SS04

# To IDB or Not to IDB

## That is the Question

Kjersten Offenbecker, Spaulding Clinical Research, West Bend, WI
Beth Seremula, Chiltern International, King of Prussia, PA

## ABSTRACT

In Shakespeare's *Hamlet* we hear Prince Hamlet ask the now cliché "To be or not to be" question as he contemplates suicide. How does this relate to ADaM integrated databases (IDBs)? As Hamlet weighs the pros and cons of death, we too must decide whether it is better to stick with the status quo or venture into the unknown world of integrating our ADaMs. We shall examine the pros and cons of ADaM IDBs as well as some of the basic pitfalls we have come across while undertaking this daunting task. Along this journey we will show why we think IDB is the future and why it is better to be on the cutting edge.

## INTRODUCTION

The trend in our industry has definitely shifted to collecting data and reporting it using the SDTM standards outlined by CDISC. More and more companies are even embracing the ADaM standards to analysis their results and create their TLFs. The big hole seems to be in regards to what to do with all this data when it comes time to create an integrated database. It can seem very overwhelming at the onset but integrating SDTM and more specifically ADaM is really not all that different from integrating our legacy standards. They key is solid planning, watching for potential roadblocks and understanding the different approaches involved. We will navigate the options together and examine the advantages and disadvantages of the different approaches for integrating ADaM. As the curtain fails, at the end of our presentation we hope to have given you more information and helped you embrace the idea of integrating your ADaM datasets.

### ACT 1: IN THE BEGINNING

As the curtain rises we hold our breath in anticipation of what is to come. Are we about to partake in a comedy, a drama, a tragedy or something altogether different? As with any integration it is important to understand what it is we are getting into. What is the purpose of our integration and what do we hope to accomplish in the end. 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. There are several options available when deciding on how to submit our ADaM data. Each study can be submitted individually; one large integrated database (IDB) can be created or a combination of both can be used. There are advantages and disadvantages to each of these approaches and IDB presents the most challenges.

### ACT 2, SCENE 1: CONSIDERATIONS

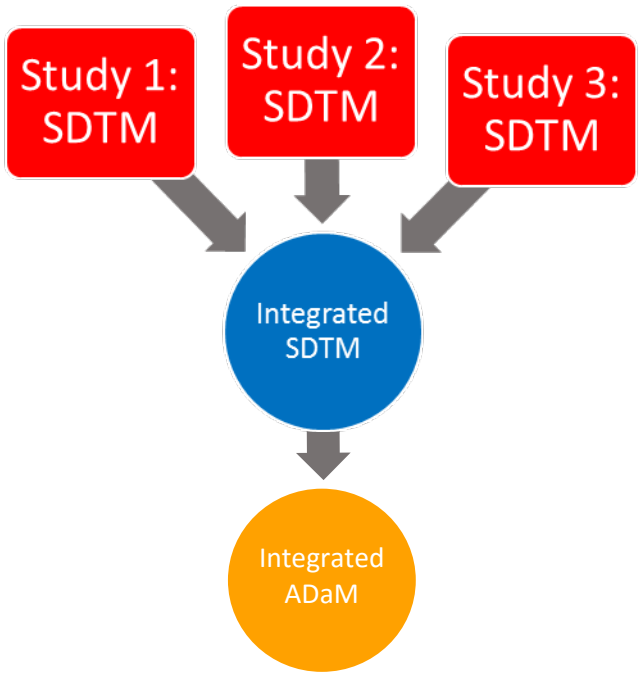
Just like any submission careful planning is the key to success with an ADaM IDB. It is vitally important to pull all the stakeholders together and plan, plan, plan. What is the purpose of your submission, what is the design of each study you want to integrate, what are the indications, endpoints, durations, etc? Think about what the story is that you are trying to tell and whether an IDB is the right approach for your submission. You want to start with the end in mind, how will all of this data be displayed on the TLFs? Do you need to pool treatment groups together, what about the visit information, how will that be displayed? What about harmonization? Will you need to create new variables, redefine existing variables and what about coding? These studies may have been conducted over a substantial period of time and recoding may be required. All of these questions and many more will help drive the content of your IDB.

You will want to frequently meet with all the key actors to ensure everyone is on the same page and any script changes are understood by everyone. Don't forget to include experts from all the different disciplines in these meetings. You will want members from data management, programming, statistics, medical writing and clinical, as well as SDTM and ADaM experts. All of these members bring a different perceptive and will help ensure nothing is overlooked and left behind. Everyone's opinions matter, but it is important to assign a director who will keep things moving and help make decisions and track changes. Every good team needs a strong leader; be sure you have identified yours.

One of the biggest decisions that needs to be made by the team is what approach will be used for the integration. The IDB can be created from study level SDTM, integrated SDTM or study level ADaM. Again, each of these has pros and cons and they all take careful planning to ensure a quality product is created.

#### APPROACH #1: INTEGRATED SDTM

This approach will directly support ADaM by creating one set of SDTM domains which will be used to create the ADaM used for the integration. Study level SDTM is used to create the integrated SDTM, which in turn is used to directly create the integrated ADaM.




