

Presenters

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Amber is a Sr. Manager, SCHARP Data Analytics Unit at Fred Hutch. She previously led the statistical programming group at Axio Research.

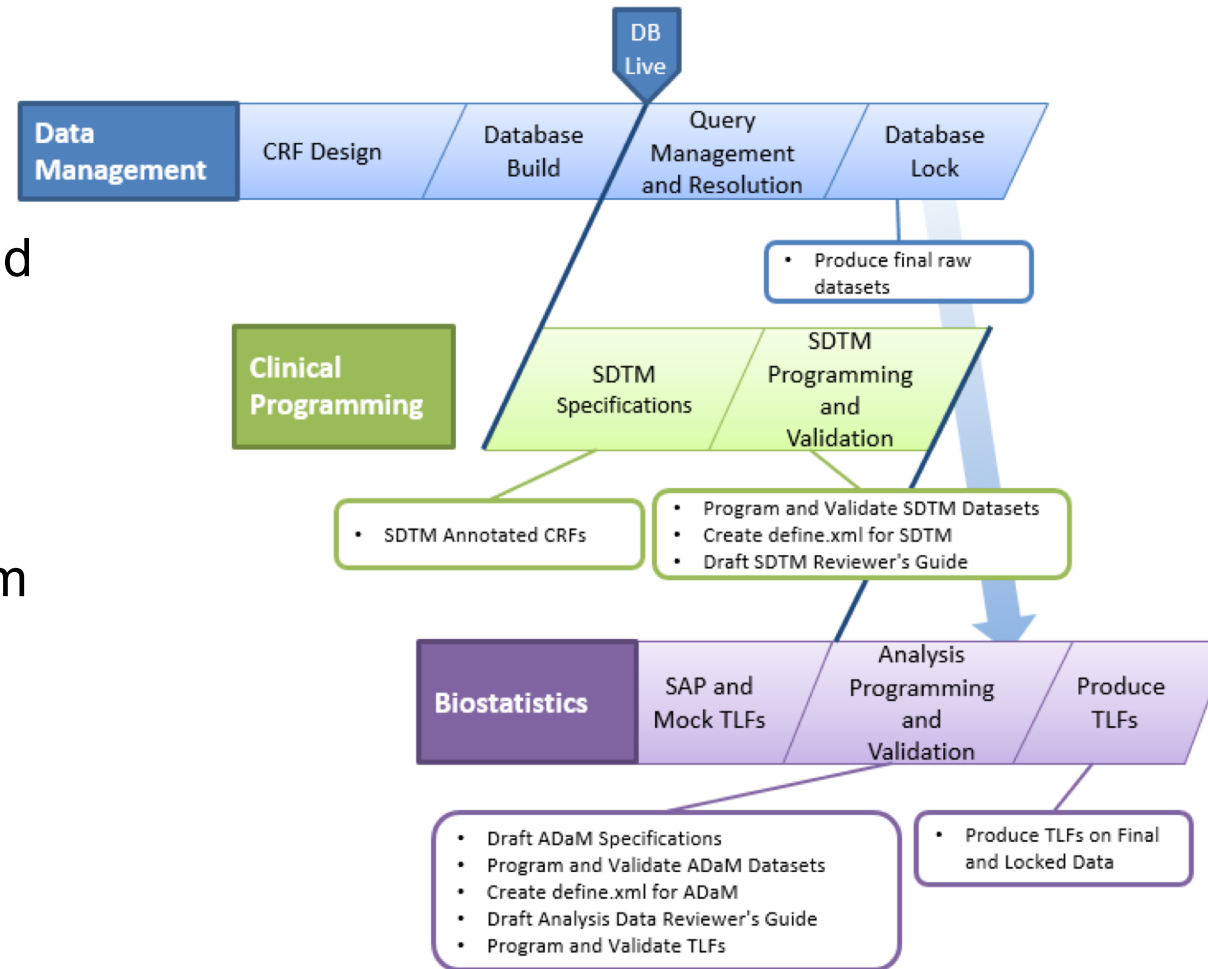
CDISC in Phase I/II Studies: Approaches to Adopting Standards for CSR Deliverables

- Motivation – Why CDISC from trial inception?
- Deviation – Why not CDISC from trial inception?
- Case Studies – How to manage deviations
- Q & A

Motivation

What components support a CDISC compliant process?

