

# Review-Ready Submissions: Helpful Tips when Preparing Submissions to FDA

*Results from OB Easy/Difficult Reviews Survey*

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# Disclaimer

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

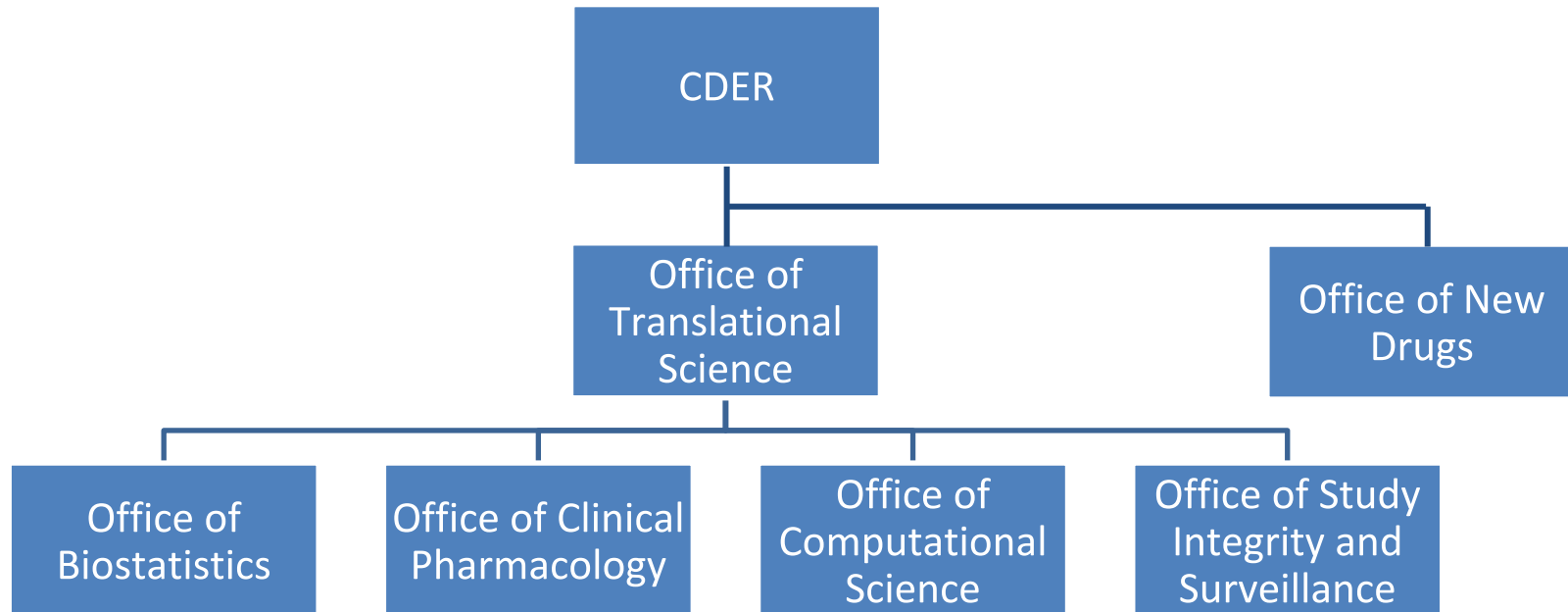
# Acknowledgements

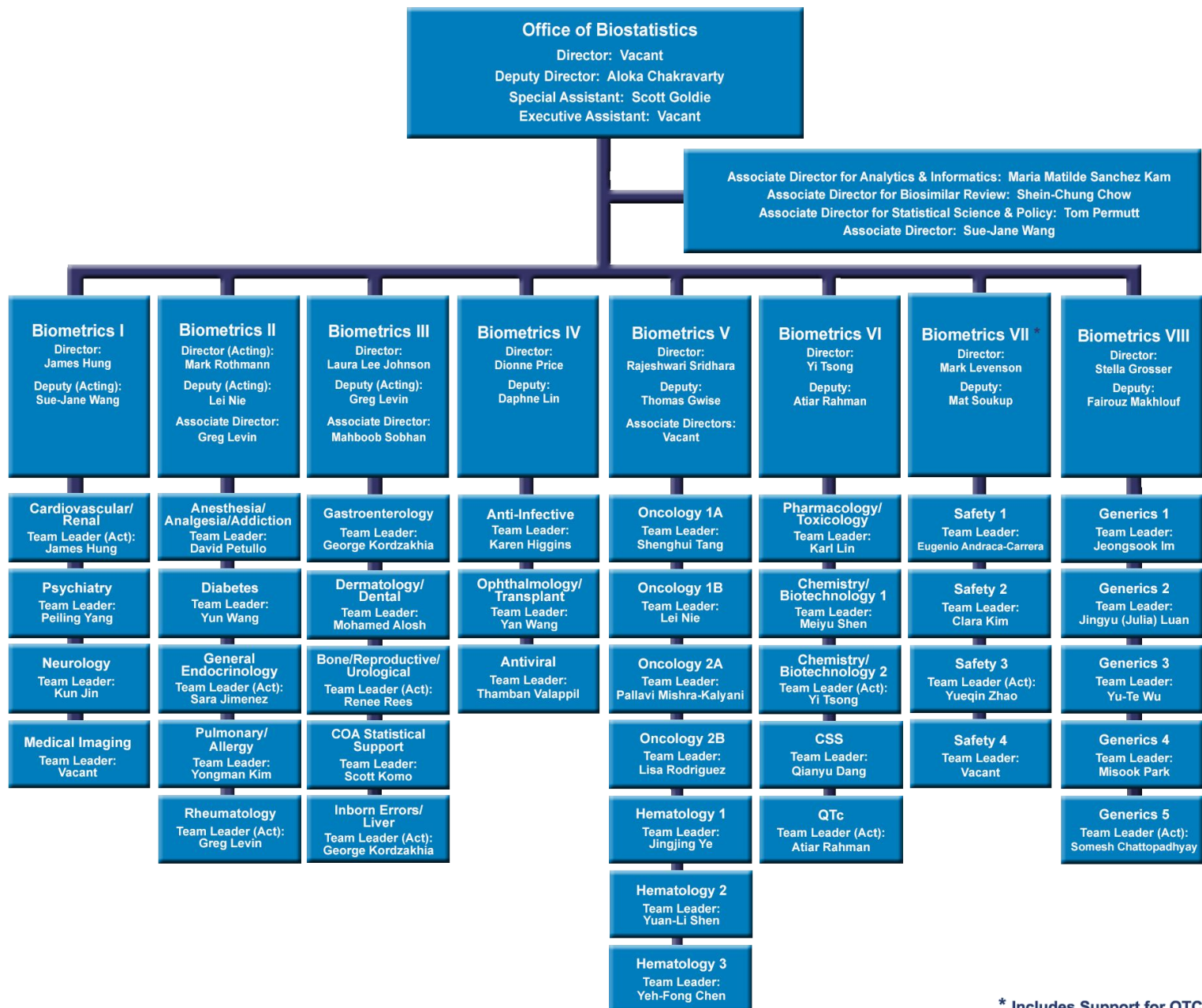
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- OB Data Review Committee

# Outline

- Office of Biostatistics (OB) Overview
- OB Survey Project Description
- Survey Results
  - Submission Documentation
  - Submission Analysis Datasets
- Summary

# CDER Organizational Chart





\* Includes Support for OTC

# OB Analytics and Informatics Group

- Supports all 8 Divisions of Biometrics (DB) within OB and in collaboration with colleagues in OB, supplies leadership in the areas of
  - Data Standards
  - Data Integrity and Data Quality
  - Scientific and Statistical Computing
  - Data Science and Data Tools for OB reviewers
- Establish group of statistical analysts to provide support for IND/NDA/BLA review

