Data Monitoring Committees: An Independent Group Safeguarding Patient Interests

Bill Coar
Axio, A Cytel Company

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Outline

- Requirement for safety monitoring
- Data Monitoring Committee (DMC)
- Operational Models
- DMC reports
- Leveraging Data Standards and Reporting
- Essential records
- Concluding Thoughts

Requirement for Safety Monitoring

- All clinical trials require safety monitoring
  - ICH E6 Good Clinical Practice
  - ICH Guideline for Clinical Safety Data
- Not ethical to wait for the primary analysis to assess patient safety
- Important data should be monitored throughout the course of the study to allow appropriate course correction if unforeseen challenges arise

Preliminary Definitions

- **Sponsor**: Company conducting clinical trials
- **External CRO**: Vendor for Sponsor company performing DM and Statistics
- **Data Monitoring Committees**: Group of experts reviewing unblinded data to assess risk/benefit in order to protect patients and trial integrity
  - Independent data monitoring committee (IDMC), Data Safety Monitoring Board (DSMB), Data Safety Monitoring Committee (DSMC)
- **Statistical Analysis Data Center**: Vendor independent of the group performing DM and Statistics who is unblinded during the study to support DMCs
  - Independent CRO, Independent Data Analysis Center (IDAC), Independent Statistical Reporting Group (ISRG)

Data Monitoring Committee

- Group of 3-5 (**independent**) experts including a statistician
- Periodically review by-arm results based on interim data to make recommendations about the continuation of the trial
- Traditionally focus on safety
- Supported by Statistical Analysis Data Center
- Not all studies require a DMC
  - FDA: Use of Data Monitoring Committees in Clinical Trials

Data Monitoring Committee

- FDA: “All clinical trials require safety monitoring, but not all trials require monitoring by a (DMC)… We recommend sponsors consider using a DMC when:”
  - Large, long, randomized multi-center study
  - Primary endpoint for treatment is to prolong life or reduce major morbidity (or a seriously sick population even if a lesser endpoint used)
  - Fragile population (children, elderly, diminished capacity)
  - a priori safety concerns or possible serious toxicity
  - Highly favorable or unfavorable or futility could ethically require termination of study

Data Monitoring Committee

- Operate under a DMC Charter that describes
  - Responsibilities of the DMC, Sponsor, and SDAC
  - Confidentiality and CoI
  - Timing and conduct for open/closed sessions of meetings
  - Minutes and recommendations
  - General content of open and closed reports (TLFs)
  - Communication process

Data Monitoring Committee

- Landscape is changing
  - Assessment of early stopping for efficacy and/or futility
  - Evaluation of sample size increases
  - Make recommendations about pre-planned adaptations
- Electronic review of (static) TLFs
- Increased development of open-source technologies to facilitate dynamic review
  - Technology is advancing faster than DMC practices
- Desire to leverage industry standards for data and reporting

Data Monitoring Committee

- Different programming models exist for the open/closed report:
  - SDAC develops programs
  - External CRO develops programs on blinded data
  - Sponsor develops programs on blinded data
    - Unblinded run within SDAC
    - Unblinded run in restricted area in Sponsor system
- Quality control at all levels
- Communication is key across various vendors