- Define the tables, listings, and figures (TLFs) and *back-engineer* the supporting components
- *Build CDISC compliance* from the eCRFs onward
- *Substantial planning* for smooth, seamless execution



Motivation

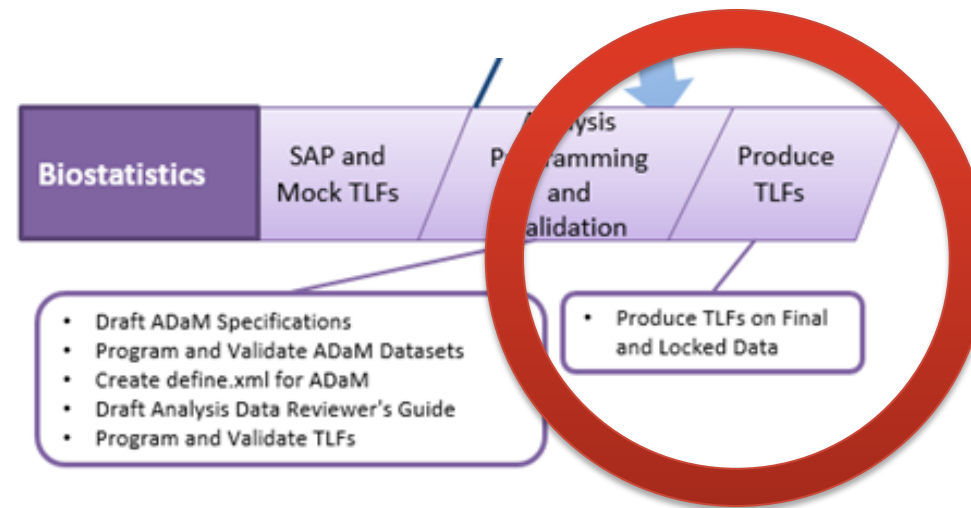
What components support a CDISC compliant process?

- Smaller, early phase drug development programs can be understandably concerned about the time and costs associated with implementing these standards
- Often not confident in the efficacy or marketability of their product
- Questions:
 - What is the purpose of each component?
 - What are the implications of deviating from this process?

Motivation

What components support a CDISC compliant process?

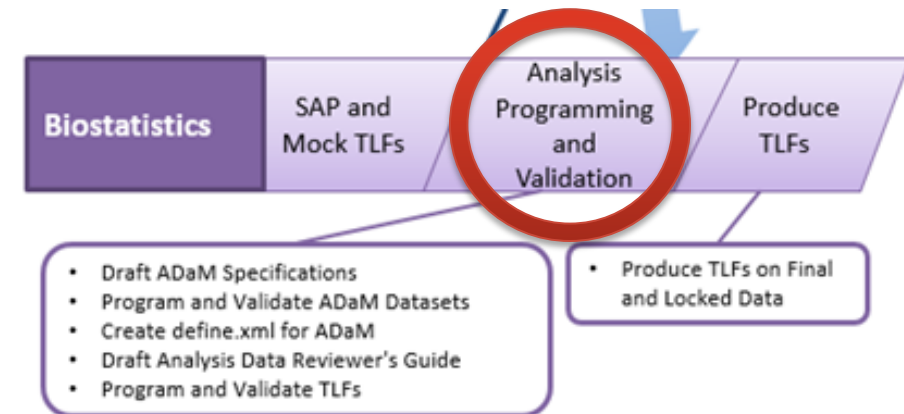
- End product is **tables, listings, and figures (TLFs)** to support the CSR
- Supported by **ADaM datasets**



Motivation

What components support a CDISC compliant process?

