Data Monitoring Committees - Advancing Best Practices and Developing Next Generation Experts

The opinions of the panellists reflect personal opinions and not necessarily those of their institutions or employers

"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."

Session Agenda

- Opening remarks and BSLC DMC Workstream Introduction
  - ***Martin Jenkins**, Senior Director, R&I biometrics, AstraZeneca*
- Panel member introduction and statements
  - Requirement for and importance of IDMCs to industry
    - ***Chrissie Fletcher**, VP statistics, GSK*
  - DMC experience and best practice
    - ***Sue Todd,** Dept. Mathematics, University of Reading;*
    - ***Tim Friede**, Dept. Medical Statistics, University Medical Center,Göttingen*
  - Regulatory expectations
    - ***Elina Asikanius**, FIMEA*
- Panel discussion including questions from audience

BSLC DMC Workstream Introduction

- synthesizing current best practices and evolving regulatory guidance
- establishing industry consensus positions that promote consistency and clarity across sponsors while preserving DMC independence
- creating sustainable infrastructure for cultivating the next generation DMC experts

Collaboration across academic, industry, government sectors, professional societies, and DMC members

*BSLC=Biopharmaceutical Statistics Leadership Consortium
https://www.zs.com/capabilities/research-and-development/clinical-development
https://www.linkedin.com/company/pharma-bslc/about/

Panellist position statements

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Chrissie Fletcher – background and experience

- VP Respiratory, Immunology and Inflammation Statistics at GSK
- Management sign-off for Statistics on process documentation at GSK
- 35 years Industry experience, primarily in clinical development, medical and market access
- Experience of designing, conducting, analysing and reporting clinical trials using IDMCs and internal Data Review Committees in various disease areas and across different phases of drug development
- Participated in EFSPI and EFPIA related activities reviewing regulatory guidance on DMCs

Sponsor perspective

- DMC* definition (FDA): *A clinical trial DMC is a group of **independent** experts with **pertinent expertise** that reviews on a regular basis **accumulating data** from one or more ongoing clinical trials. The DMC **advises** the sponsor regarding the continuing **safety** of trial subjects and those yet to be recruited to the trial, as well as the continuing **validity and scientific merit** of the trial*
- DMCs are widely used in early and late phases and there is an expectation for using a DMC (not internal Data Review Committee) in trials generating confirmatory evidence
- Importance of ensuring study and data integrity is maintained when DMCs are being used
- Pre-specification of all decision rules in DMC charter
- Processes in place to describe end to end how DMCs are planned, conducted and documented and how DMC recommendations are communicated to sponsors.

Regulatory Agency	Guidance Document
U.S. Food and Drug Administration	Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006, OMB Control Number: 0910-0581)
European Medicines Agency	Guideline on Data Monitoring Committees (January 2006, EMEA/CHMP/EWP/5872/03 Corr.)
Japanese Pharmaceutical & Medical Device Agency	Guideline on Data Monitoring Committee PFSB/ELD Notification No. 0404-1 April 4, 2013
Drug Controller General of India	National Ethical Guidelines For Biomedical And Health Research Involving Human Participants. Indian Council Of Medical Research, 2017
Chinese National Medical Projects Administration	Ethics Guide

*DMC/DSMB/IDMC

Sue Todd – background and experience

- **Professor of Medical Statistics** at The University of Reading with research interests combining methodological developments for adaptive designs with practical research to facilitate implementation
- Prior to this, 13 years in a university based self-financing unit working directly with the pharmaceutical industry undertaking collaborative research, consultancy, DMCs, software development, short course provision
- **Serving as an independent statistician on DMCs and Trial Steering Committees for 30 years** for both industry and academic trials
- **Have prepared Efficacy Interim Analysis reports for DMCs** where trials used a sequential stopping rule for the primary analysis
- **Collaborate on projects developing best practice recommendations** for undertaking and reporting trials

An external statistician's perspective

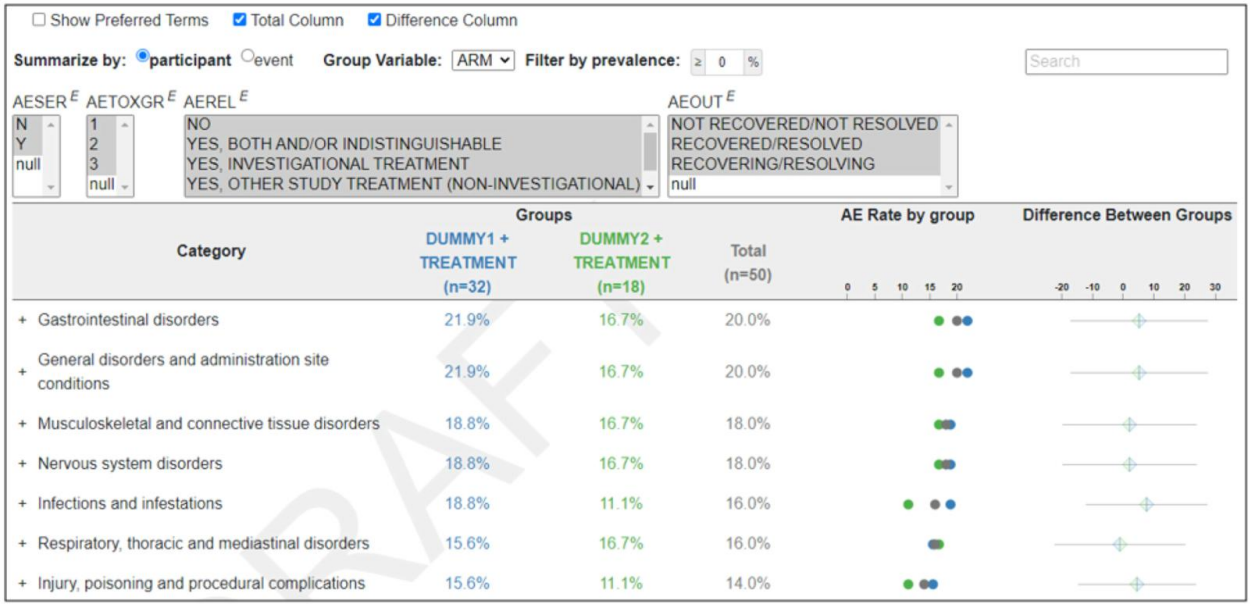
- DMCs vary immensely in size, membership composition, remit, and reporting structure. It is not the case that one-size fits all.
- There is ever increasing complexity of trial designs and decision rules meaning DMCs must accommodate greater statistical and administrative complexity.
- Appointing DMC members with key relevant experience – clinical, statistical and ethical – is crucial.
- Early dialogue between the sponsor and potential DMC members is needed to establish that everyone understands expectations.
- All parties need to think carefully in advance about what is to be presented to the DMC and how.

