Statistically Speaking Lecture Series

Sponsored by the Biostatistics Collaboration Center

DSMBs: Doing Study Monitoring Better with Data and Safety Monitoring Boards

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February 6, 2025

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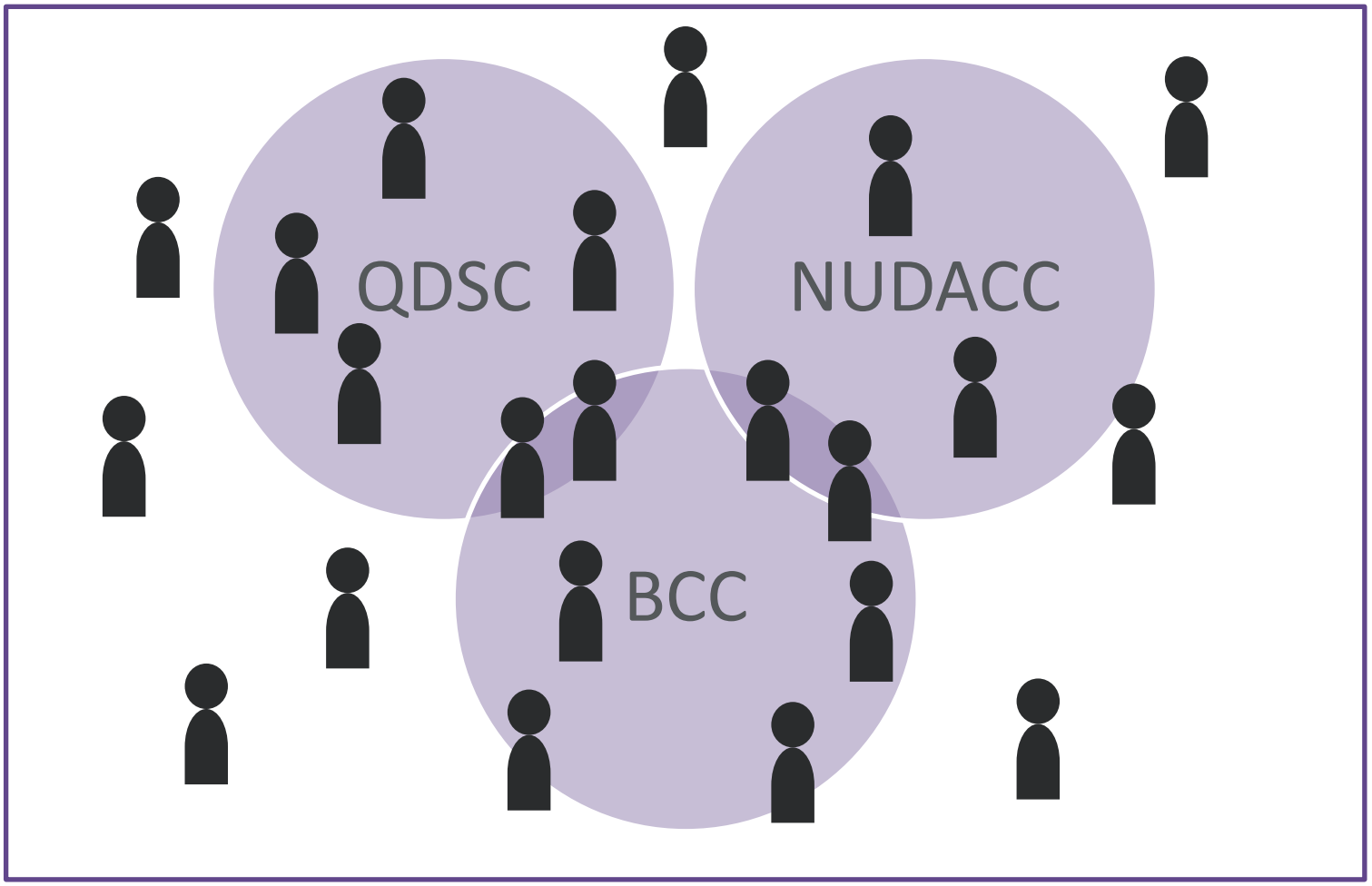
Before we begin…

Biostatistics at NU

Overview

Division of Biostatistics and Informatics (Chief: Denise Scholtens),
Department of Preventive Medicine (Chair: Mercedes Carnethon)



Biostatistics Centers and Cores

Overview

Northwestern Medicine | NUCATS Clinical and Translational Sciences Institute

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Biostatistics Collaboration Center (BCC)

