DATA MONITORING COMMITTEES FOR INDUSTRY-SPONSORED TRIALS: ONGOING AND EMERGING CHALLENGES

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BACKGROUND

- My initial experience with DMCs was with NIH-sponsored trials
- Over the past 20 years I have served on numerous DMCs for industry- as well as NIH-sponsored trials
- Major differences between DMCs for industry trials and DSMBs for NIH trials
- NIH DSMBs
  - Statistical center reporting to DSMB is usually academic
  - Representative(s) of NIH funding group has access to interim data and attends closed sessions
- Industry DMCs
  - Statistical center reporting to DMC is usually a for-profit CRO
  - No representative of trial sponsor has access to interim data

TOPICS FOR DISCUSSION

- Reports to DMCs
- DMC Charters
- Confidentiality
- Liability

DMC REPORTS

- The DMC for industry trials has sole responsibility for reviewing the emerging comparative data from an ongoing trial to
  - Make sure the trial continues to be safe for participants
  - Make sure it is being conducted in a high quality way
- The DMC relies on the independent statistical center preparing the reports to present it with the data necessary to fulfill this responsibility
- It is unfortunately the case that many such centers do a very poor job of providing reports that are complete, clear, well organized and can be efficiently assessed

AN OPTIMAL REPORT

- Table of contents allowing clicks to pages
- An executive summary briefly describing key aspects of the emerging data
- Data are current as of no more than 4 weeks prior to meeting
- Tables formatted to minimize white space with attention to readability
- Use of graphics for continuous variables such as laboratory values
- Information on timeliness of data
- Long listings provided separately in appendices
- Identification of coded treatments in a separate file

AN OPTIMAL CLOSED SESSION

- Statistician presenting data is knowledgeable about the study, has reviewed the material and is able to answer DMC questions
- Safety issues of high importance have been updated to within a few days of the meeting

SOME EXPERIENCES

- Report with each table in a separate file, requiring DMC members to open many files
- Tables for trials with multiple arms not showing data for each arm on a single page
- Multi-page tables in which the data were all zeros
- Tables with font too small to read easily
- Reports without pagination
- Reports without a table of contents
- Presenting statisticians unfamiliar with study protocol and unable to respond to questions
- Presenting statistician unfamiliar with analytical approach used to create table or plot

THE PROBLEMS

- There are excellent resources for developing optimal reports to DMCs,* but most independent statistical centers (ISCs) seem to be unaware of them
- No attention is given to optimal formatting
- An informative executive summary is often missing
- ISCs often do not have access to the entire database, preventing them from preparing additional analyses requested by the DMC without alerting the sponsor
- Information on data quality often lacking
  - Timeliness
  - Response to queries

*Buhr, Downs, Rhorer et al, *Therapeutic Innovation and Regulatory Science*, 2018

*Neaton, Grund, Wentworth, *Clinical Trials*, 2018

MY RECOMMENDATIONS

- To lead statisticians in industry
  - Review prior DMC reports made by CROs being considered for your company's study
  - Persuade clinical colleagues of importance of providing a high quality report to the DMC (even if it costs a bit more)
- To potential members of DMCs
  - When invited to serve, ask for the name of the CRO who will be preparing the interim reports
  - If group is unfamiliar, ask to see a sample of a prior report before agreeing to serve

DMC CHARTERS

- The DMC Charter is intended to serve as an agreement between the DMC and the sponsor in regard to DMC operation
- It should describe
  - Approaches to monitoring efficacy, safety and data quality
  - Structure and frequency of DMC meetings
  - Conflict of interest considerations
  - Responsibility for meeting minutes
  - Process of making recommendations to sponsor
- It should lay out guidelines for DMC decision-making but allow for the DMC to exercise judgment

THE ISSUE WITH CHARTERS

- DMC Charters are hidden from everyone except the DMC and the sponsor
- Clinicaltrials.gov does not provide for Charters to be uploaded
- The Charter may contain details about how the data are reviewed that could shed light on the credibility of the study
- This is particularly worrisome at a time when Charters are increasingly lengthy and legalistic, and sometimes include potentially controversial provisions
  - Who sees data by treatment arm, and when
  - What information is provided to sponsor after DMC review

CALL FOR TRANSPARENCY

- DeMets D, Zarin D, Rockhold F, Ellenberg S, Fleming T & Wittes J, Bring data monitoring committee charters into the sunlight, *Clinical Trials*, 2023

- Zarin D,1 Wittes J , Fleming T , Rockhold F, Ellenberg S & DeMets D, The Case for Access to Data Monitoring Committee Charters, *New Eng J Med Evidence*, 2024