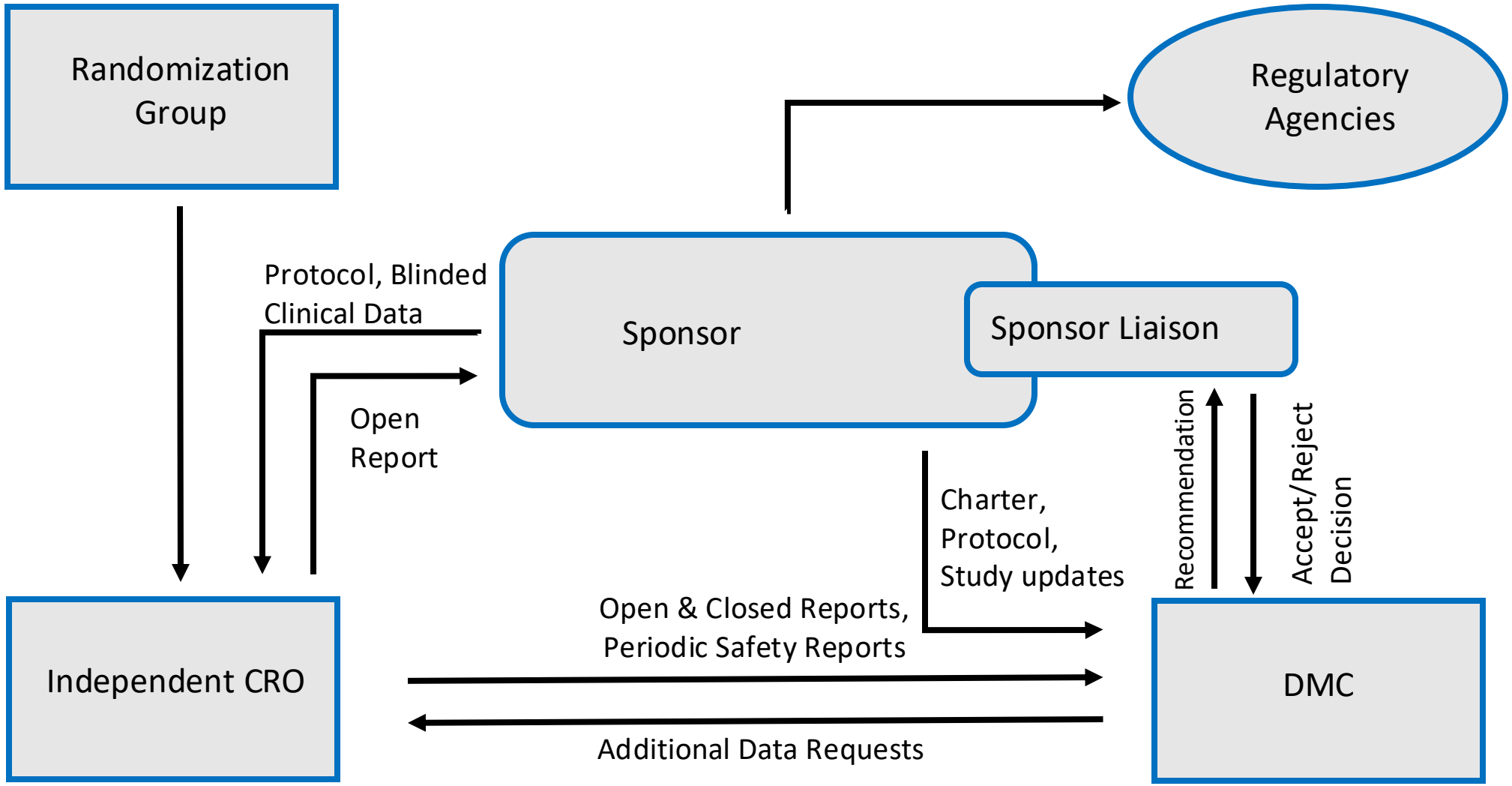
Blinded vs Unblinded

- Blinded/masked:
  - Data and/or output that is based on artificial randomization or no treatment information at all
  - Output summarized by only a total column
- Unblinded/unmasked:
  - Data and/or output that is based on true randomization
  - Output summarized by-arm that may include a total column
- Pseudo Blinded
  - Results are by-arm labeled Arm A /Arm B/etc
  - DMC is not initially aware of label assignments
  - Not best practice