- Supports **non-cancer** research at NU
- Initial 1-2 hour consultation subsidized by FSM Research Office
- Grant, Hourly
- https://www.feinberg.northwestern.edu/sites/bcc/

Quantitative Data Sciences Core (QDSC)

- Supports **cancer-related** research at NU
- Free to Lurie Cancer Center (LCC) members
- Grant
- https://www.cancer.northwestern.edu/research/shared-resources/quantitative-data-sciences.html

Northwestern University Data Analysis and Coordinating Center (NUDACC)

- Prospective, large **multicenter research**
- Comprehensive support (e.g., clinical monitoring, data analysis, project management)
- Grant
- https://www.feinberg.northwestern.edu/sites/nudacc/

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Disclaimer:

The views presented today are my own. They do not represent those of the statistical community nor those of Northwestern University at large.

I have no relevant conflicts of interest.

Goals for today

- Provide an **overview** of typical Data and Safety Monitoring Board (DSMB) processes
- Review **expectations** for those serving on DSMBs and those reporting to DSMBs
- Discuss statistical and trial **methodology relevant** to DSMBs
- Provide time for questions & answers / scenarios / tips / etc.

Background – What is a DSMB

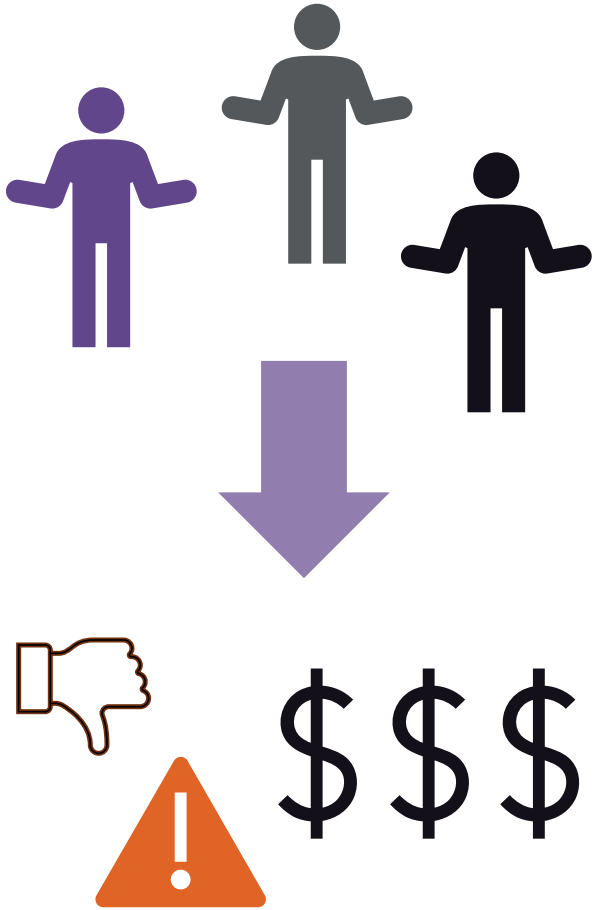
- Regarding the **naming conventions**
  - DMC = Data Monitoring Committee
  - DSMB = Data and Safety Monitoring Board
  - DSMC = Data and Safety Monitoring Committee
  - IDMC = Independent Data Monitoring Committee
  - OSMB = Observational Safety Monitoring Board
  - They are all essentially synonymous

- What is a DSMB?
  - A DSMB is an **independent group of experts** (and potentially patient representative[s]), **appointed by a sponsor/investigator** to **review accumulating clinical study data** on a regular basis.
  - They often play a crucial role in ensuring participant safety and general study integrity.

Background – Why all this talk about DSMBs?

In general, "DSMB" is a somewhat familiar term for those involved in clinical research, particularly those in clinical trials, BUT…

- Very few DSMB **members** receive formal training on how to be an effective DSMB member
- Very few **investigators** receive formal training on how to convene/report to a DSMB
- DSMBs are also **heterogeneous** (yet ubiquitous)
- Trial designs are also **increasingly complex**



***Plenty* of training materials, guides, templates exist, but their reach is limited**

My own story related to DSMB member service…

- Prior to coming to Northwestern, I had worked at a Contract Research Organization (CRO) for a couple of years
  - Large volume of trials, from phase I to phase III/IV
  - Much of my role involved **reporting to DSMBs**

Emmes

- Upon coming to Northwestern (2013), a colleague reached out about serving on a DSMB

Can I ask you a favor…would you serve on Dr. X's DSMB? I cannot as I am conflicted.

