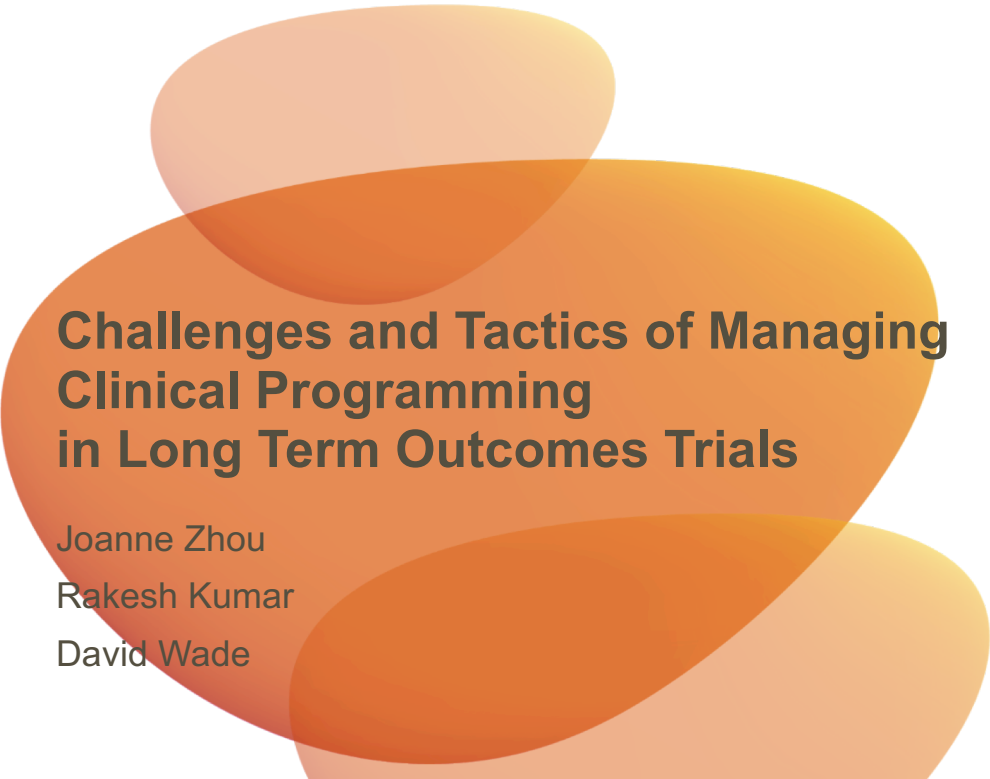




# **Challenges and Tactics of Managing Clinical Programming in Long Term Outcomes Trials**

Joanne Zhou

Rakesh Kumar

David Wade

- 
- **Introduction**
  - **Managing programming deliverables in a long term cardiovascular trial setting**
    - **Evolving data standard requirements**
    - **Managing the quality of sponsor study records**
    - **Considerations for dictionary version updates**
  - **Specialized dataset requirements for cv outcomes trials**
  - **Maintaining team resiliency**
  - **Interims and futility analyses - strategy for applying resources**
-

# Long Duration of the Study



## Challenge: Evolving Data standards

### Solutions:

- Pick the latest and the greatest
- Establish early and strong communications with the regulatory agency with respect to the selection of data standards
- Keep informed of the changing and future version requirements
- Engage with the regulator in proactive negotiations for any exemptions which may arise unavoidably

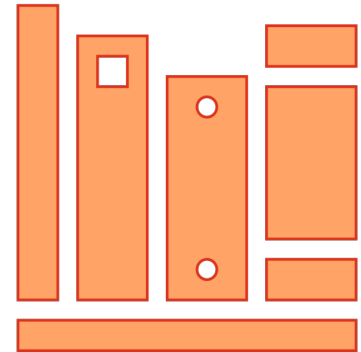
CDR Data Standards Catalog v3.0 (04-20-2010) - Supported and Required Standards