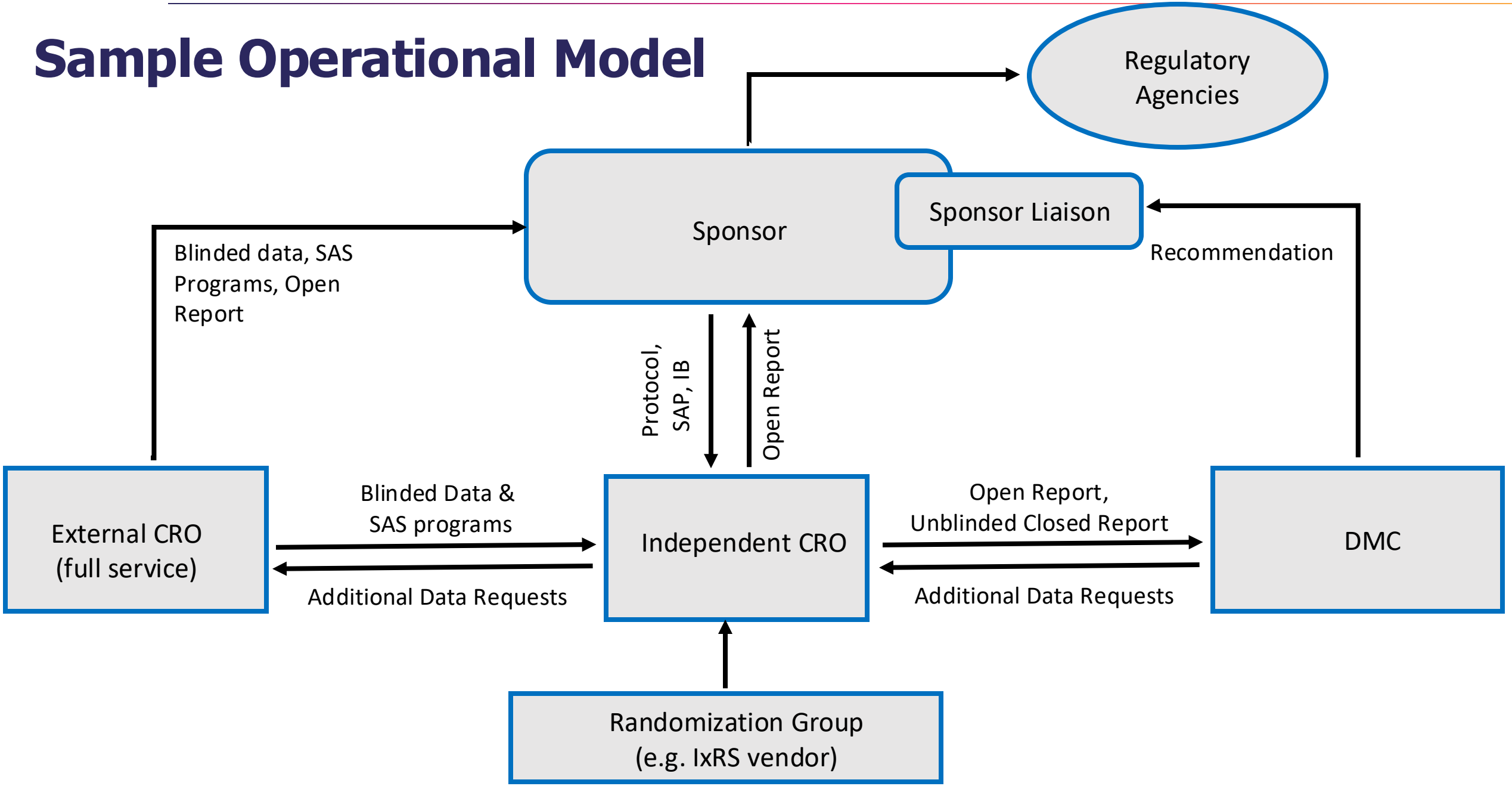
Open vs Closed Reports (TLFs)

- Open Report:
  - Historically a subset of outputs with **no by-arm** information
  - By-arm outputs based on fake randomization not advisable as an open report due to risk/confusion with DMC members
  - Available to the Sponsor and DMC
  - Discussed in the Open Session of a DMC meeting
- Closed Report:
  - Outputs by-arm
  - Available only to the DMC
  - Discussed only in the Closed Session of a DMC meeting