My first thought…I am not qualified

After speaking with my mentor + finding out more about it…

"Actually, you are likely among the most qualified here to serve on a DSMB, especially given your previous experience and general research interest and expertise."

After sitting in a few DSMB meetings + also getting my bearings as a reporting statistician to several DSMBs in an academic research setting…

- **I found myself very confused – both sitting on and reporting to DSMBs + I began to notice this pattern of issues…**

- **Lack of training**
- **Heterogeneity**
- **Study complexities**

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Overview of DSMBs and Processes

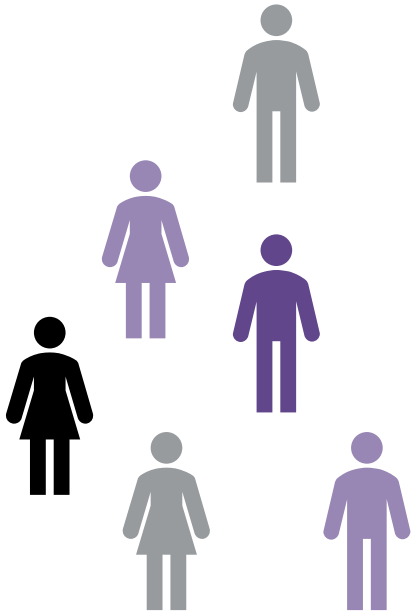
Introduction to DSMBs

- NOT necessarily legally required for all studies
  - prioritized for trials and, increasingly, for large-scale observational studies
  - sponsor or IRB may require

- **Required** for studies in **emergency** settings with **waiver of informed consent**

Introduction to DSMBs

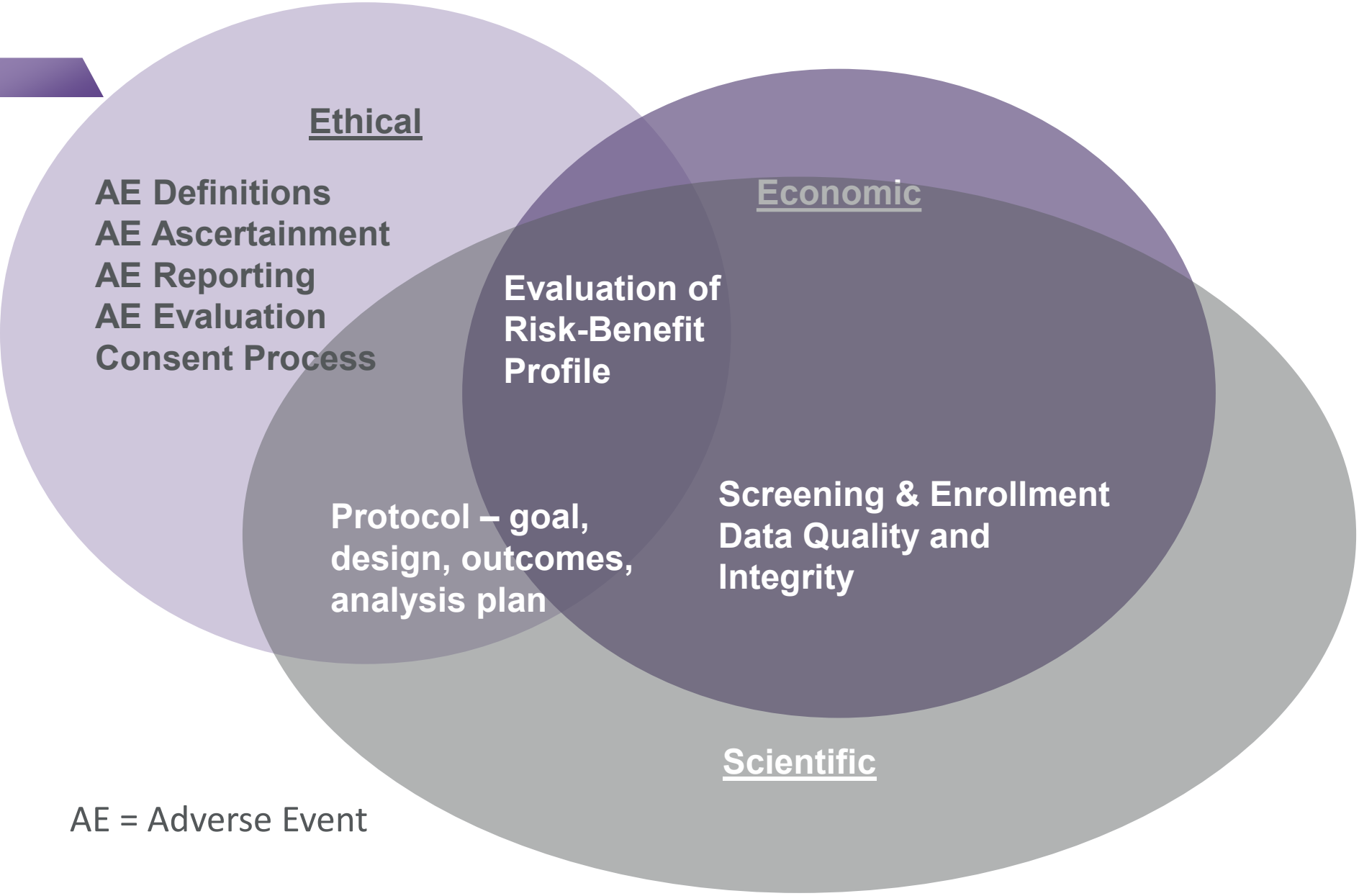
- Usually 3-5 total members (can be more)
  - **Clinical expert in relevant field(s)**
  - **Biostatistician**
  - Basic scientist
  - Regulatory specialist
  - Ethicist
  - Patient representative



