TO IDB OR NOT TO IDB

That is the Question

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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

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Act 1: In the Beginning

- 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

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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.
- Harmonization
  - Controlled Terminology
  - Algorithms
  - Dictionaries
- Traceability

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Act 2, Scene 1: Considerations

- Should meet frequently as a whole team
  - Clinical
  - Medical Writing
  - Statistics
  - ADaM
  - SDTM
  - Programming
  - Data Management

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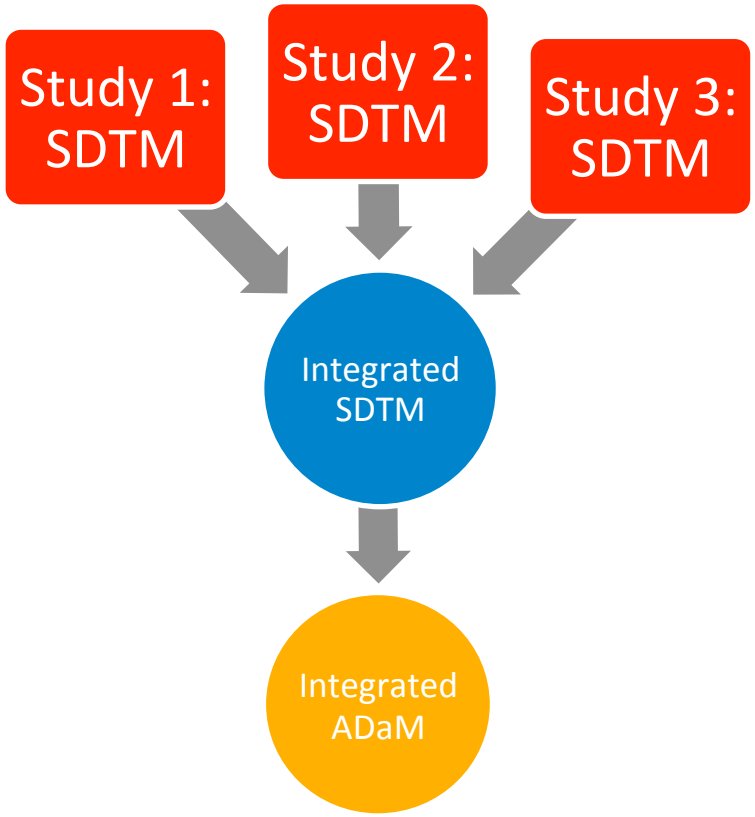
Act 2, Scene 1: Considerations

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)

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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

Variable Name	Variable Label	Source / Derivation
ASTDT	Analysis Start Date	datepart of EX.exstdtc
ASTTM	Analysis Start Time	timepart of EX.exstdtc
ASTDY	Analysis Start Relative Day	ASTDT - ADSL.trtsdt+1
ASTDTM	Analysis Start Date/Time	EX.exstdtc, completely missing if time is missing.

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Act 2, Scene 1: Considerations

- Approach #1, Example 2:

Study-Level SUPPAE:

Study #	QNAM	QLABEL	QVAL
Study 1	AEREL1	Relation to Paclitaxel	Definite, Probable, Possible, Unrelated
Study 2	AEREL1	Relation to Docetaxel	Definite/Certain, Probable, Possible, Not Related
Study 3	AEREL1	Relation to Irinotecan	Definitely, Probably, Possibly, Not Related
Study 3	AEREL2	Relation to Docetaxel	Definitely, Probably, Possibly, Not Related

Integrated SUPPAE:

QNAM	QLABEL	QVAL
AERELPAC	Relation to Paclitaxel	Definite, Probable, Possible, Unrelated
AERELDOC	Relation to Docetaxel	Definite, Probable, Possible, Unrelated
AERELIRI	Relation to Irinotecan	Definite, Probable, Possible, Unrelated

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Act 2, Scene 1: Considerations

- Approach #1, Example 2 *(continued)*:

Integrated SUPPAE:

QNAM	QLABEL	QVAL
AERELPAC	Relation to Paclitaxel	Definite, Probable, Possible, Unrelated
AERELDOC	Relation to Docetaxel	Definite, Probable, Possible, Unrelated
AERELIRI	Relation to Irinotecan	Definite, Probable, Possible, Unrelated

Integrated ADAE:

Variable Name	Variable Label	Source / Derivation
RELCHMFL	Related to Any Chemotherapy Flag	Set to 'Y' if SUPPAE.qval in ('Definite' 'Possible' 'Probable') when SUPPAE.qnam= in ('AERELPAC' 'AERELDOC' 'AERELIRI')

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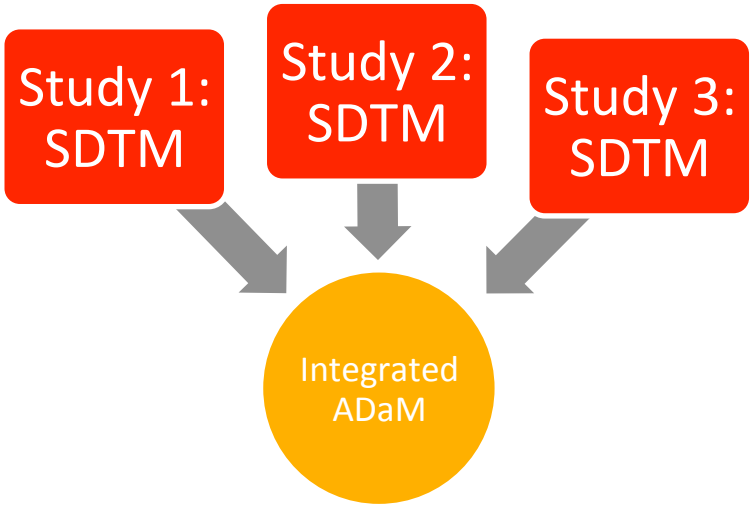
Act 2, Scene 1: Considerations

Approach #2:
Study Level SDTM



This approach eliminates the intermediate step of creating integrated SDTM, but then the integrated ADaM team needs to harmonize.

