms for the analyses were derived from the ISAP, and the building blocks for the ADaM datasets themselves were derived from the ISAP table shells.
- As a result, we only needed to develop three ADaM datasets for the regulatory response, but they were quite complicated in nature and would have been impossible to complete without this SDTM repository.



How ADaM helped build a better repository

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- ▶ Creating ADSL and the other two ADaM datasets led us to discover several inconsistencies in the SDTM CDISC-compliant repository that at the time were difficult to identify without time-consuming checks:
 - ARM/ARMCD needed harmonization
 - Gaps in exposure
 - Missing age
 - Missing coded terms
 - DM vs. EX: Incorrect treatment assignments
 - Help in the development of tracking unique subjects (USUBJID) throughout the lifecycle of the repository. Some subjects participated in up to six studies – all within the SDTM repository!



How ADaM helped build a better repository

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- Improved transparency and traceability by using a single data source.
- Able to readily predict data trends for future analyses.
- With each iteration, the SDTM repository became more “tried and tested” and ready to serve as the source for many other deliverables.
- In our case, we still have a lot of work to complete to get at the optimal level of usability, but we can use what we have learned to build a truly consistent and SDTM CDISC-compliant repository that will be built to last.



Summary

- ▶ In this presentation we have provided you with an introduction to the challenges and benefits of building integrated ADaM datasets for regulatory responses from an internal SDTM CDISC-compliant repository:
 - Start early
 - Develop a plan of action
 - Communicate all challenges and document every decision and issue that may arise
 - Include legacy studies and use a retrospective mapping technique when combining with current SDTM studies
 - Validate everything
 - Harmonize coding
 - Use ADaM to help test your repository



Questions

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