- Important to ensure members **do not have conflicts of interest**: financial, clinical involvement, intellectual investment

Introduction to DSMBs

- DSMBs typically focus on **three** key domains in reviewing studies and providing **guidance**:
  - **Ethical** considerations – ensuring patient safety
  - **Scientific** aspects – monitoring conduct, ensuring sound design, operation, data integrity, analyses
  - **Economical** considerations – preventing resource waste
- These three domains are not necessarily mutually exclusive



AE = Adverse Event

DSMB Review Process

X X X X X X X X

Typically, prior to initiation - close in time to initial Institutional Review Board (IRB) review

- Interim review schedules may vary…
  - Usually at least yearly
  - Often guided by study milestones (e.g., 25%, 50%, etc. recruitment or endpoint goals)
  - Be prepared for ad hoc review: Serious Adverse Events (SAEs) occurrence, related events, blinding issues, conduct issues, etc.

Final review of study findings and reporting plans

DSMB Review Process – Meeting Format

Open Session → Closed Session → Executive Session → Debrief

- **All key parties** involved
- Review data in aggregate
- No unblinded data (if applicable)

DSMB Review Process – Meeting Format

Open Session → **Closed Session** → Executive Session → Debrief

- Just **DSMB** + **unblinded members** (usually statistician)
- Review data by study arm
- Sometimes still coded: “Arm A” vs. “Arm B” + identity of “A” and “B” revealed during, if needed
- Typically, not needed if blinding is not part of study design

DSMB Review Process – Meeting Format

Open Session → Closed Session → **Executive Session** → Debrief

- Just **DSMB** members
- Not always requested/required

DSMB Review Process – Meeting Format

Open Session → Closed Session → Executive Session → **Debrief**

- All key players, as needed
- Not always requested/required
- DSMB may use to communicate recommendations + summarize discussion

DSMB Reporting

- Study teams typically report two sets of information – blinded and unblinded
- Report format typically agreed upon with DSMB prior to study start
- Blinded or **open reports**: data in aggregate without any potential unblinding information
- Unblinded or **closed reports:** during closed session only, information stratified by treatment arm
- **Example report templates…**

DSMB Reporting – Open Report Example

- Presented during open session, often by principal investigator and/or study statistician
- Usually includes a table of contents, data cutoff date
- General summary of study status, updates on recruitment, retention, protocol changes, protocol (non)compliance →

XXX Study - DSMB Report Template

<Date>

Executive Summary

Report Overview

The purpose of this report is to review cumulative enrollment and safety data for the participants enrolled in XXX Study. The information below utilizes Protocol (Version XX; Date). The following report uses the current data pull (<Date>).

Study Site Status

- XX sites are actively enrolling participants

Enrollment Status

- XX Participants have been consented for this study
- XX Participants have been enrolled in this study

Participant Status

- XX Participants remain actively enrolled
- XX Participants completed the screening / baseline visit (visit 1)
- XX Participants completed the 6 month visit (visit 2)
- XX Participants completed the 12 month visit (visit 3)
- XX Participants completed the 18 month visit (visit 4)
- XX Participants completed the 24 month visit (visit 5)
- XX Participants completed the 30 month visit (visit 6)
- XX Participants completed the 36 month visit (visit 7 / exit)

Safety Summary

- XX adverse events (AEs) have occurred in XX participants
- XX serious adverse events (SAEs) have occurred in xx participants

Protocol Deviations

- XX protocol deviations have been reported to date

DSMB Reporting – Open Report Example

- A protocol synopsis is really helpful to remind the DSMB members about the general study design and objectives
- Sometimes the whole protocol + other supporting documents are included in a "packet" to the DSMB

Protocol Synopsis

Summary

The XXXX Study is a XXXX study designed to …. Visits will include collection of questionnaire data and the in-person visits will include questionnaires, physical exams, imaging, and sample collection.