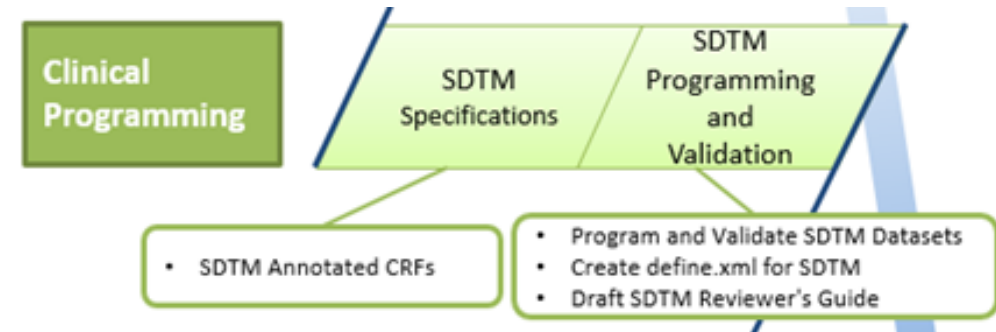
- **ADaM datasets** facilitate production of TLFs
- **Analysis Dataset Reviewer's Guide (ADRG)** orients a reviewer to the ADaM datasets
- **Define.xml** details the metadata used to create the ADaM datasets
- Supported by **SDTM domains**



Motivation

What components support a CDISC compliant process?

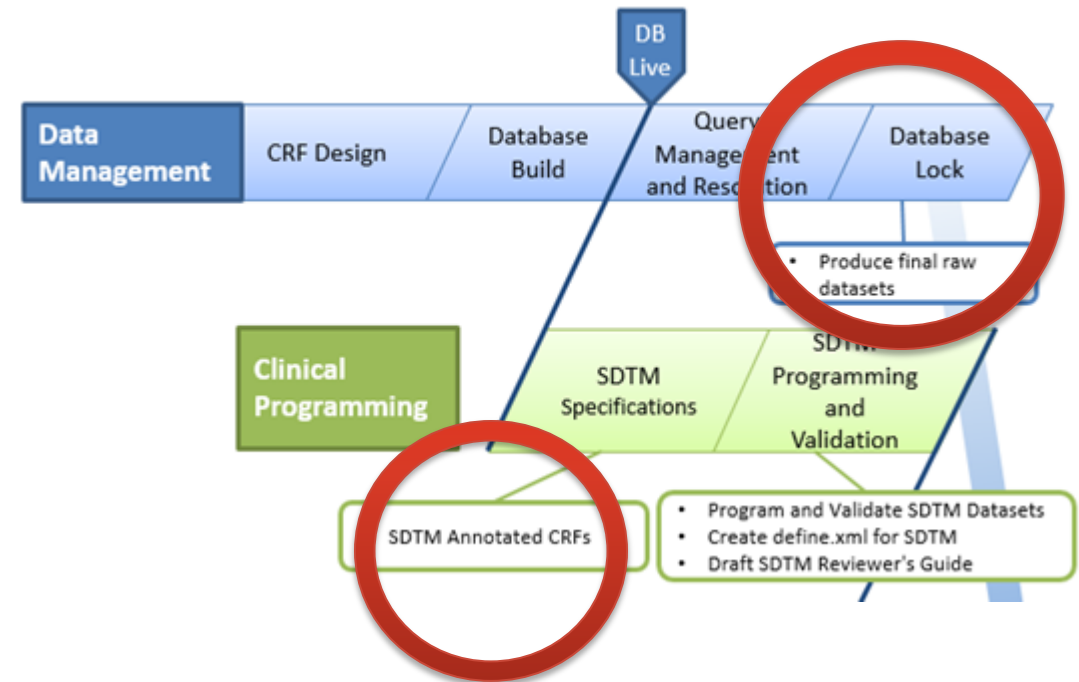
- **SDTM domains** organize raw clinical data by topic
- **Study Data Reviewer's Guide (SDRG)** orients a reviewer to the SDTM domains
- **Define.xml** details the metadata used to create the SDTM domains
- Supported by **raw clinical data**



Motivation

What components support a CDISC compliant process?