# Survey Project Description

- Identification of “Easy to Review” and “Difficult to Review” NDA/BLA data submissions
  - Surveyed statistical reviewers from 8 DBs
- Assessment of identified submissions
  - Examined aspects contributing to ease or difficulty of review
  - Analyzed corresponding Information Requests (IRs)

# Submissions Characteristics

| Submission Type                                                      |              | Difficult to review | Easy to review | Total     |
|----------------------------------------------------------------------|--------------|---------------------|----------------|-----------|
| Submissions Reviewed (N)                                             |              | 17 (40%)*           | 25 (60%)       | 42 (100%) |
| Submission Type                                                      |              |                     |                |           |
|                                                                      | Original     | 10 (59%)            | 17 (68%)       | 27 (67%)  |
|                                                                      | Supplemental | 7 (41%)             | 8 (32%)        | 15 (36%)  |
| Year Submitted                                                       |              |                     |                |           |
|                                                                      | 2015         | 1                   | 0              | 1         |
|                                                                      | 2016         | 2                   | 3              | 5         |
|                                                                      | 2017         | 4                   | 8              | 12        |
|                                                                      | 2018         | 9                   | 13             | 22        |
|                                                                      | 2019         | 1                   | 1              | 2         |
| *Only 17 of 18 difficult surveys contained valid submission numbers. |              |                     |                |           |

| Indications                       |                                 |
|-----------------------------------|---------------------------------|
| Allergic Rhinitis                 | Neurotrophic Keratitis          |
| Ankylosing Spondylitis            | Non-Hodgkin's Lymphoma          |
| Asthma                            | NSCLC (2)                       |
| Bacterial Skin Infection          | Opioid Related (2)              |
| Bacterial Vaginosis               | Osteoporosis                    |
| cUTI (2)                          | Pain (2)                        |
| CV/Mortality in T2DM (3)          | Parkinson's                     |
| Diabetes (4)                      | Post Partum Depression          |
| DVT prevention                    | Pregnancy Prevention            |
| Hereditary Angioedema             | Psoriasis or RA (3)             |
| Hypoactive Sexual Desire Disorder | Schizophrenia (2)               |
| IBS / IBS-C (2)                   | Seizures (2)                    |
| Migraine                          | Urothelial Carcinoma            |
| Multiple Sclerosis                | Vascular Ehlers Danlos Syndrome |

# Survey Results: Submission Documentation

|                   |                                 | Difficult Submissions | Easy Submissions |
|-------------------|---------------------------------|-----------------------|------------------|
| Surveys Completed |                                 | 18                    | 25               |
| Documentation     |                                 |                       |                  |
|                   | ADRG                            | 7 (39%)               | 16 (64%)         |
|                   | Define.xml derivations: detail  | 7 (39%)               | 21 (84%)         |
|                   | Define.xml derivations: clarity | 6 (33%)               | 20 (80%)         |

Submission of programs emerged as important documentation for review

- 94% of difficult submissions received an Information Request for programs
- 60% of difficult submissions vs 100% of easy submissions provided any programs
- OB reviewers confirmed that readable, annotated programs are critical for review

# ADRG: Dos and Don'ts

## ADRG: Dos

- Submit a clear, concise ADRG
- Include important study-level information
- Include data dependencies
- Describe analysis data and processing irregularities

## ADRG: Don'ts

- Put derivation information in ADRG instead of define
- Repeat information across ADRG
- Require frequent navigation between define and ADRG

## Define.xml: IR Examples

- Provide more details regarding logic & variables
- Provide readable derivations and pseudo-code
- Provide information on handling of missing data
- Identify parameters that support endpoints
- Define purpose of flags and provide derivations

# Define.xml Derivation Examples

## Difficult Examples

**(ADEFF)** [Location: [adeff.xpt](#)]

| Variable | Label                   | Type | Length / Display Format | Controlled Terms or Format | Source/Derivation/Comment |
|----------|-------------------------|------|-------------------------|----------------------------|---------------------------|
| ANL01FL  | Analysis Record         | text | \$1                     |                            |                           |
| ANL02FL  | Analysis Record Flag 02 | text | \$1                     |                            |                           |

