TO IDB OR NOT TO IDB
That is the Question
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Beth Seremula, Chiltern
Setting the Scene

Act 1: In the Beginning
Act 2, Scene 1: Considerations
Act 2, Scene 2: Advantages
Act 2, Scene 3: Disadvantages
Act 3: Decision Time
One important use of integrated clinical data is to support the safety and efficacy analyses for new and supplemental drug and device applications as required by regulatory agencies.

Several options for submissions:
- Each study individually
- One integrated database (IDB)
- Combination – some individual and some integrated

Each approach has advantages and disadvantages.
Integration presents several challenges.
Act 2, Scene 1: Considerations

- ADaM IDB datasets should be designed to meet the analysis needs of the submission
- Purpose of integration
  - Study designs, indications, endpoints, durations, comparators
- How will the data be displayed (TLFs)?
  - Treatment group combinations, visits, etc.
- Traceability
- Harmonization
  - Creation of new variables
  - Recalculating existing variables
  - Recoding dictionaries
Act 2, Scene 1: Considerations

- Should meet frequently as a whole team
  - SDTM
  - ADaM
  - Data Management
  - Programming
  - Statistics
  - Clinical
  - Medical Writing
Act 2, Scene 1: Considerations

Approach #1: Integrated SDTM

This approach directly supports ADaM IDB

- Treatment Groups
  - Pooling (ADaM IDB)
- Adverse Events
  - TE definition (ADaM IDB)
  - Dictionary recoding (SDTM IDB)
- Conmeds & Medical History
  - Dictionary recoding (SDTM IDB)
- Timepoints and Visits
  - Windowing (ADaM IDB)
- Controlled Terminology
  - Consistent set of terms (SDTM IDB)
Act 2, Scene 1: Considerations

- **Approach #1, Example 1:**
  - Set together study-level EX domains into an integrated EX
  - Then use integrated EX to make integrated ADEX

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Variable Label</th>
<th>Source / Derivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTDT</td>
<td>Analysis Start Date</td>
<td>datepart of EX.exstdtc</td>
</tr>
<tr>
<td>ASTTM</td>
<td>Analysis Start Time</td>
<td>timepart of EX.exstdtc</td>
</tr>
<tr>
<td>ASTDY</td>
<td>Analysis Start Relative Day</td>
<td>ASTDT - ADSL.trtsdt+1</td>
</tr>
<tr>
<td>ASTDTM</td>
<td>Analysis Start Date/Time</td>
<td>EX.exstdtc, completely missing if time is missing.</td>
</tr>
</tbody>
</table>
Act 2, Scene 1: Considerations

Approach #1, Example 2:

<table>
<thead>
<tr>
<th>Study #</th>
<th>QNAM</th>
<th>QLABEL</th>
<th>QVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>AEREL1</td>
<td>Relation to Paclitaxel</td>
<td>Definite, Probable, Possible, Unrelated</td>
</tr>
<tr>
<td>Study 2</td>
<td>AEREL1</td>
<td>Relation to Docetaxel</td>
<td>Definite/Certain, Probable, Possible, Not Related</td>
</tr>
<tr>
<td>Study 3</td>
<td>AEREL1</td>
<td>Relation to Irinotecan</td>
<td>Definitely, Probably, Possibly, Not Related</td>
</tr>
<tr>
<td>Study 3</td>
<td>AEREL2</td>
<td>Relation to Docetaxel</td>
<td>Definitely, Probably, Possibly, Not Related</td>
</tr>
</tbody>
</table>

Integrated SUPPAE:

<table>
<thead>
<tr>
<th>QNAM</th>
<th>QLABEL</th>
<th>QVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERELPAC</td>
<td>Relation to Paclitaxel</td>
<td>Definite, Probable, Possible, Unrelated</td>
</tr>
<tr>
<td>AERELDOC</td>
<td>Relation to Docetaxel</td>
<td>Definite, Probable, Possible, Unrelated</td>
</tr>
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<td>AERELIRI</td>
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</tbody>
</table>
Act 2, Scene 1: Considerations

- Approach #1, Example 2 (continued):

<table>
<thead>
<tr>
<th>QNAM</th>
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<tbody>
<tr>
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Integrated SUPPAE:

Integrated ADAE:

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>RELCHMFL</td>
<td>Related to Any Chemotherapy Flag</td>
<td>Set to ‘Y’ if SUPPAE.qval in (‘Definite’ ‘Possible’ ‘Probable’) when SUPPAE.qnam= in (‘AERELPAC’ ‘AERELDOC’ ‘AERELIRI’)</td>
</tr>
</tbody>
</table>
Act 2, Scene 1: Considerations