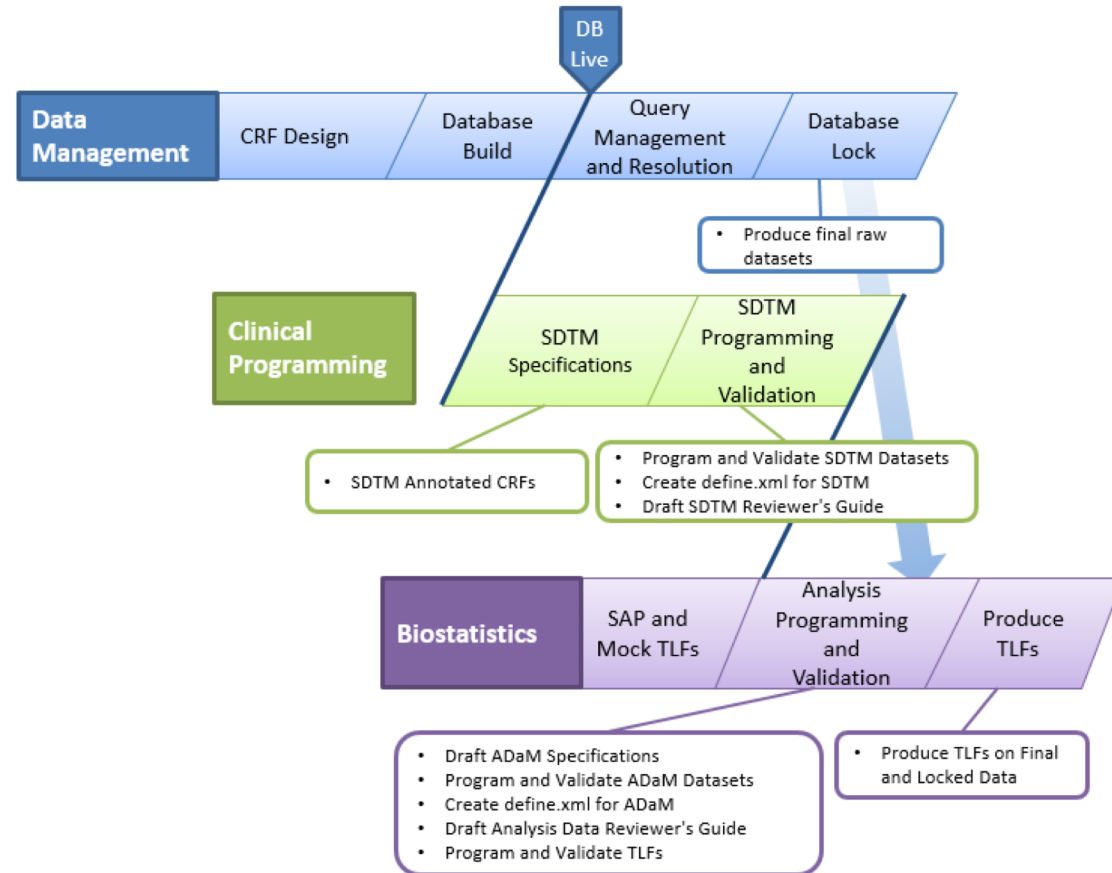
- **Raw clinical Data** collected per eCRF design
- Database design should reflect content and structure of the eCRFs
- **Annotated Case Report Form (aCRF)** layers raw data annotations and SDTM annotations



Motivation

What components support a CDISC compliant process?

- Implementation can be **complex** and **costly**
- Ensuring compliance is difficult
- **Upstream** and **downstream** consequences of decisions
- Limitations may require **strategic decisions**



Deviation

Why not adopt standards from the start?

- Breadth of Development Program
 - Smaller sponsor or small development program may prefer minimal data collection
 - Little internal utility or funding for SDTM and data mapping files such as define.xml
- Unknown Asset Viability
 - With little data to indicate efficacy, economize wherever possible
 - If CDISC is not required, produce small set of analysis datasets to support TLFs
 - Consider CDISC for future studies if the first study was successful. Then retrofit the first study as needed.

Deviation

Why not adopt standards from the start?

- Potential Partnerships
 - Create SDTM for a number of small studies with simple endpoints
 - Strategic positioning can result in later requests for compliant ADaM data
- Compatibility with Prior Precedent
 - Similar studies may have used non-standardized eCRFs to support analysis
 - Use of the same eCRFs and analysis programs could reduce efforts

- Define difficulties
- Specify the deviation
- Discuss solutions

Case Study #1

CDISC from SDTM Onward

Scenario

- Development program was initiated well before the requirement for standardized study data for submission
- Study Design: Double-blind period followed by open label extension
- CRFs
 - Sponsor wanted to use non-standardized paper CRFs consistent with other studies
 - Did not use CDASH standards
 - Did not use SDTM controlled terminology
- Database format not easily wrangled into SDTM structures
- Development program increased in size over the course of several years