The main advantage to this approach is that the harmonization will occur at the SDTM level, giving the ADaM team a consistent set of data to begin with where recoding has already occurred, as well as mapping to a consistent set of controlled terminology. It will also be easy to pool the treatment groups and define variables like Treatment Emergent flags directly in ADaM. However, this approach requires a highly knowledgeable SDTM team who can create a complete set of integrated SDTM domains. It also results in recreating the ADaM datasets and the need to ensure consistency with the original study level ADaM datasets. This can be time consuming, and in some cases very difficult to achieve.

**APPROACH #1: EXAMPLE 1**

In this example EX is simply set together to create the integrated at the SDTM level and the ADaM integration is pretty straightforward. ASTDT, ASTTM, ASTDY and ASTDTM are created directly from the integrated SDTM data.

| 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. |

**APPROACH #1: EXAMPLE 2**

In this example the integration of the SDTM requires more thought and harmonization. Each of the 3 studies being integrated contains an AEREL1 variable in the SUPPAE domain however the meaning of each is different. In Study 1 AEREL1 refers to the relationship to Paclitaxel, in study 2 it refers to the relationship to Docetaxel and in study 3 it refers to the relationship to Irinotecan. To muddy the waters even more in study 3 we have AEREL2 which refers to the relationship to Docetaxel which is the same as AEREL1 in Study 2. For clarity and consistency in the integrated SDTM it makes sense to create three relationship variables in the new SUPPAE - AERELPAC (Relationship to Paclitaxel), AERELDOC (Relationship to Docetaxel) and AERELIRI (Relationship to Irinotecan). Once this integrated SUPPAE domain is available it becomes very straightforward to create a flag to indicate relationship to any chemotherapy in the integrated ADaM.

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 |

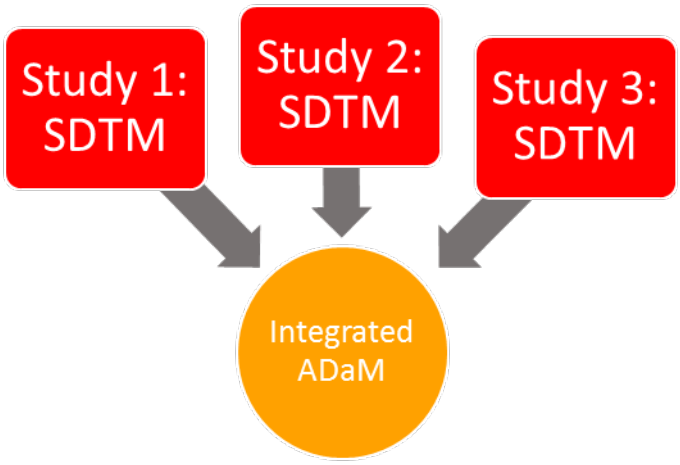
Integrated SUPPAE:

| 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 |

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') |

**APPROACH #2: STUDY LEVEL SDTM**
This approach uses the study level SDTM without integration prior to creation of the integrated ADaM.




With this approach there is no need for a dedicated SDTM team to create the integrated SDTM. However, all the harmonization which occurred in approach #1 now has to happen in the integrated ADaM. This includes recoding of Adverse Events, Medications and potentially Medical History as well as mapping to a controlled terminology. The team will need to be well versed in SDTM standards as well as ADaM standards. In approach #1 there were two separate teams – one for SDTM and one for ADaM – but in this approach you have one team that tackles both. This approach also requires recreation of the ADaM and therefore it is important to maintain consistency with the study-level ADaM.

**APPROACH #2: EXAMPLE 1**
Using the same example we saw in approach #1 we see that in this example the creation of the integrated ADaM is pretty straightforward since there is little harmonization that needs to occur. The three study level SDTM datasets are set together in the integrated ADEX dataset and ASTDT, ASTTM, ASTDY and ASTDTM are created relatively easily.

| 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. |

**APPROACH #2: EXAMPLE 2**

Again let's look at example 2 from approach #1 where we need to integrate the relationship to drug. When integrating ADaM directly from the study level SDTM we again create one variable which creates a flag indicating if the observation is related to any chemotherapy. The ADaM specifications are a bit more complicated since each study needs to have a separate set of instructions.

Study-Level SUPPAE:

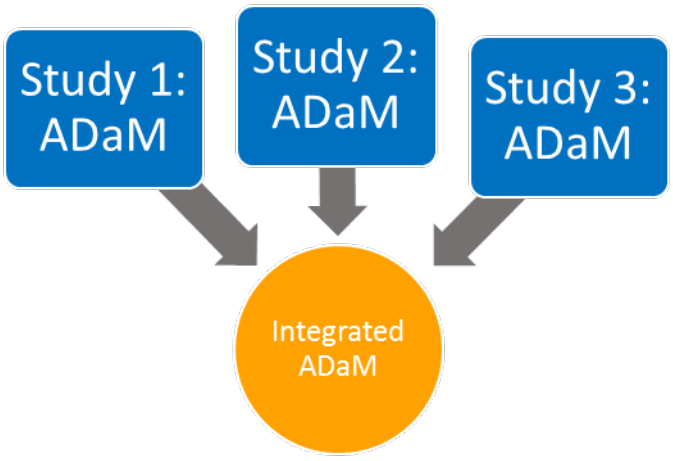
| Study # | QNAM | QLABEL | QVAL |
|---|---|---|---|
| Study 1 | AEREL1 | Relation to Paclitaxel | Definite, Probable, Possible, Unrelated |
| Study 2 | AEREL1 | Relation to Docetaxel | Definite/Certain, Probable, Possible, Not Related |
| Study 3 | AEREL1 | Relation to Irinotecan | Definitely, Probably, 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'.<br>For Study 2, set to 'Y' if SUPPAE.qval in ('Definite/Certain' 'Probable' 'Possible') when SUPPAE.qnam='AEREL1'.<br>For Study 3, set to 'Y' if SUPPAE.qval in ('Definitely' 'Possibly' 'Probably') when SUPPAE.qnam in ('AEREL1' 'AEREL2'). |

**APPROACH #3: STUDY LEVEL ADAM**

This approach allows for direct mapping of the variables from ADaM to ADaM.




This approach does not require a complete re-write of the ADaM and can be completely created by your ADaM team. It may seem like the easiest and most straightforward approach, but there are still many things to consider. What happens if one or more of your studies does not have study level ADaM? You will still need to harmonize across the studies to get a consistent set of variables which all mean the same thing. Analysis rules may have different meanings in different studies, such as baseline flags, visit windows, analysis flags and imputation algorithms. It is important to figure out up front how you are going to handle these potential stumbling blocks. Do you create new variables or redefine existing ones? How will this affect the results in the individual studies if you redefine how something is created?

**APPROACH #3: EXAMPLE 1**

Again we will use the same example we saw in approach #1 and #2 we see that in this example the creation of the integrated ADaM is pretty straightforward since there is little harmonization that needs to occur. The three study level ADaM datasets are set together in the integrated ADEX dataset and ASTDT, ASTTM, ASTDY and ASTDTM are created relatively easily.

| 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 |

This is straightforward on the surface but beware - AVISIT and AVISITN may have different meaning in each of the individual studies. For instance Visit 3 in study 1 is Week 8 but in study 2 Visit 3 is Week 4. How are these going to be integrated? What harmonization needs to occur?

**APPROACH #3: EXAMPLE 2**

Using example 2 from approach #1 and #2 we need to set ADAE together to create the integrated ADAE. To create this integrated dataset what is the new meaning of Treatment-Emergent (TE)? Are the definitions from each study the same? For example, in Study 1 TE is +7 days from last dose but +30 days from last dose in Study 2. Do these need to be harmonized? Maybe not, maybe it is acceptable that they are different but it is important to decide. Similarly, the relationship and action taken variables may have different variables name in the different studies and may require adjustment.

**ACT 2, SCENE 1: CONSIDERATIONS – FINAL THOUGHTS**

When considering which approach is appropriate for your study and your team, don't forget to think about how you are going to create the electronic submission (define.xml). It is important to think about this early because the specifications really drive its creation and can make it easier or much, much more complicated. Also, remember that Pinnacle21 (aka OpenCDISC) is not designed for integrations and can result in many items that do not require an update in the data. These things may seem trivial now, but when you get to them they will be big deals.

**ACT 2, SCENE 2: ADVANTAGES**

Integrating ADaM for submission has many advantages of which the most obvious would be consistency, allowing your reviewer to compare apples to apples and clearly see the road you have mapped out for them. If the need arises, it will be much easier and quicker to create adhoc analysis. The upfront planning sets the stage for a well thought-out submission package. Your team may decide not to change definitions but at least you thought them out and have justification.

**ACT 2, SCENE 3: DISADVANTAGES**

Integration work is very time consuming and this is probably the number one disadvantage to the process. There is a lot of up front work that needs to happen and many people who need to be involved. You need to create a very detailed map which outlines exactly where you are starting, where you are going and how you are getting there. All of that takes a tremendous amount of time and effort. You need to ensure you have all the right people with the right qualifications available to help make decisions quickly and accurately. Time up front will save time later.

**ACT 3: DECISION TIME**

We all know how Hamlet ends. He decides against suicide, travels a very unhappy road and ends up dead in the end. Hamlet is a tragedy but ADaM IDB does not need to be. The integration of ADaM gives us greater consistency and helps us clearly examine the results of our submission. Don't be afraid of the future; be brave and embrace the challenge head on. As more and more companies travel down this road, we will all reap the benefits.

**Contact Information**

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


Kjersten Offenbecker
Director of Biometrics
Spaulding Clinical Research
525 S Silverbrook Dr
West Bend, WI 53095
Work Phone: (616) 777-0653
Kjersten.Offenbecker@SpauldingClinical.com
Web: www.SpauldingClinical.com

Beth Seremula
Director Statistics
Chiltern International
1016 East Ninth Avenue
King of Prussia, PA 19406
Work Phone: (484) 679-2418
Beth.Seremula@Chiltern.com
Web: www.Chiltern.com