PUBLICATION OF CHARTER

- Since Charters typically include information about the process of interim analysis and the criteria for considering early termination, it seems best to delay publication until the trial is completed
  - Investment firms look for information to help them make good guesses on the likelihood of a positive trial
  - The more information they have on the monitoring process the better they will be able to simulate possible trial outcomes

MY RECOMMENDATION

- To those involved in preparing a report of the trial for publication
  - Encourage team of investigators to include DMC Charter in a supplementary appendix

CONFIDENTIALITY

- Two areas for discussion
  - Accelerated approval
  - Formal interim analyses

CONFIDENTIALITY

- Limiting accessibility of emerging clinical trial data to those on the DMC has long been a fundamental principle of clinical trial conduct
- Knowledge of emerging data could
  - Influence investigators in recruiting, treating and/or managing patients
  - Influence prospective trial participants
  - Influence trial sponsors in considering changes to protocol
  - Lead to premature termination of trial

SPONSOR PROTECTION

- Need for protocol amendments often arise
- Knowledge of interim data may affect perspective on potential modifications
  - Too few primary endpoint events—what other events to add to a composite endpoint?
  - Accrual slower than anticipated but very strong effect emerging—need for enlarging study?
- If changes are influenced by interim data, interpretability of findings is muddied
- Impossible to know whether or not there was influence, but you can't "un-know" what you know

IMPORTANCE OF CONFIDENTIALITY

- We have learned over the decades about the importance of maintaining confidentiality of interim results
- In first few decades of randomized trials, many trials never completed accrual due to investigator disappointment in early results
- Endpoint changes, or other major protocol changes, proposed with knowledge of interim data will not be accepted by regulators
- Trials intended to continue after regulatory evaluation of "accelerated approval" endpoint present challenges to confidentiality
- Important to converge on optimal approach for such trials, to protect sponsor and trial integrity while allowing regulatory agency data needed for approval decisions
- Accelerated approval of cancer drugs based on progression-free survival (PFS): case in point

SITUATION

- Study intends to show advantage in PFS, with plans to continue follow-up after target progression events reached, to assess overall survival
- DMC is monitoring study
- Target number of PFS events is reached; company unblinds PFS and adverse event data, remains blinded to comparative survival data
- PFS data shows significantly longer PFS on treatment arm than on control arm
- Company prepares and submits application for accelerated approval

NEW FDA GUIDANCE

- Guidance issued March 2023: *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*
- This guidance emphasizes the need to maintain trial integrity when a trial continues to assess the primary clinical outcome
  - "…blinding of data for the endpoint supporting verification of clinical benefit should be maintained until the endpoint's protocol-specified analysis time point is reached to ensure a robust assessment of this endpoint."
  - Guidance does not say exactly who should remain blinded
- Guidance does indicate that FDA will want to review the summary survival data at the time accelerated approval is considered

WHAT DOES FDA NEED TO KNOW?

- Full data on overall survival?
- Full analysis of all data up to that point?

- Or…does FDA really just need to know that survival is in an acceptable range
  - Hazard ratio <1?
  - Hazard ratio < 1.X?

HYPOTHETICAL

- If company knew that the PFS benefit was statistically significant but survival was worse (say, HR of 1.4, not significant) would they want to submit an application for accelerated approval to the FDA—or would they want to wait and see if the survival deficit diminished?
- If practitioners knew that the HR for survival was 1.4 but there was an advantage for PFS, would they want to use the drug?

POSSIBLE SOLUTIONS?

- Provide regulators with interim value of difference in overall survival?
  - With knowledge of sponsor
  - Without knowledge of sponsor (via the independent statistical center or DMC)
- Provide regulators with information that difference is or is not going in the "right" direction?
  - With knowledge of sponsor
  - Without knowledge of sponsor

ANOTHER POSSIBLE APPROACH

- Consider a new oncology drug that might be eligible for accelerated approval on the basis of PFS
- If a significant benefit on PFS is found, regulators will want to be sure that there is a reasonable probability that there is also an overall survival benefit (or at least no detriment)
- The DMC monitoring the study could be given the following guideline

DMC CONSIDERATIONS

- When the requisite number of PFS events have been observed, review the "final analysis" for PFS and the interim analysis for overall survival
- If there is a significant benefit on PFS, and if the data on overall survival meets a threshold determined in advance by the regulatory agency, provide data on PFS to sponsor to prepare regulatory submission
- If significant benefit on PFS but survival data do not meet the threshold (but do not rule out acceptable effect on survival), recommend study continue
- If no benefit on PFS, release study data to sponsor
- If the interim data on overall survival rule out an acceptable survival finding, recommend study termination on the basis of futility