Request: CDISC-compliant deliverables from SDTM onward to support a submission

Case Study #1

CDISC from SDTM Onward

■ **Difficulty:** Determining Visit Numbers

- Database did not have a 1:1 mapping of visit and visit number due to reuse of forms to decrease costs
 - Visit numbers from the double-blind period were repeated in the open label extension
 - All unscheduled visits were assigned visit number 99 regardless of phase or number of unscheduled visits per subject

Need a 1:1 relationship between visit and visit number (Section 4.1.4.5 SDTMIG v3.2) where visit names are unique and meaningful

■ **Deviation from the ideal process in visit/visitnum**

- The CRFs were not set up to allow for multiple unscheduled visits per subject and to collect those visits in the order in which they happened.
- Visit number and page report variables were collected and could provide direction for a mapping, but they did not guarantee the correct calendar time sequence.
- Enormous delays in data entry due to paper CRFs -> would have required constantly revisiting a mapping scheme where correct calendar time could not be guaranteed.

Case Study #1

CDISC from SDTM Onward

■ **Solution**

Deal with the visit names and visit dates issue once in the Subject Visits (SV) domain

- Wrangle all visits by date
- Create unique visit names and visit numbers
- Derive EPOCH
- Use SV in all other findings domains

Case Study #1

CDISC from SDTM onward

- **Deviations from the ideal process in laboratory data collection**

- Lab units and tests (absolute versus percent) were not consistent within subjects across visits
- Data was not collected using controlled terminology for units and tests

- **Solutions**

- Created a laboratory data standardization plan per sponsor-defined criteria
- Each test was represented by one unit with a standard test name and code
- Inconsistent collection of percent versus absolute results impacted ADaM and TLF development. Summarized shifts in clinical significance only.

Case Study #1

CDISC from SDTM onward

- Let's assess the impact

- **Visits**

- Strategic programming mitigated the impact of deviations at the SDTM level
 - Increase in programming effort, slightly impeded traceability, overall little cost

- **Laboratory data**

- Many queries for units that didn't make sense
 - Necessitated lab standardization plan
 - Limited ADaM and TLF development
 - Substantially greater cost than the visits example
 - Some deviations not ideal when trying to collect complete data regardless of standards

Case Study #2

Potential retrofit for CDISC after non-standard analysis

Scenario

- Prioritized fewer deliverables due to unknown asset viability
- May want to retrofit for CDISC compliance
- Asked for a strategy to meet their current needs while allowing for the possibility of creating all needed CDISC-compliant components

Request: Quick analysis datasets and TLFs and future potential retrofit

Case Study #2

Potential retrofit for CDISC after non-standard analysis

- **Deviations from the ideal process**

- SDTM and supporting files not created
- ADaM and supporting files not created

- **Solution**

- eCRFs
 - Used CDASH standards
 - Used SDTM controlled terminology
- Database format could be easily wrangled into SDTM structures
- ***Specify analysis datasets to closely resemble the future ADaM datasets***

Case Study #2

Potential retrofit for CDISC after non-standard analysis

Raw data (VS)