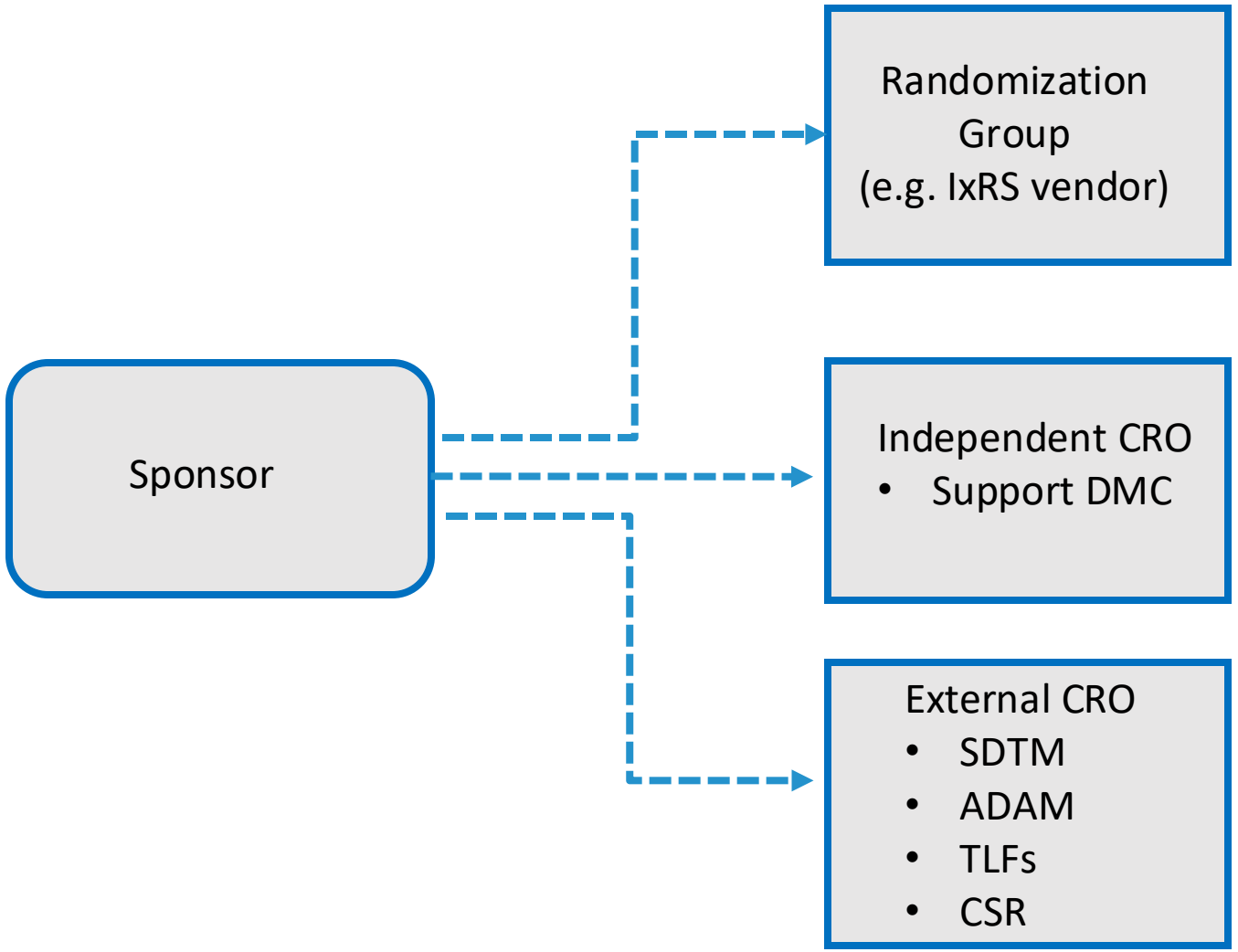
Data Monitoring Committee Flow Diagram



Sample Operational Model



Contractual Model



- No contractual link between vendors
- Communication plans between organizations are essential
- Desire find efficiencies within/between CRO

Cross-functional Collaboration

- Various vendors
  - Timing and expectations via data transfer agreements
- With Data Management
  - Data cleaning and query resolution
  - Transfers of randomization data
- With Statistics and Programming
  - Analysis rules for reporting using interim/sometimes erroneous data
- DMC
  - Timing to review DMC reports, meet, form recommendations
- Senior Management
  - Receives and decides action taken on recommendations

Meeting Preparation: A report to assess Risk/Benefit

- By-arm assessment without compromising trial integrity
- DMC Report
  - Usually in the form of tables, listings, and figure (TLF)
  - May have a written executive summary or detailed statistical report
- Standard safety data: AE, LB, VS, ECG
- Some form of efficacy
- Study drug exposure
- Trial conduct
  - Early discontinuations, and why?
  - Quality of data capture
  - Assessments per protocol