Primary Objective

To evaluate XXX in YYYY…..

Primary Outcome

Time-to-XXXX

Population

The study will include participants with cirrhosis of the liver. A total sample size of 1200 is planned.

Inclusion Criteria

- Criterion 1
- Criterion 2
- …

Exclusion Criteria

- Criterion 1
- Criterion 2
- …

Number of Sites

XX Clinical Centers in the United States

Scientific and Data Coordination Center

XXXX

Study Duration

XX years

Participant Participation Duration

XX years

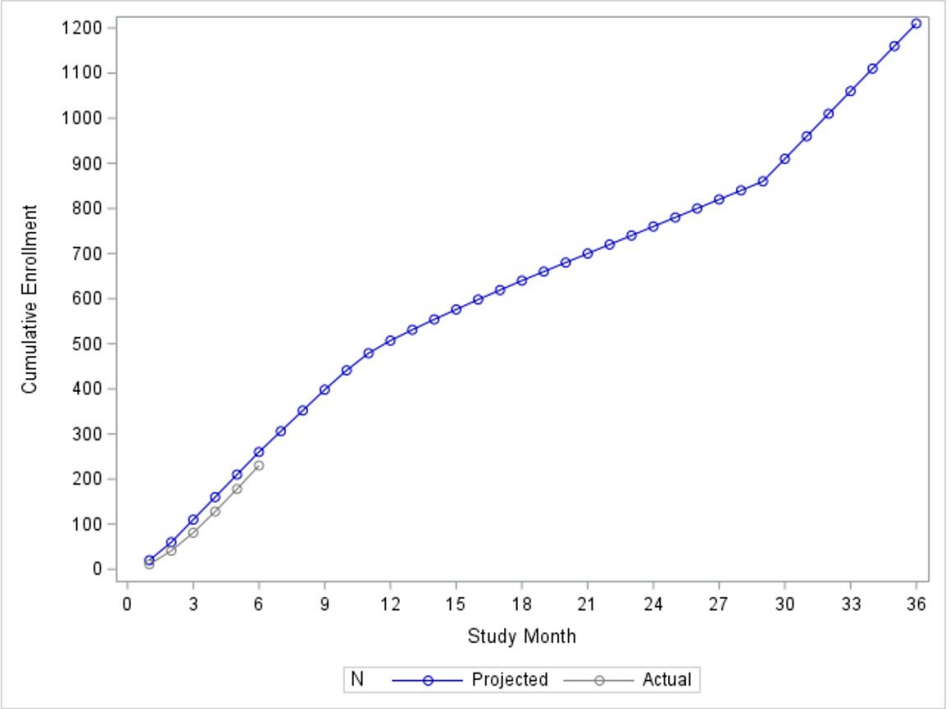
DSMB Reporting – Open Report Example

Enrollment Status

Table 1. Enrollment Summary

Clinical Center	Total Enrolled	Date Site Released to Begin Enrollment	Date of First Enrollment	Days Since Last Enrollment	Monthly Enrollment Rate
Overall	N		XX-XX-XX	XX	XX
Site 1		XX-XX-XX			
Site 2					
…					

Figure 1. Projected versus Actual Enrollment



- Data reports group all study participants together
- Typically limited to baseline clinical and demographic summaries, study procedure completion rates, data quality metrics (see next couple of slides for examples)
- Outcome summaries are not generally included
- Safety events presented **blinded** to treatment allocation

More example table shells..