USUBJID	TEMP_VSORRES	TEMP_VSORRESU	HR_VSORRES	HR_VSORRESU
1	37	C	60	beats/min

**Approach without
CDISC standards**

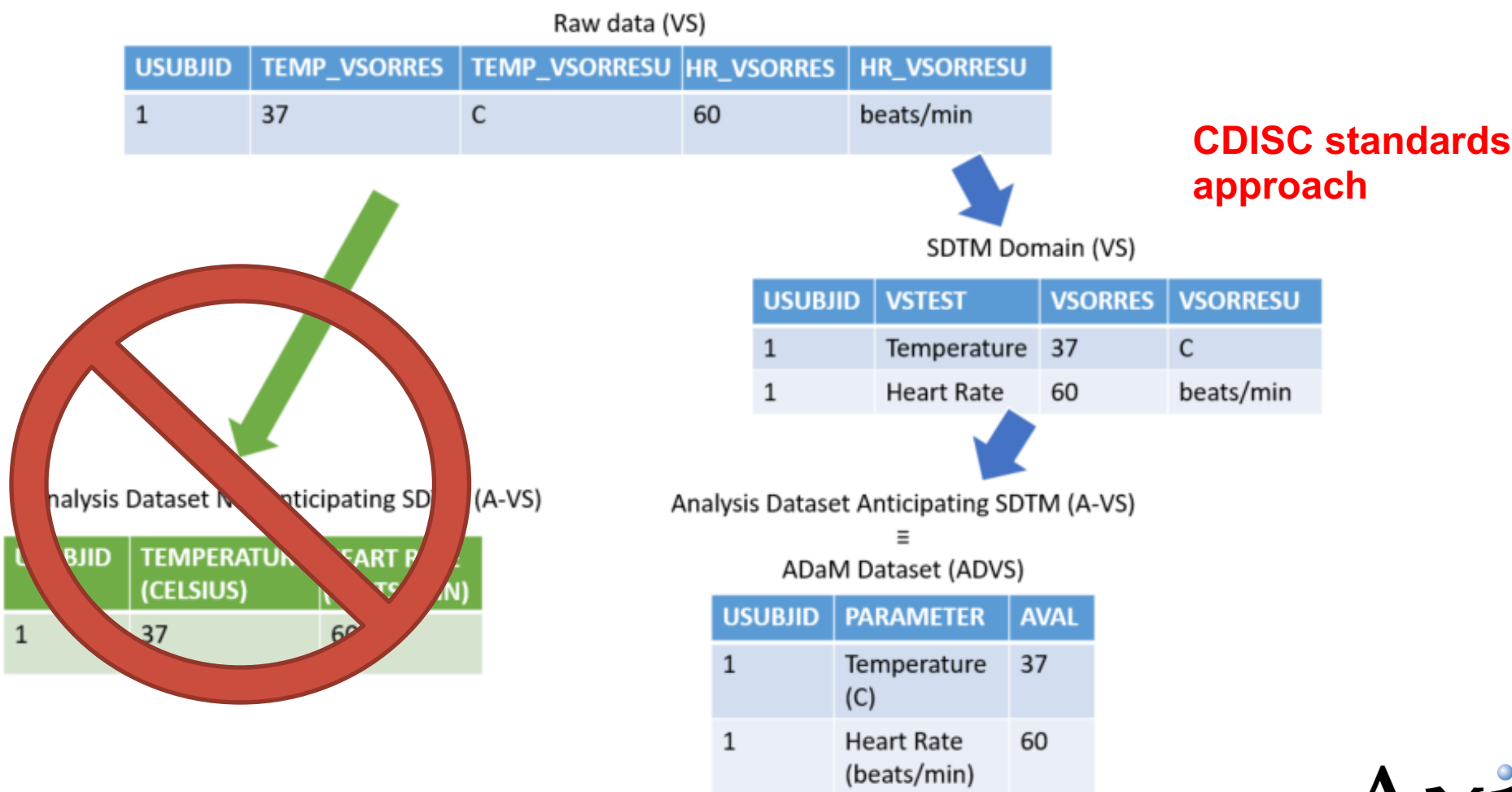


Analysis Dataset Not Anticipating SDTM (A-VS)