For full description of column headings, see Instr. & Column Descriptions tab

| Data Exchange Standard     | Supported Implementation Guide Version | FDA Center(s) | Date Support Begins (MM/DD/YYYY) | Date Support Ends (MM/DD/YYYY)   | Date Requirements Begins (MM/DD/YYYY)              |
|----------------------------|----------------------------------------|---------------|----------------------------------|----------------------------------|----------------------------------------------------|
| SOTM                       | 3.1.2                                  | CDER, CBER    | 10/30/2009                       | 03/15/2019 [1]<br>03/15/2020 [2] | 12/17/2016 [1]<br>12/17/2017 [2]                   |
| SOTM                       | Version 3.1.2 Amendment 1              | CDER, CBER    | 08/07/2013                       | 03/15/2019 [1]<br>03/15/2020 [2] | 12/17/2016 [1]<br>12/17/2017 [2]                   |
| SOTM                       | 3.1.3                                  | CDER, CBER    | 12/01/2012                       |                                  | 12/17/2016 [1]<br>12/17/2017 [2]                   |
| SOTM                       | 3.2                                    | CDER, CBER    | 08/17/2015                       |                                  | 03/15/2018 [1]<br>03/15/2019 [2]                   |
| Analysis Data Model (ADaM) | 1.0                                    | CDER, CBER    | Ongoing                          | 03/15/2019 [1]<br>03/15/2020 [2] | 12/17/2016 [1]<br>12/17/2017 [2]<br>03/15/2019 [1] |

## Challenge: Managing the Quality of Sponsor Study Records

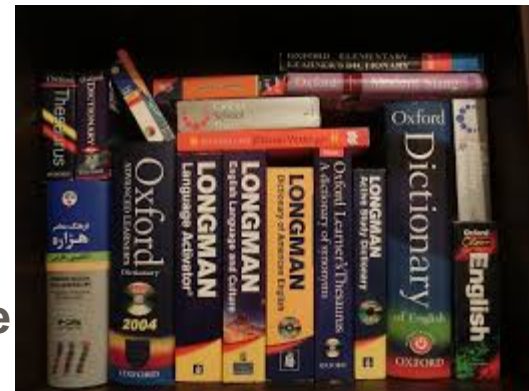
**Solution: Maintain a high quality eTMF periodic review plan. Identify clearly what is required and who is responsible?**



## Challenge: Dictionary version updates

### Solutions:

- Plan to update Terms of Interest (TOIs) throughout the life cycle of the project
- Develop programming tools for dictionary compare
- Develop a communication strategy is in accordance with good pharmacovigilance practices (GVP) in case a previously rarer or undetected event appears to be occurring at a higher rate because of evolving sensitivity of SMQs



**Challenge: Specialized CDISC datasets – SDTMs and ADaM**

**Solutions:**

- **Educate the study team of the TAUG-CV ASAP in the study conduct to enable the electronic data capture system to be designed proactively to support TAUG-CV implementation**
  
- **TAUG-CV introduces a number of new important SDTM variables for separating the investigator and adjudication data.**
  - EVAL**
  - EVALID**
  - ACPTFL**