Approach #2: Study Level SDTM

All of these items need to be considered by the ADaM IDB team:
- Treatment Groups
  - Pooling
- Adverse Events
  - TE definition
  - Dictionary recoding
- Conmeds & Medical History
  - Dictionary recoding
- Timepoints and Visits
  - Windowing
- Controlled Terminology
  - Use a consistent set of terminology

This approach eliminates the intermediate step of creating integrated SDTM, but then the integrated ADaM team needs to harmonize.
Approach #2, Example 1:
- Set together study-level EX domains into integrated ADEX

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Act 2, Scene 1: Considerations

- **Approach #2, Example 2:**

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<td>Relation to Docetaxel</td>
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</tr>
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</table>

Study-Level SUPPAE:

**Integrated ADAE:**

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<tbody>
<tr>
<td>RELCHMFL</td>
<td>Related to Any Chemotherapy Flag</td>
<td>For <strong>Study 1</strong>, set to ‘Y’ if SUPPAE.qval in (‘Definite’ ‘Probable’ ‘Possible’) when SUPPAE.qnam=‘AEREL1’. For <strong>Study 2</strong>, set to ‘Y’ if SUPPAE.qval in (‘Definite/Certain’ ‘Probable’ ‘Possible’) when SUPPAE.qnam=‘AEREL1’. For <strong>Study 3</strong>, set to ‘Y’ if SUPPAE.qval in (‘Definitely’ ‘Possibly’ ‘Probably’) when SUPPAE.qnam in (‘AEREL1’ ‘AEREL2’).</td>
</tr>
</tbody>
</table>
All of these items need to be considered in the ADaM IDB

- Do ADaMs exist for every study?
- Requires harmonization of values
  - PARAM/PARAMCD, AVISIT/AVISITN, ATPT/ATPTN
- Differences in analysis rules
  - Imputation algorithms
  - Baseline definition
  - Visit windows
  - Analysis flags

Approach #3: Study Level ADaM

This approach allows for direct mapping of variables
Approach #3, Example 1:

- Set together study-level ADEXs into integrated ADEX

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<td>Analysis Start Date</td>
<td>Study1/Study2/Study3.ADEX.astdt</td>
</tr>
<tr>
<td>ASTTM</td>
<td>Analysis Start Time</td>
<td>Study1/Study2/Study3.ADEX.asttm</td>
</tr>
<tr>
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- Caution: AVISIT/AVISITN from different studies may have different meanings – do they need to be harmonized/re-derived/windowed? (e.g., Visit 3 in Study 1 is Week 8, but Visit 3 in Study 2 is Week 4)
Act 2, Scene 1: Considerations

- Approach #3, Example 2:
  - Set together study-level ADAEs into integrated ADAE
    - Caution: Treatment-Emergent definitions from different studies may have different meanings
      - e.g., +7 days from last dose in Study 1, but +30 days from last dose in Study 2 – is this OK, or do they need to be harmonized/re-derived?
    - Caution: Relationship and Action Taken variables may come from different variable names in different studies, may need to adjust.
Act 2, Scene 1: Considerations

- **Define.xml**
  - How will you document this?
  - Specifications drive the define file

- **OpenCDISC**
  - Not designed for integrations, you may get errors or warnings that are ok because of the integration

- **Naming conventions**
  - Do the IDB names have to match the study level ADaM names?

- Integrated TFLs may not necessarily be the sum of the study-level TFLs if you changed algorithms
Act 2, Scene 1: Considerations

SDTM Study 1:
ARM values:
- 50 mg
- 100 mg
- 200 mg

SDTM Study 2:
ARM values:
- 75 mg
- 125 mg
- 225 mg

TRACEABILITY

ADaM IDB
TRT01P values:
- <100 mg
- 100-200 mg
- > 200 mg

Suggest keeping ARM in integrated ADSL to have TRACEABILITY of how TRT01P was derived from the original study-level treatment groups.
Act 2, Scene 2: Advantages

- Consistency
- A means A, or at least you have created a definition (treatment emergent for instance)
- Get a clear picture
- Easier to produce Adhoc requests
Act 2, Scene 3: Disadvantages

- Time consuming
- Needs lots of up-front thought process
- Documentation can be very complicated
Act 3: Decision Time

- Hamlet is a tragedy but ADaM IDB does not need to be.
- After being involved in several ADaM IDB projects, we believe that the pros definitely outweigh the cons.
- ADaM IDB gives us greater consistency and helps us clearly examine the results of a submission.
- Don’t be afraid of the future, be brave and embrace the challenge head on.
Questions
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