Participant Status

Table 2a Participant Disposition

Clinical Center	Total Enrolled	Completed Study	Actively Enrolled	Lost to Follow-up	Withdrew Consent	Died
Overall	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Site 1						
Site 2						
…						

Table 2b Visit Completion

Clinical Center	Visit 1			Visit 2			Visit 3		
	Eligible	Completed	Missed	Eligible	Completed	Missed	Eligible	Completed	Missed
Overall	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Site 1									
Site 2									
…									

Additional key tables/summarizations: demographics, clinical characteristics, safety data

DSMB Reporting

- Study teams typically report two sets of information – blinded and unblinded
- Report format typically agreed upon with DSMB prior to study start
- Blinded or **open reports**: data in aggregate without any potential unblinding information (previous)
- Unblinded or **closed reports:** during closed session only, information stratified by treatment arm

DSMB Review Process – Meeting Format

Open Session → **Closed Session** → Executive Session → Debrief

- Just **DSMB** + **unblinded members** (usually statistician)
- Similar look/feel to open report, but main difference is inclusion of a "study arm" variable in report + can include outcome summaries
- Sometimes still coded: "Arm A" vs. "Arm B" + identity of "A" and "B" revealed during, if needed
- Can include interim analyses (if applicable) as well as additional information requested by DSMB

DSMB Report Timelines

To allow adequate time for review yet with most current data possible, reporting is often on a timeline negotiated between DSMB and study team

Keep the timeline in mind…

1. Timing of **database freeze** (export/cutoff date)
2. Time to **generate, review, iterate** the report (internally / with study team)
   a. Analysis quality control requirements
   b. Are there added/unmonitored data to include
3. Distribution of report(s) with a defined **review period for DSMB**

DSMB Report Delivery

- Maintaining confidentiality of DSMB reports requires a partnership between DSMB and study team

- Documents may be **protected** in multiple ways
  - Password protected
  - Restricted from download
  - Restricted from printing
  - Issued in numbered paper copy and returned after the meeting

- DSMB members should adjust work habits to accommodate need for confidentiality…

Documenting DSMB Deliberations

- It varies.
- During the **open session**, the study team is typically present and responsible for documenting deliberations.
- During the **closed session**, the unblinded study statistician may be delegated the task of minutes and sometimes preparing DSMB recommendations. Sometimes this is a designee from the sponsor instead.
- Documentation of deliberations and recommendations may fall to the DSMB Chair for **Executive Sessions** or as otherwise agreed.

DSMB Recommendations

- Ultimately, the DSMB provides **recommendations** to the study team, sponsor, etc.

- They usually take one of the following forms:
  - **Continue with the protocol as planned** with no modifications – most common
  - Continue with the protocol with **some suggested modifications** – still common
  - **Halt enrollment until further notice** / more information can be gathered – less common
  - **Study termination** – least common

Communicating DSMB Recommendations

- The **DSMB Charter** will often determine how the DSMB communicates its recommendations to the study team.
  - Verbal summary immediately following the closed session
  - Written summary within a defined time period

- If patient safety or study integrity are at risk, communication should be swift.

- The **study team communicates recommendations to the IRB.**

- If the study investigators disagree with DSMB recommendations, they must report this to the IRB.

Why would the DSMB recommending stopping the study?

- Unequivocal **evidence of treatment benefit or harm** (usually based on **statistical tools**)
- Unexpected, unacceptable **side effects**
- **No emerging trends**/no reasonable chance of demonstrating benefit (**futility**; usually based on **statistical tools**)
- **Overall progress/conduct of trial** – not enough patients at a sufficient rate, lack of compliance in large numbers, poor follow-up, poor data quality
- Based on **external information** – other studies answer questions, other studies or data illustrate risks
- **Caution – do not use statistical tools as "law"; they are tools (i.e., guidelines)**

Side note: for those interested in interim analysis methods in clinical trials…

Journal of Clinical and Translational Science

www.cambridge.org/cts

Clinical Research Review Article

Cite this article: Ciolino JD, Kaizer AM, and Bonner LB. Guidance on interim analysis methods in clinical trials. *Journal of Clinical and Translational Science* **7**: e124, 1–9. doi: 10.1017/cts.2023.552

Received: 25 January 2023
Revised: 8 May 2023
Accepted: 9 May 2023

Keywords:
Interim analysis; clinical trials; randomized controlled trial; guidance; efficacy; futility

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Guidance on interim analysis methods in clinical trials

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Abstract

Interim analyses in clinical trials can take on a multitude of forms. They are often used to guide Data and Safety Monitoring Board (DSMB) recommendations to study teams regarding recruitment targets for large, later-phase clinical trials. As collaborative biostatisticians working and teaching in multiple fields of research and across a broad array of trial phases, we note the large heterogeneity and confusion surrounding interim analyses in clinical trials. Thus, in this paper, we aim to provide a general overview and guidance on interim analyses for a nonstatistical audience. We explain each of the following types of interim analyses: efficacy, futility, safety, and sample size re-estimation, and we provide the reader with reasoning, examples, and implications for each. We emphasize that while the types of interim analyses employed may differ depending on the nature of the study, we would always recommend prespecification of the interim analytic plan to the extent possible with risk mitigation and trial integrity remaining a priority. Finally, we posit that interim analyses should be used as tools to help the DSMB make informed decisions in the context of the overarching study. They should generally not be deemed binding, and they should not be reviewed in isolation.