**Parameter Value List - ADSRS [AVALC]**

| Variable | Where                                                                       | Type | Length / Display Format | Controlled Terms or Format | Origin      | Derivation/Comment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------|-----------------------------------------------------------------------------|------|-------------------------|----------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AVALC    | <a href="#">PARAMCD</a><br>NE<br>SCLINOUT                                   | text | 53                      |                            | Predecessor |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AVALC    | <a href="#">PARAMCD</a><br>EQ<br>SCLINOUT<br>(Sensitivity Clinical Outcome) | text | 16                      |                            | Derived     | All the core symptoms of cUTI (i.e., resolution of dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain) used for Sensitivity Clinical Outcome (i.e. SCLINOUT) derivation as follows: if resolution or improvement of all the core baseline symptoms at TOC then 'CLINICAL CURE', if no resolution or improvement of some core baseline symptoms at TOC then 'CLINICAL FAILURE', and if any core symptoms either at baseline or at TOC are missing then 'INDETERMINATE' assigned. Values were adjusted in the following cases: 1. After receiving the prohibited medication, sensitivity clinical outcomes replaced with "CLINICAL FAILURE" regardless of assessment in CRF. 2. For the missing at TOC visit, LOCF applied, i.e. if the last available AVALC on or after EOT (including 'Not Windowed' visits) is 'CLINICAL FAILURE', 'CLINICAL FAILURE' carried over; otherwise, 'INDETERMINATE' assigned. |

## Easy Example

This date is used for per-protocol record-level exclusion for month 24 period. Take the minimum date from following scenarios.

- the investigational product not matching the subject's randomized treatment group: set to the earliest date of wrong IP dosing during double-blind period (WTR01DTC)
- proscribed therapy on study: [dv.DVSTDTC](#) where [dv.DVSCATCD](#)='XM' and [\(AP01SDTC<=dv.DVSTDTC<= AP02EDTC or dv.DVSTDTC is missing\)](#)
- if subject received < 9 dose in DB period (select records from EX where EXTRT  
 $\wedge$ ='INVESTIGATIONAL PRODUCT' and EXDOSE >   ):
  - [dv.DVSTDTC](#) if [dv.DVSCATCD](#)='502' ;
  - else Min of (AP01EDT, AP01SDT + round ((4 + # of doses received in DB period - 1)\*30.4375))
- if AP02SDTC not missing and missed >=1 dose of Investigational Product:
  - if missing INVESTIGATIONAL PRODUCT at MONTH 12 from ex SDTM domain, then [PPPM24DTC](#)=[min](#)(365+ARFSTDT-1, AP02EDT);
  - else if missing INVESTIGATIONAL PRODUCT at MONTH 18 from ex SDTM domain, then [PPM24DTC](#)=[min](#)(548+ARFSTDT-1, AP02EDT);

## Other Views of Derivation is Helpful

|          |                                   |         |     |                                                                 |                                                                                                                                                                           |
|----------|-----------------------------------|---------|-----|-----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AVAL     | Analysis Value                    | integer | 8   |                                                                 | Derived:<br>Please see detail in the section of ADTTE_info of document 'additional-derivations'.<br>Additional Derivations ( <a href="#">additional-derivations.pdf</a> ) |
| EVENT    | Free of Sign or Symptom of ABSSSI | text    | 2   | ["Y" = "Yes"]<br><Y Response Only>                              | Derived:<br>If subject has first confirmed none of specified sign/symptom of ABSSSI post treatment before end of study, then EVENT="Y"                                    |
| EVNTDESC | Event or Censoring Description    | text    | 100 |                                                                 | Derived:<br>Please see detail in the section of ADTTE_info of document 'additional-derivations'.<br>Additional Derivations ( <a href="#">additional-derivations.pdf</a> ) |
| CNSR     | Censor                            | integer | 8   |                                                                 | Derived:<br>Please see detail in the section of ADTTE_info of document 'additional-derivations'.<br>Additional Derivations ( <a href="#">additional-derivations.pdf</a> ) |
| TRTP     | Planned Treatment                 | text    | 50  | ["Iclaprim", "Vancomycin"]<br><Planned Treatment for Period 01> | Derived:<br>Set to ADSL.TRT01P                                                                                                                                            |
| TRTPN    | Planned Treatment (N)             | integer |     |                                                                 |                                                                                                                                                                           |
| TRTA     | Actual Treatment                  | text    |     |                                                                 |                                                                                                                                                                           |
| TRTAN    | Actual Treatment (N)              | integer |     |                                                                 |                                                                                                                                                                           |
| RANDDT   | Date of Randomization             | integer |     |                                                                 |                                                                                                                                                                           |
| BASEC    | Baseline Value (C)                | text    |     |                                                                 |                                                                                                                                                                           |