---

**Challenge: Specialized CDISC datasets – SDTMs and ADaM**

**Solution:**

- **Develop custom ADaM standards**

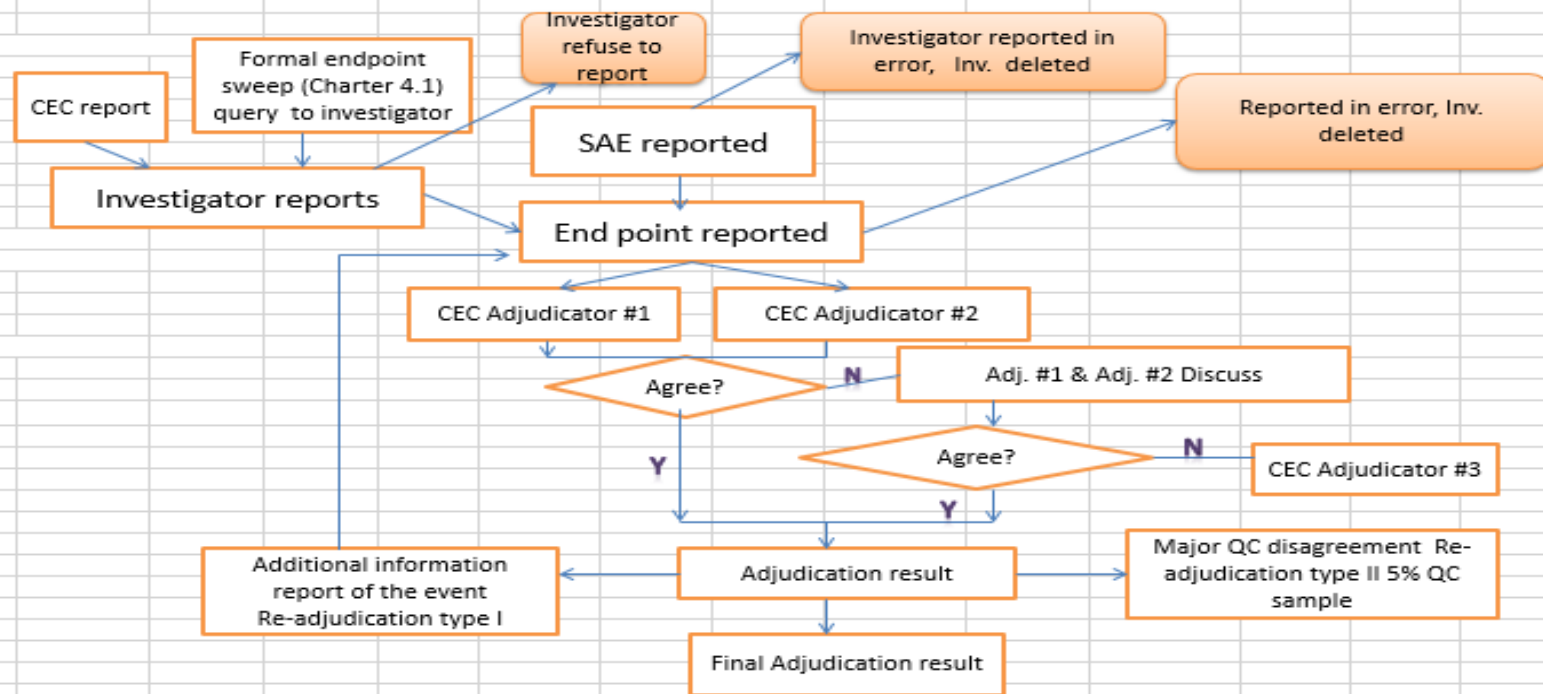
- **ADEVENT dataset in BDS data structure**

- Joanne Z, Rakesh K, David W. Developing ADaM Dataset for Cardiovascular Outcome Studies. 2017. Available at:

- <https://www.lexjansen.com/pharmasug/2017/PO/PharmaSUG-2017-PO13.pdf>

- **ADTTE**

## Challenge: Reviewer Level Dataset –CEC Process



## **Challenge: Reviewer Level Dataset**

### **Solutions:**

- **Communicate early with the regulatory reviewers to plan for submission products to support this need**
  
- **Design and submission of diagnostic datasets to address FDA's concern**
  - **NDA Submissions: Red Flags for FDA (Hicks, 2015)**

# Specialized Data Requirement

## Reviewer Level Dataset – Example



| Subjid | Re-adj.? | Reason for re-adj. | Unique event number | AE ref. ID | Event type | Event trigger | Inv. -CEC conc. | Event sweep type | Adj.      | Adj. Results |
|--------|----------|--------------------|---------------------|------------|------------|---------------|-----------------|------------------|-----------|--------------|
| 3      | N        |                    | 102                 | 3.001      | MI         | Inv.          | Yes             | none             | Dr. A     | MI           |
| 3      | N        |                    | 102                 | 3.001      | MI         | Inv.          | No              | none             | Dr. B     | not MI       |
| 3      | N        |                    | 102                 | 3.001      | MI         | Inv.          | No              | none             | Dr. A & B | not MI       |
| 3      | Y        | Addt. Info.        | 102                 | 3.001      | MI         | Inv.          | Yes             | none             | Dr. B     | MI           |
| 3      | Y        | Addt. Info.        | 102                 | 3.001      | MI         | Inv.          | Yes             | none             | DR. A     | MI           |
| 3      | Y        | Addt. Info.        | 102                 | 3.001      | MI         | Inv.          | Yes             | none             | Dr. A & B | MI           |

# Specialized Data Requirement

## Reviewer Level Dataset –Controlled Terminology

---



### Challenge: Reviewer Level Dataset

#### Event sweep type:

- AE
- Procedures/Hospitalizations
- Troponin/CKMB
- ECG
- SAE narrative
- TIMI and MM review SAE in real time
- Source data R/V