Tim Friede - background and experience

- **Statistician** at the University Medical Center Göttingen (Germany), previous academic appointments at Heidelberg, Lancaster and Warwick Uni
- Short spell in the pharmaceutical industry with Novartis Pharma AG in Basel (Switzerland)
- **Serving on data monitoring committees** of academic and industry studies in various disease areas for about 20 years
- **Contributed to workshops on DMC** at conferences including PSI and the Central European Network (CEN) of the International Biometric Society (IBS)
- **Published on DMC** including
  - Cartwright MJ, Friede T, Lawrence D, May E, Mütze T, Roes K (2024) Stakeholders' perspectives on current issues in Data Monitoring Committees. Biometrical Journal 66: e202300384.
  - Mütze T, Friede T (2020) Data monitoring committees for clinical trials evaluating treatments of COVID-19. Contemporary Clinical Trials 98: 106154.
  - Filippatos GS, …, Anker SD (2017) Independent Academic Data Monitoring Committees for Clinical Trials in Cardiovascular and Cardiometabolic Diseases. European Heart Failure Journal 19, 449–456.

DMC reports and interactive displays

- **DMC reports often overwhelm DMC members** by volume (several hundred or even thousands of pages) and format of data presentation (tables and listings)
- Improvements include **visualizations and interactive displays**
- For instance, created with **Shiny**, an R package for building web apps



- Figure 1 in Mütze & Friede (2020) CCT
- **Drill down options**: Details (listings) obtained by clicking on "Gastrointestinal disorders" in the display; subgroup filters

Estimating adverse event risks

- **With varying follow-up times** (the usual situation in DMCs) **incidence proportions** (“x out of y”) **are not interpretable as probabilities (risks)**
- **Incidence rates** can deal with censoring, but assume constant rates and are inappropriate with competing events
- **Kaplan-Meier (KM) estimator** can deal with censoring and time-varying rates, but is inappropriate with competing events
- **Aalen-Johansen estimator (cumulative incidence function)**, a generalization of KM to multi-state models, can deal with censoring, time-varying rates and competing events
- **Challenge from a practical point of view**: what constitutes a competing event (beyond death)?
- **References**: Stegherr et al (2021) Trials https://doi.org/10.1186/s13063-021-05354-x ; SAVVY https://numbersman77.github.io/savvy/

Elina Asikanius - background and experience

- Statistical Assessor at Finnish Medicines Agency since 2020
  - Main tasks: Marketing Authorisation assessment, Scientific Advice, CTA assessment
- Member of Methodology Working Party
- Member of Scientific Advice Working Party
- Member of ICH E20 Expert Working Group
- Co-lead of Biostatistics Special Interest Area

- Before joining FIMEA, over 10 years industry experience

Points from a regulator

- Roles and responsibilities and expectations (!) need to be clear for all parties and transparently disclosed to the regulator
- If the sponsor cannot endorse the iDMC recommendation without access to the results, the adequacy of the design may need to be considered

- All decisions are not the same; has the primary analysis been reached?
  - a positive efficacy IA or futility decision → Sponsor access to data less controversial
  - a dose selection or sample size re-estimation → Sponsor access to data more controversial
  - other aspects: objectivity of endpoints, double blind vs open-label, amendments

- Complexity of iDMC decisions has multiple dimensions
  - multitude of data: efficacy, PK safety, surrogate endpoints
  - complex decision criteria, potentially incorporating external evidence
  - multiple objectives, for example a platform trial
  - number of interim decisions, for example repeated efficacy interim analyses

Panel Discussion

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- What access to efficacy data does a DMC require at the time of safety review meeting?

- When can a DMC deviate from a pre-defined decision rule and should the sponsor be told?

- Who at the sponsor should receive an IDMC recommendation and what processes should be in place to separate them from the project team?

- How should an understanding be reached with DMC members prior to study outset on the scope and decisions to be made, particularly in the case of adaptive designs?

- What are some pieces of practical advice for user-friendly DMC reports?

- How do we maintain and build a pool of DMC experts with understanding of industry context whilst avoiding conflicts of interest?

- What particular considerations exist for drug-program-level DMCs?

- How may the operation of DMCs change in the coming years?

Questions from audience