| PARAMN | PARAM                                                | PARAMCD | PARCAT2 | AVAL                                          | EVNTDESC                                                                                                                                                                                                                                      | CNSR                                                                                                                                                                                                                    | ADT                                                                                                                                                                                                                                                                                                               |
|--------|------------------------------------------------------|---------|---------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1      | Time to Resolution of Tenderness to palpation (Days) | TRTEN   | Signs   | (ADT - adsl.RANDDT + 1) If AVAL<0 then AVAL=1 | if EVENT="Y" then EVNTDESC="Free of Tenderness to palpation";<br><br>if EVENT=missing, then the last day recorded available sign/symptom on eCRF is used as censoring day.<br>EVNTDESC="Censored - No Resolution of Tenderness to palpation". | CNSR=1 if EVNTDESC in ('Censored - XXXXX')<br><br>CNSR=0 if EVNTDESC="Free of XXXXX";<br><br>If subject did have "None" at baseline or no baseline record then EVENT="Null", CNSR=1 if EVNTDESC in ('Censored - XXXXX') | If subject had first confirmed free of this sign then this ADT is equal to QS.QSDTC.<br><br>Else if no baseline or no post-baseline sign of ABSSSI then ADT=ADSL.RANDDT.<br><br>Else if no resolution of this sign until End of Study then, the last day recorded available sign/symptom on eCRF is equal to ADT. |
| 2      | Time to Resolution of Erythema (Days)                | TRERY   | Signs   | (ADT - adsl.RANDDT + 1) If AVAL<0 then AVAL=1 | if EVENT="Y" then EVNTDESC="Free of Erythema";<br><br>if EVENT=missing, then the last day recorded available sign/symptom on eCRF is used as censoring day.<br>EVNTDESC="Censored - No Resolution of Erythema".                               | CNSR=1 if EVNTDESC in ('Censored - XXXXX')<br><br>CNSR=0 if EVNTDESC="Free of XXXXX";<br><br>If subject did have "None" at baseline or no baseline record then EVENT="Null", CNSR=1 if EVNTDESC in ('Censored - XXXXX') | If subject had first confirmed free of this sign then this ADT is equal to QS.QSDTC.<br><br>Else if no baseline or no post-baseline sign of ABSSSI then ADT=ADSL.RANDDT.<br><br>Else if no resolution of this sign until End of Study then, the last day recorded available sign/symptom on eCRF is equal to ADT. |

## Difficult Submissions: Missing or Inadequate Programs

|                                  |                               | Difficult Submissions | Easy Submissions |
|----------------------------------|-------------------------------|-----------------------|------------------|
| Submissions Reviewed             |                               | 17                    | 25               |
| Programs Submitted               |                               |                       |                  |
|                                  | Both CSR Results and Dataset  | 7 (41%)               | 21 (84%)         |
|                                  | Either CSR Results or Dataset | 3 (18%)               | 4 (16%)          |
|                                  | No Programs                   | 7 (41%)               | 0 (0%)           |
| Information Request for Programs |                               | 16 (94%)              | 5 (20%)          |