#### Reason for Re-adjudication

- Additional information
- Due to findings from QC (in the 5% QC sample)

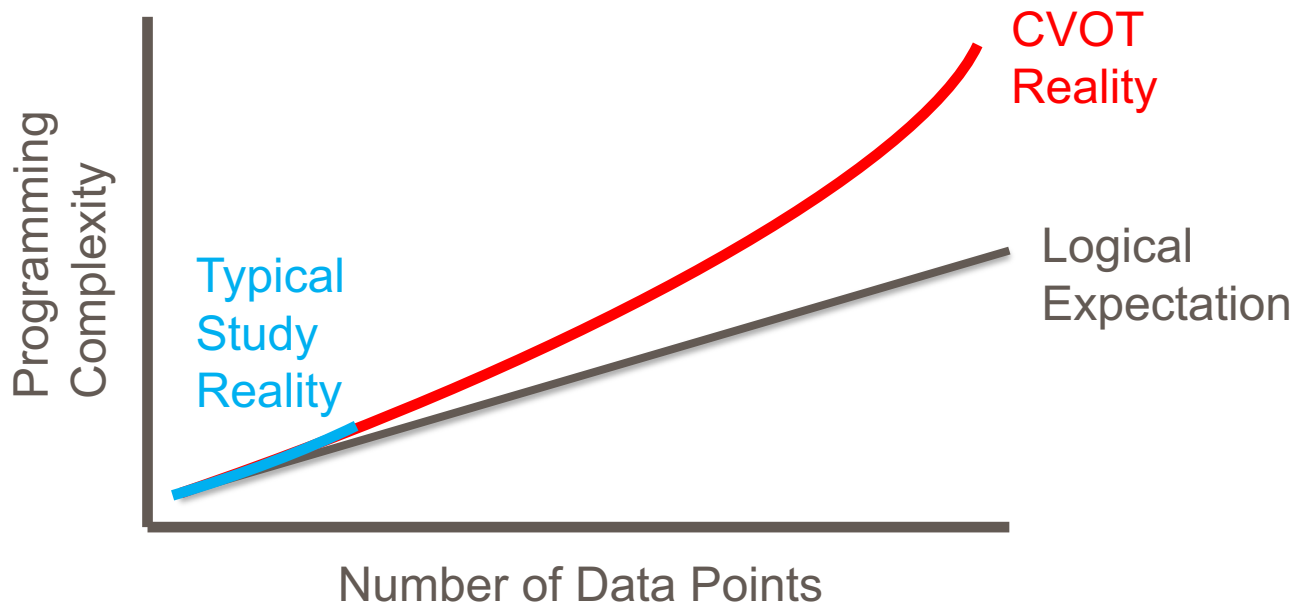
#### Event trigger

- Investigator Initiates
- CEC initiates

## **Challenge: Long periods of intensive work pressure**

- **Health impacts and stress on staff**
- **Delayed careers (promotion opportunities)**
- **Normal staff loss over longer time periods**
- **Difficult to retain team knowledge in complex areas**
- **Natural tendency to under-report effort hours spent**

Challenge: Programming complexity increases in a non-linear rate with the number of data points collected.



**Challenge: Long periods of intensive work pressure**

**Solutions:**

- **Health and stress resiliency programs**
- **Proactive career management**
- **Succession planning**
- **Lattice resourcing**
- **Avoidance of resource recording bias**

## Classic Matrix Management

|                  | Programmer A                | Programmer B                | Programmer C                |
|------------------|-----------------------------|-----------------------------|-----------------------------|
| Outcomes Trial 1 | <b>Lead Programmer Role</b> | Supporting Programmer Role  | Supporting Programmer Role  |
| Outcomes Trial 2 | Supporting Programmer Role  | <b>Lead Programmer Role</b> | Supporting Programmer Role  |
| Outcomes Trial 3 | Supporting Programmer Role  | Supporting Programmer Role  | <b>Lead Programmer Role</b> |

- **Pro-active career management for all team members**
- **Allow for career development and maintain continuity of technical roles**
- **Focus on shared goals across studies**