Ciolino JD, Kaizer AM, Bonner LB. Guidance on interim analysis methods in clinical trials. Journal of Clinical and Translational Science. 2023 Jan;7(1):e124.

Discussion on this very topic in previous Statistically Speaking seminar:
https://www.feinberg.northwestern.edu/sites/bcc/education/index.html

Summary of Expectations for Potential DSMB Members

- Protocol + supporting documents review
- Meetings at regular intervals (depends on monitoring plan) – quarterly, every 6 months, yearly, ad hoc
- Meetings are usually accompanied with several documents to review:
  - Updated protocol
  - Open report
  - Closed report
  - Often review in advance of meeting + come with questions and points of discussion

Summary of Expectations for Potential DSMB Members

- Meeting duration varies: typically, about 2-3 hours, some can be half-full day
- May or may not be in-person: large studies typically have an in-person meeting once/year
- May or may not be compensated – if so, modest amount (typically around $200 per meeting)
- Format, conduct, governance, etc. of DSMBs will vary as well!

Summary of Expectations for Potential DSMB Members

Lots. Of. Variety.

Some Resources: Manuscripts

- Data Monitoring Committees: Promoting Best Practices to Address Emerging Challenges
- NEJM Evidence, DSMB mini-series: The Data and Safety Monitoring Board: The Toughest Job in Clinical Trials
- NEJM Evidence, DSMB mini-series: Data and Safety Monitoring Board Monitoring of Clinical Trials for Early Efficacy
- NEJM Evidence, DSMB mini-series: Early Termination of Clinical Trials for Futility — Considerations for a Data and Safety Monitoring Board
- NEJM Evidence, DSMB mini-series: The Impact of Landscape Changes on Data and Safety Monitoring Board Oversight of Clinical Trials
- NEJM Evidence, DSMB mini-series: Stopping Trials Early Due to Harm
- NEJM Evidence, DSMB mini-series: Independent Oversight of Clinical Trials through Data and Safety Monitoring Boards

Resources, Cont'd

Training manuals and guides

- DSMB Training Manual: CTSA Collaborative DSMB Workgroup
- Society for Clinical Trials (SCT) Online Resources

Charters, templates and checklists

- NIH resources, by institute and center
- FDA Guidance on establishment and operation of clinical trial data monitoring committees

Textbook

- Ellenberg, Susan S., Thomas R. Fleming, and David L. DeMets. Data monitoring committees in clinical trials: a practical perspective. John Wiley & Sons, 2019.

Recent Webinar through TIN – November 4, 2024

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Some notes on issues surrounding DSMBs

- Jody D. Ciolino, PhD – Northwestern University
- Christopher Lindsell, PhD – Duke University
- Heidi Spratt, PhD – University of Texas Medical Branch

While there are A LOT of resources for DSMB conduct, methodology related to interim monitoring, and templates…

- There is **no formal training** requirement in general
- AND most researchers and DSMB members do not have protected time to read, review, watch videos, etc. to obtain a more formal education on the subject
- More ‘on the job training / learn as we go’
- DSMB service is often ‘extra’ + not a part of typical scope of work

What we believe is the heart of the issue

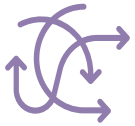
- **Lack of education + time** (noted on previous slide)

- Lack of proper **orientation** to the study and to the DSMB's charge for the given study

- Failure to recalibrate and *adapt* for the given context; for example…
  - Observation vs. interventional
  - Low-risk vs. high-risk
  - Structure and conduct is VERY different for small "R01"-like studies vs. large multicenter studies
  - Academic/government vs. industry DSMBs tend to be very different
  - Phase of study (I, II, III, IV, etc.) – there is no "one size fits all"

Examples of issues we have personally encountered

Confusion on…



- Role of executive secretary/sponsor representative
- Blinding versus not of sponsor
- Independence of DSMB from sponsor
- Communication between DSMB and IRB
- Role of DSMB in ensuring data timeliness, completeness and quality
- Role of participants on a DSMB
- Who is taking notes, providing documentation of recommendation, etc.
- Who are fellow DSMB members vs. study team members

Examples of issues we have personally encountered

Some red flags:

- DSMB members from the same institution
- No charter
- No opportunity for a closed/executive session
- Meetings that are planned for just 1 hour – there's no way we can get through all the components in 1 hour

- Just 3 DSMB members for a high-risk study

- "I don't know why the IRB/Sponsor/etc. insists on a DSMB, but…"

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Issues noted so far are more on the structure/organization; the following are issues surrounding DSMB conduct and recommendations…

Examples of issues we have personally encountered, cont'd

- DSMB getting **too authoritative** and forgetting that these are *recommendations* and similarly, investigators/sponsors taking what DSMB says as "law".