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

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Act 2, Scene 1: Considerations

- Approach #2, Example 1:
  - Set together study-level EX domains into integrated ADEX

Variable Name	Variable Label	Source / Derivation
ASTDT	Analysis Start Date	datepart of Study1/Study2/Study3.EX.exstdtc
ASTTM	Analysis Start Time	timepart of Study1/Study2/Study3.EX.exstdtc
ASTDY	Analysis Start Relative Day	ASTDT - ADSL.trtsdt+1
ASTDTM	Analysis Start Date/Time	Study1/Study2/Study3.EX.exstdtc, completely missing if time is missing.

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Act 2, Scene 1: Considerations

- Approach #2, Example 2:

Study-Level SUPPAE:

Study #	QNAM	QLABEL	QVAL
Study 1	AEREL1	Relation to Paclitaxel	Definite, Probable, Possible, Unrelated
Study 2	AEREL1	Relation to Docetaxel	Definite/Certain, Probable, Possible, Not Related
Study 3	AEREL1	Relation to Irinotecan	Definitely, Probably, Possibly, Not Related
Study 3	AEREL2	Relation to Docetaxel	Definitely, Probably, Possibly, Not Related

Integrated ADAE:

Variable Name	Variable Label	Source / Derivation
RELCHMFL	Related to Any Chemotherapy Flag	For Study 1, set to 'Y' if SUPPAE.qval in ('Definite' 'Probable' 'Possible') when SUPPAE.qnam='AEREL1'. For Study 2, set to 'Y' if SUPPAE.qval in ('Definite/ Certain' 'Probable' 'Possible') when SUPPAE.qnam='AEREL1'. For Study 3, set to 'Y' if SUPPAE.qval in ('Definitely' 'Possibly' 'Probably') when SUPPAE.qnam in ('AEREL1' 'AEREL2').

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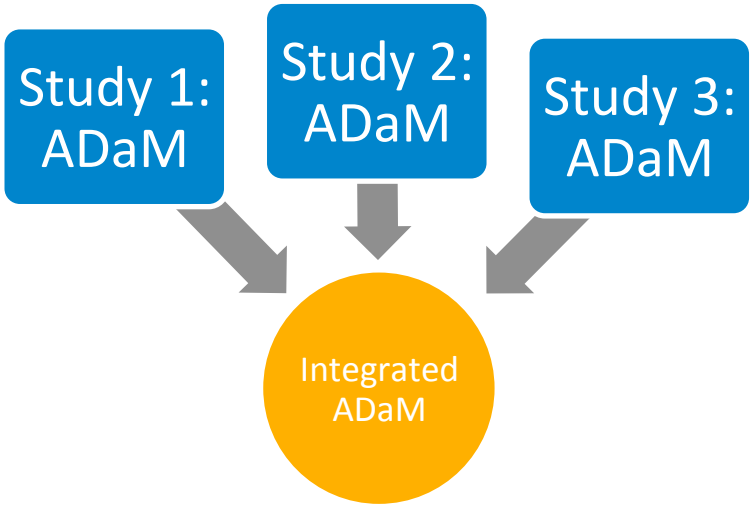
Act 2, Scene 1: Considerations

Approach #3: Study Level ADaM



This approach allows for direct mapping of variables

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

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Act 2, Scene 1: Considerations

- Approach #3, Example 1:
  - Set together study-level ADEXs into integrated ADEX

Variable Name	Variable Label	Source / Derivation
ASTDT	Analysis Start Date	Study1/Study2/Study3.ADEX.astdt
ASTTM	Analysis Start Time	Study1/Study2/Study3.ADEX.asttm
ASTDY	Analysis Start Relative Day	ASTDT - ADSL.trtsdt+1
ASTDTM	Analysis Start Date/Time	Study1/Study2/Study3.ADEX.astdtm

  - 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)

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Act 2, Scene 1: Considerations

- Approach #3, Example 2:
  - Set together study-level ADAEs into integrated ADAE
    - Caution: Relationship and Action Taken variables may come from different variable names in different studies, may need to adjust.
    - 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?

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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?

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Act 2, Scene 1: Considerations

TRACEABILITY

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

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

ADaM IDB
TR01PG1 values:
<100 mg
100-200 mg
> 200 mg

Suggest in addition to TRT01P in integrated ADSL to have TRACEABILITY of how TR01PG1 was derived from the original study-level treatment groups.

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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

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Act 2, Scene 3: Disadvantages

- Time consuming
- Needs lots of up-front thought process
- Documentation can be very complicated

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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.

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Questions

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