USUBJID	TEMPERATURE (CELSIUS)	HEART RATE (BEATS/MIN)
1	37	60

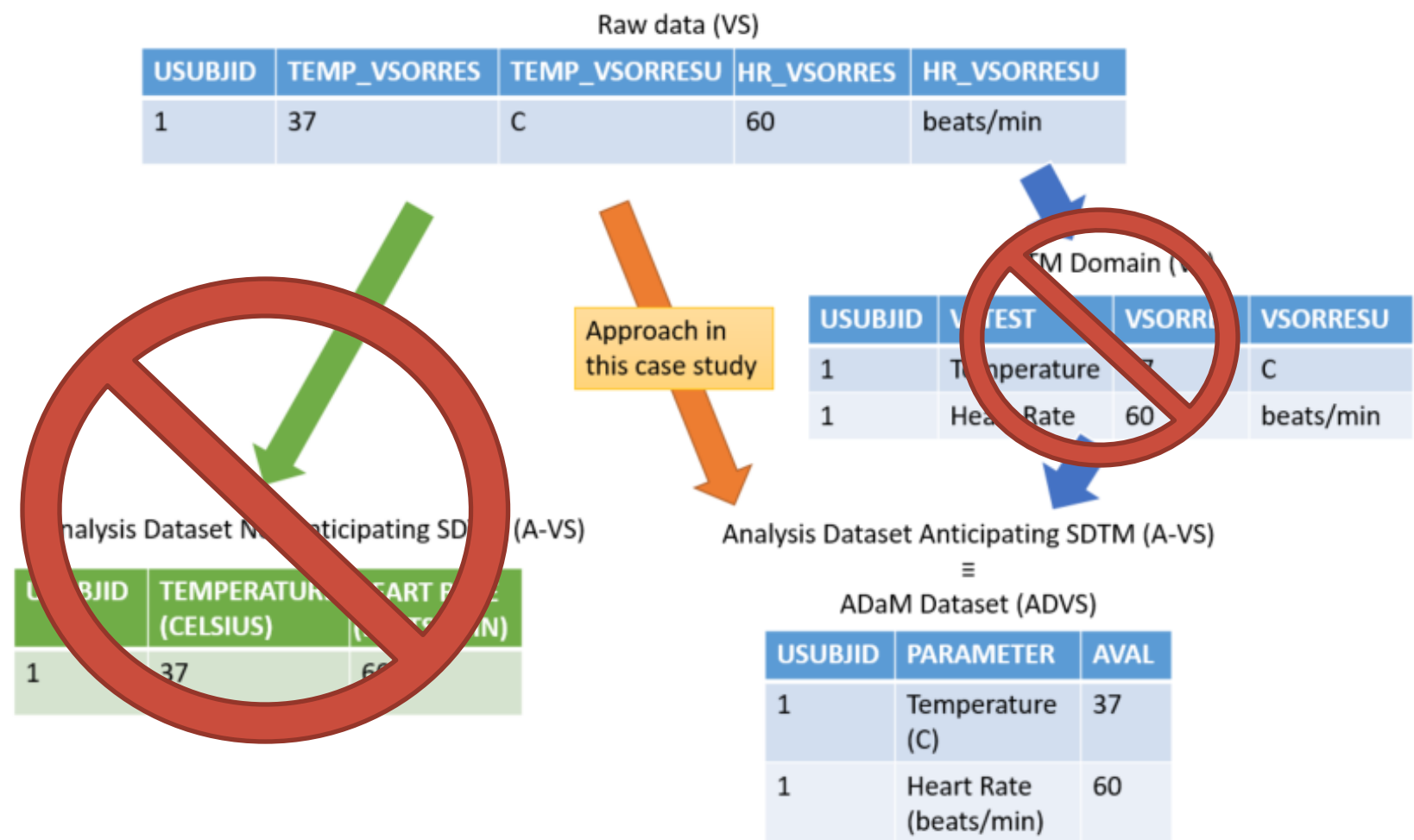
Case Study #2

Potential retrofit for CDISC after non-standard analysis



Case Study #2

Potential retrofit for CDISC after non-standard analysis



Case Study #2

CDISC from SDTM onward

- Let's assess the impact
 - **TLFs**
 - Can be programmed from analysis datasets
 - Minimal cost to update in the future
 - **SDTM, SDRG, define.xml, ADaM, ADRG, define.xml, aCRF**
 - Not produced under the current scope
 - Major change in scope only justified from the sponsor's perspective after the trial is positive
 - Increase in timeline for submission ready package

Concluding Thoughts

1. What's the end goal?
2. What is required to meet that end goal?
3. What resources are available? *Expertise, time, finances*



Architect a strategy to best meet the client's end goal within their resources

Concluding Thoughts

- These strategies required a firm understanding of CDISC standards in conjunction with regulatory requirements
- **Case Study #1 – no prior planning:** If little attention is paid to the possibility of submission and the creation of CDISC compliant deliverables, mitigating earlier decisions can be difficult
- **Case Study #2 – prior planning:** Informed strategy reduces the likelihood of unpleasant surprises when the study is converted

Thoughtful planning is the key to successfully adopting CDISC standards at different points in the data collection and analysis process, just as it is the key to successfully using data standards from the start.

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