- DSMB focusing in on minutia that are outside of their purview and sometimes a waste of time.

- Push for interim analyses when they are not planned and seem unmerited.

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Issues encountered from the investigative team reporting to the DSMB…

Examples of issues we have personally encountered, cont'd

- Receiving reports with little time to review in advance (especially if they are LONG)

- PI doing all of the presenting rather than the reporting statistician or quantitative team

- Clear manual entry into tables or figures (rather than export from software)

- Failure of investigators to listen to the DSMB recommendation/ignore/not follow-up on those recommendations

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Ideas on solutions…

Some Ideas on Solutions

- "**Orientation**" for DSMB members AND for investigators: study status, meeting structure, scope within context of study, etc.
  - Perhaps a pre-DSMB meeting with just the members
  - Perhaps a pre-meeting with the reporting investigators/study team

- **Advanced scheduling** – usually 6+ months in advance

- Thoughtful **consideration on the DSMB chair** – their experience and availability, perhaps separate training for the chair; could consider rotating chair

Some Ideas on Solutions, Cont'd

- Continual **reminders**: re-introductions of members, study team members, re-introduction of study design and goals (something simple – on zoom: update name in tile), scope, authority and structure of decision-making

- **Standardization** AND **adaptability** at the same time

- **Resources** (effort / protected time / funds) for effective reporting to and supporting a DSMB

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Thank you for your attention!

Questions / Answer Session

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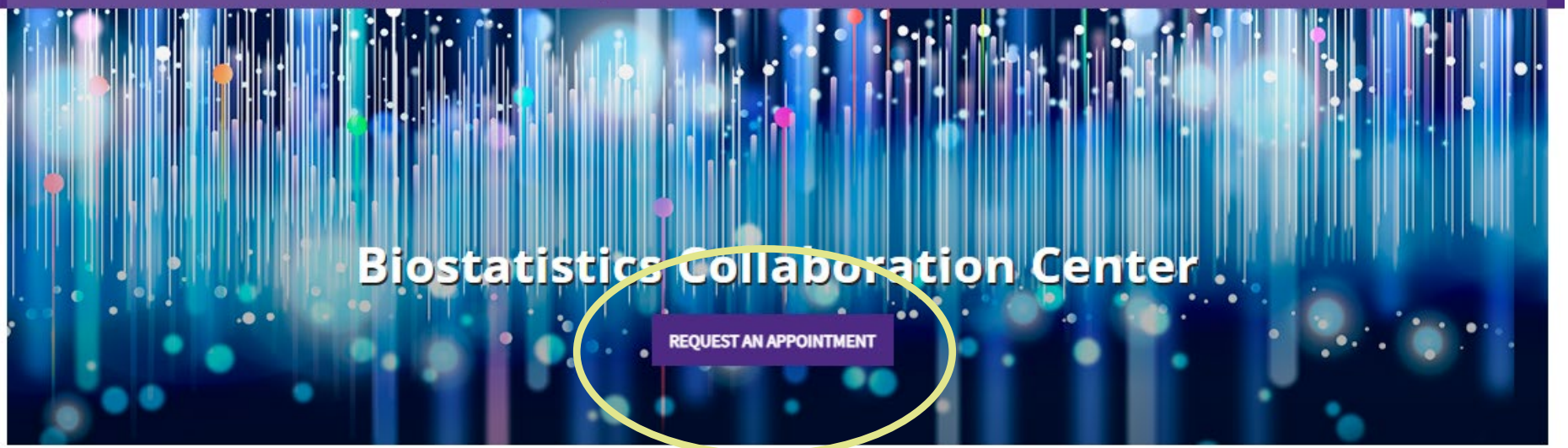

Expertise in biostatistics, statistical programming and data management

Since 2004, the Biostatistics Collaboration Center (BCC) has partnered with Northwestern investigators at every level – from residents and postdoctoral fellows to junior faculty and well-established senior investigators.

Meet Our Team

Our faculty and staff have collaborated with basic science, clinical, and health services investigators in over 60 Northwestern units across Chicago and Evanston campuses, and with all of NU's clinical partners. Meet our team and learn more about our expertise.

OUR PEOPLE