Meeting Preparation: Fit-for-Purpose DMC Report

Fit-for-Purpose

- ✓ Concise (200 pages) with hyperlinks and bookmarks
- ✓ Disposition
- ✓ Demographics/baseline characteristic
- ✓ Exposure – duration, dose modifications/delays and reasons
- ✓ TEAE/SAE/G3+TEAE/AESI
- ✓ Potentially clinically significant labs/vital signs/ecg
- ✓ Deaths
- ✓ Assessment of benefit
- ✓ Data quality/currentness
- ✓ Increased use of graphics
- ✓ Select listings

Not Fit-for-purpose

- ✗ 1000-5000k (or more) pages of output
- ✗ Pages of continuous statistics and categorical groups for exposure measures
- ✗ Continuous statistics across all visits for all labs and vital sign parameters
- ✗ Prior and concomitant medications
- ✗ All possible combinations of TEAEs by relationship
- ✗ Pages and pages and pages of all data

Meeting Preparation: Fit-for-Purpose DMC Report

- Concise with relevant information to make recommendation
- Remember the target audience
  - A DMC member has a few hours to review the data to form a recommendation
  - A Sponsor has weeks to review data to ensure data quality
- DMC can request additional data sometimes without knowledge of the study team
  - Important to understand how implement this with your programming model
- Always understand who is blinded and unblinded

DMC Meeting Conduct

- Open Session
  - Review of blinded/masked data
  - Sponsor, SDAC, DMC in attendance
- Closed Report
  - Review by-arm results to assess risk/benefit
  - SDAC, DMC in attendance
  - From recommendations about continuance of the study
- Documentation includes minutes/action items/recommendations

Subsequent DMC Meetings

- Most DMC meetings are iterative
  - Frequency specified in Charter
  - May consider enrollment rates, treatment duration, occurrence of safety signals, etc.
- Timelines often work backwards from a meeting date
- Views on data cleanliness vary widely among sponsor
- DMCs expectation is reasonably clean/reasonably complete data
  - Focus data cleaning efforts on more critical data (6-8 weeks prior)
  - Extract all available data (3-4 weeks prior)
  - Coding as complete as possible
- Programs almost always require updates

Subsequent DMC Meetings

- Contents can evolve over time
  - DMCs can request data w/o sponsor knowledge
- Specifications typically change throughout the course of a study
- Programs almost always require updates
- Quality Control measures may evolve to include comparisons against previous reports

Leveraging Data and Reporting Standards

- A fit-for-purpose DMC report is not simply a subset of CSR TLFs
- Data standards and reporting tools can be used, but…
  - DMCs may review data prior to SDTM/ADaM development
  - Early data is sparse
  - DMC report may include information that is irrelevant at the time of a locked database
  - Interim data can be incomplete and/or erroneous
  - Programming rules for interim data may differ due to interim nature of data
  - Programming tries to predict the future

Leveraging Data and Reporting Standards

- Using ADaM principles can allow for use of standard reporting macros even when the source is raw data
- Utilize code lists/controlled terminology if metadata is available early
- Recognize that the utility of an output may differ from the intended use of the reporting tool
  - Denominators by visit inherently vary with interim data
  - Missing data: truly missing, reported but not entered, not yet reported

Essential Records

- Charters are often required for protocol submission to regulatory agencies and/or IRB
- Closed session reports and minutes filed at the end of the study as essential records
  - Often remain at SDAC until primary analysis complete
- Recommendations, Action Items, Open reports and Open Session minutes stored in eTMF in real time

Conclusions

- DMCs can protect current and future patients by reviewing data to assess risk/benefit throughout the course of a study
- Independence helps protect trial integrity
- Various models exist to provide DMC with the ability to review data
- No one-size-fits all model
- Cross-functional collaboration is essential

Cytel

Thank You

William Coar, PhD| Senior Director, Biostatistics
Denver, Colorado, USA
T 720.750.8997 | M 970.219.8564
William.Coar@cytel.com | www.cytel.com