EXAMPLE

- Suppose FDA and sponsor agree that HR for survival must be < 1.2 for accelerated approval to be considered
- Suppose at the final analysis for PFS, the PFS is significantly improved
  - If HR for survival is < 1.2, PFS data would be released to sponsor to prepare regulatory submission
  - If HR for survival is ≥ 1.2, DMC would recommend trial continue, unless
  - HR for survival rules out acceptable survival outcome

CONFIDENTIALITY

- If the recommendation is to continue, survival data are not revealed
- Maintains confidentiality of survival data until study is completed
  - Protects sponsor's ability to make changes to protocol and/or the statistical analysis plan without raising concerns
- If company has access to aggregate data, company will know when final analysis of PFS is being performed, so if DMC recommends continuing at that point the company knows
  - The survival data are not promising enough (yet), or
  - An emerging safety concern makes benefit-risk considerations uncertain
- Regulators will not have information on either PFS or overall survival

MY RECOMMENDATION

- in these settings, consider an approach to minimize availability of data that could influence (and potentially bias) ultimate trial findings

ANOTHER CONFIDENTIALITY ISSUE

- Some sponsors are now specifying in the DMC Charter that the DMC must notify the sponsor if the early termination boundary for efficacy is crossed
- The DMC may still recommend that the trial continue
  - Emerging adverse events may make the risk-benefit assessment not yet clear
  - Outcomes for important secondary endpoints may not be as expected, given the finding for the primary outcome
  - Data set may not be sufficiently current
- If the sponsor accepts the recommendation to continue, the sponsor will have been unblinded to the interim results
- As in previous context, this unblinding can undermine claims of unbiased trial conduct

MY RECOMMENDATIONS

- To lead statisticians in industry
  - Argue against including such a provision in the DMC Charter
  - Support selection of knowledgeable and experienced DMC members whose judgment can be relied on
- To potential members of DMCs
  - Read the Charter carefully and forcefully object if it includes such a provision

LIABILITY

- We live in a litigious society
- Legal cases involving DMC members are exceedingly rare, but have occurred
- Contracts for DMC service may require that the DMC member indemnify the company in case of lawsuits relating to DMC decision-making
- DMC members should not have to indemnify pharmaceutical companies!
- DMC members should be indemnified by trial sponsors with exception only for flagrant misconduct

MINUTES AND MEETING NOTES

- To protect against liability issues, minutes of closed sessions should not attribute comments to specific DMC members
- Similarly, video or audio recordings of closed sessions should be proscribed

MY RECOMMENDATION

- To statisticians in Pharma: educate your colleagues about this issue. Experienced statisticians will not agree to indemnify a company
- To statisticians serving on DMCs:
  - Read contracts carefully
  - Insist that companies indemnify DMC members
  - Insist on removing provision for DMC closed sessions to be recorded
  - Instruct whoever is taking minutes to avoid attributing specific statements to DMC members

A FEW OTHER ISSUES…

MEETING LOCATION

- We have all gotten used to virtual meetings
- Most DMC meetings are now held virtually
- For a major study, at a meeting where a formal interim analysis will be presented and discussed, an in-person meeting might be warranted
  - Hard to quantify, but communication can be more effective when meeting face to face
  - When a lot is at stake, consider meeting in person

FUTILITY ANALYSIS

- Not all trials provide guidance for futility analyses
- Important for DMC members to understand whether sponsor would want a clearly negative trial terminated early
- Many considerations
  - Whether other trials of same product are ongoing
  - Adverse event profile of drug being tested
  - Burden of trial participation
  - Cost of continuing study (financial, and opportunity cost)
- If no futility analysis specified, DMC members should discuss pros and cons with sponsor at initial meeting, prior to any data review

TRAINING NEW DMC MEMBERS

- Many who have served on DMCs have felt unprepared at first
- The best way to train someone to serve on a DMC is to have them participate on a DMC!
- It would be great if trial sponsors would include at least one DMC member with no prior experience on a DMC
  - Should be someone knowledgeable about clinical trials
  - Even better if they have had experience preparing interim reports and presenting to a DMC

CONCLUDING REMARKS

- Process of monitoring the interim data from clinical trials is very important
- Basic principles for interim monitoring are well established
  - Confidentiality of process
  - Attention to conflicts of interest
  - Experienced and knowledgeable monitors trusted by trial sponsors
  - Prespecified plans for early termination
- New challenges continue to emerge