## Lattice Resourcing

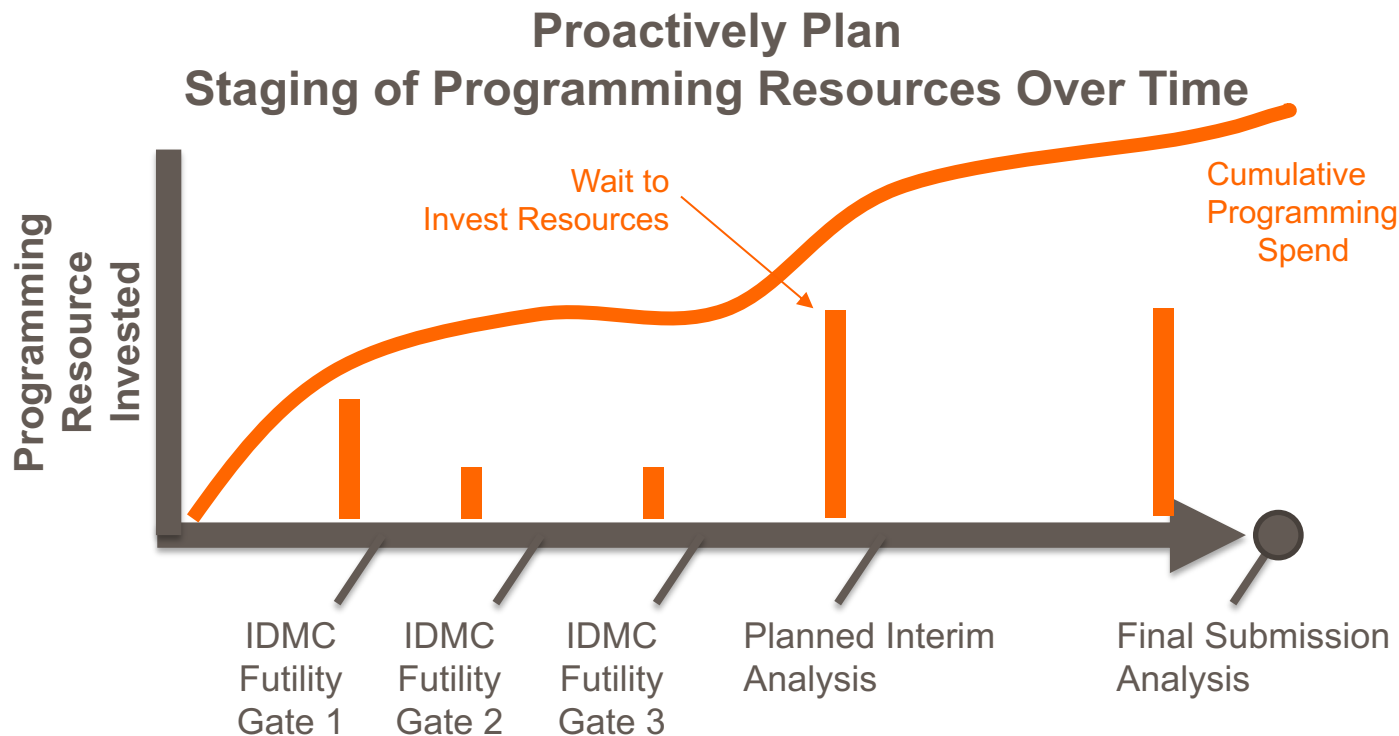
|                  | Prog. A | Prog. B | Prog. C | Prog. D |
|------------------|---------|---------|---------|---------|
| Specialty Task 1 | Lead    | Co-Lead |         |         |
| Specialty Task 2 |         | Lead    | Co-Lead |         |
| Specialty Task 3 |         |         | Lead    | Co-Lead |
| Specialty Task 4 | Co-Lead |         |         | Lead    |

- Pro-active planning of within-study assignments
- Ensure each programmer has a reasonable work load/area of expertise
- Ensure specialty knowledge is covered in case of a loss of a key team member

## Application of Resources Over Time

**Challenge:** Minimize the risk of resource waste on a failed development program, and ensure timely deliverables for successful development program

**Solution:** Stage application of resources in a carefully planned timeline as each development risk is discharged



Three overlapping, rounded, organic shapes in shades of orange and yellow, creating a layered, abstract background for the text.

**Thank you**