# Common Issues with Programs

- Missing macros and programs
- Programs too complex to understand
- Program steps not annotated

# Best Practices: Programs Submission

- Follow all TCG recommendations re submission of programs
- Program header
  - ID software name / version / platform
  - Define important variables and input datasets
  - For dataset programs, include run order
- Program body
  - Annotate important programming steps
  - Minimize use of complex macros to create key parameters or results
  - One study per program, e.g., no “if study = ...”
  - Output programs should have minimal data manipulation

# Survey Results: Analysis Datasets

|                   |                                 | Difficult Submissions | Easy Submissions |
|-------------------|---------------------------------|-----------------------|------------------|
| Surveys Completed |                                 | 18                    | 25               |
| Datasets          |                                 |                       |                  |
|                   | Tracing data to SDTM            | 6 (33%)               | 18 (72%)         |
|                   | Validating sponsor results      | 8 (44%)               | 22 (88%)         |
|                   | Performing sensitivity analysis | 5 (28%)               | 17 (68%)         |

# Easy Submission: Intermediate Event Dataset Can Support Traceability

ADINTEV - Intermediate Event Dataset

| USUBJID | PARAM                               | ADY | ADT        | Traceability back to SDTM |          |        | Traceability to TTE |
|---------|-------------------------------------|-----|------------|---------------------------|----------|--------|---------------------|
|         |                                     |     |            | SRCDOM                    | SRCVAR   | SRCSEQ | ASEQ                |
| 1001    | Date of Randomization               | 1   | 5/3/2016   | ADSL                      | RANDDT   |        | 1                   |
| 1001    | Date of Progression Per BICR        | 84  | 7/25/2016  | RS                        | RELPSDTC | 912    | 2                   |
| 1001    | Date of Last Non-PD Assess per BICR | 37  | 6/8/2016   | RS                        | RSDTC    | 915    | 3                   |
| 1001    | Date of Progression Per INV         | 37  | 6/8/2016   | RS                        | RSDTC    | 649    | 4                   |
| 1001    | Date of Death                       | 195 | 11/13/2016 | DD                        | DDDTTC   | 672    | 5                   |
| 1001    | Date of Treatment Discontinuation   | 151 | 9/30/2016  | ADSL                      | TR01EDT  |        | 6                   |

ADTTE - Final TTE

| USUBJID | PARAM                       | AVAL | STARTDT  | ADT        | EVNTDESC    | Traceability back to ADINTEV |        |        |
|---------|-----------------------------|------|----------|------------|-------------|------------------------------|--------|--------|
|         |                             |      |          |            |             | SRCDOM                       | SRCVAR | SRCSEQ |
| 1001    | PFS (INV Primary Analysis)  | 37   | 5/3/2016 | 6/8/2016   | PROGRESSION | ADINTEV                      | ADY    | 4      |
| 1001    | PFS (BICR Primary Analysis) | 84   | 5/3/2016 | 7/25/2016  | PROGRESSION | ADINTEV                      | ADY    | 2      |
| 1001    | Overall Survival            | 195  | 5/3/2016 | 11/13/2016 | DEATH       | ADINTEV                      | ADY    | 5      |

## Difficult Submissions: Submit **All** Data

- Important baseline information needed in subject-level dataset
- PK/PD datasets
- Reference datasets used in programming
- Source randomization or adjudication data
- Intermediate analysis datasets
- Datasets used for
  - pharmacogenomic/genetic analyses
  - FDA requested analyses prior to submission

## Difficult Submissions: Dataset Issues

- Imputations performed but DTYPE not set
- No flags to indicate records or subjects to select
- No key variables for selecting unique rows
- Unmanageable dataset sizes
- Dataset complexity prevented results replication

# Summary

- ADRG should be clear, complete and concise.
- Complete descriptions and logic should be included in the define.xml.
- Programs should follow good programming practice.
- Intermediate datasets can support traceability.
- All datasets used for analyses should be provided.

