

ASA Biopharmaceutical Section

Data Monitoring in Practice: Making Your Data Monitoring Committee Effective

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What we are going to cover

- Introduction (Janet): ~15 minutes
- Operations (Matt): ~ 40 min
- Break (5 minutes)
- Safety assessment (Janet): ~30 min
- Issues related to programs (Matt): ~15 min
- Questions and discussions (15 min)

What we are not going to cover

- Regulatory issues
 - The FDA guidance
 - International Conference on Harmonization
- Technical statistical issues
 - Efficacy “boundaries”
 - Futility rules
 - Safety guidelines

Reading material – regulatory etc.

Guidance for Clinical Trial Sponsors ICH E6 (5.5);
E9 various places

Establishment and Operation of
Clinical Trial Data Monitoring
Committees

Ellenberg, Fleming, DeMets. Data Monitoring Committees in Clinical Trials. Wiley

Herson. Data and Safety Monitoring Committees in Clinical Trials. Chapman & Hall.

Technical statistical

- Jennison and Turnbull
Group Sequential Methods
(with Applications to Clinical Trials)
Chapman and Hall, 1999
- Proschan, Lan, Wittes
Statistical Monitoring of Clinical Trials
(A Unified Approach)
Springer, 2006

Data Monitoring Committee (DMC)

Group of independent experts who:

- Monitor safety and efficacy
- Monitor scientific integrity of a clinical trial
- Make recommendations regarding trial design and conduct

DMC: aka DSMB, DSMC, IDMC, SMC,
SEMC.....

Mission of the Data Monitoring Committee

1. To protect the interests of study participants
2. To preserve trial integrity and credibility

In a manner enabling the clinical trial to provide timely and reliable insights to the broader clinical community

Theme 1: Plan early

- Consider the DMC process a design feature
 - Plan it as part of protocol development
 - Establish procedures before trial initiation
 - Unplanned interims possible
 - but generally discouraged and complicated
 - Consult with FDA!

Other themes

- Each DMC has its own sociology
- Role of the DMC must be clear
- DMC needs tools for good decision-making
- Trust among all players necessary
- Communication is complex
- Problem: crucial players lack experience
 - Not FDA, industry, or most CROs

Suggestions from the WHI DSMB

- DMC should be multidisciplinary
- Members should be committed to the trial
- Meet in person when possible
- Reporting group must understand the trial
- DMC must have right to
 - get additional presentations without telling sponsor
 - hold executive sessions
- Charter should say how membership can change
 - Wittes *et al.*, *Clinical Trials* (2007) 4:218ff.

Why are DMCs needed

- Ethical compact protecting participants in trials
- Sponsor
 - Regulatory responsibilities for reporting during trial
 - Financial incentive to end trial early
 - If drug has no effect
 - If drug is a smashing success
- May advise re change in protocol & procedures

Who watches safety in ongoing trial?

- Investigator
- Clinical monitor
- Sponsor's pharmacovigilance (SAEs, case by case)
- IRB-SAEs at local site
- FDA/EMA-reportable SAE
- DMC-Aggregate data by treatment groups

Composition, roles, and responsibilities

- **Internal vs external DSMB**
 - Internal composed of Sponsor members
 - External no Sponsor members

Internal DMC

- **Advantages:**
 - First-hand knowledge of compound
 - Understands regulatory implications
 - Understands company needs and dynamics
 - Easier logistics (arrangement of meetings, etc.)
- **Disadvantages:**
 - Less objective
 - Study integrity can be questioned

External DMC

- 3-10 experts in disease, drug, clinical trials
- Independent (but paid by Sponsor)
- Disinterested – no conflict of interest
- Experience on other DMCs –chair and statistician
 - Some inexperienced as “trainees”
- Potential legal liability
- DMC takes responsibilities seriously

Advantages of External DMC

- Unbiased recommendations (at least perception)
- Scientific objectivity
- Leading experts may be outside of Sponsor
- Consistent with FDA Guidance

Disadvantages of External DMC

- Sponsors make the final decision whether to accept DMC recommendations
- Sponsor and regulators are blinded
 - Difficult for Sponsor to make informed decision
 - Difficult for regulators to aid in the decision
- Difficult to go against the vote of the DMC

Members and chair

- Voting
 - Effective chair
 - Other members with relevant expertise
- Non-Voting
 - Study or steering committee chair
 - Sponsor representatives
 - Reporting statistician

Suggested guidelines

Members are free of apparent conflicts of interest involving financial, scientific, or regulatory matters. In case of any question of conflict of interest, standards used by the FDA in determining COI for advisory committee members shall apply.

J Herson

DMC Roles

- Advisory - only make recommendations
- Does not alleviate sponsor's responsibilities
- DMC decisions can be significant
 - Future of trial
 - Future of product
 - Regulatory activities
 - Investors and stock pricing

Purpose of DMC:
In decreasing order of importance

- 1. Protect the safety of participants**
- 2. Ensure the integrity of the trial**
- 3. Identify beneficial treatments early**
- 4. Stop trial early if treatment ineffective**

DMCs sometimes required

- Studies with a “waiver of informed consent”
- Emergency treatment trials
- Stroke, status epilepticus, traumatic brain injury
- Certain psychiatric conditions

If not required, what trial needs a DMC?

- Large, multicenter, long, randomized double-blind
- Fragile population
- Death is outcome (or clinically irreversible event)
- Patients with a high intrinsic mortality risk
 - HIV infection, cancer, sepsis, cardiac failure, elderly
- New chemical entity
 - worry: unexpected new events

Trials that DON'T need a DMC

- One that is so short the DSMB can't operate
- One that doesn't fulfill previous guidelines
- Many sponsors think FDA requires nearly all trials have DMC

Dixon et al., Guideline for data and safety monitoring for clinical trials not requiring traditional data monitoring committees. Clinical Trials, 2006; 3:314-339

DMC Roles

- Review prior to study
 - Protocol and design (ideally before finalization)
 - Ensure appropriate data for DMC are collected
- Review in real time (can act as bad cop)
 - Trial progress
 - Data quality

DMCs Can Recommend

- Protocol modification
- Early termination
- Temporary hold until issues are resolved
- Most common: continue as scheduled

DMC Can (if asked): Assess Design Assumptions

- Variability
- Control group response rate
- Event rates
- If necessary, use observed information to:
 - Recalculate sample size
 - Modify duration of follow-up
 - Help plan future studies
 - (see new guidance on adaptive designs!)

Who else monitors

- Safety – already discussed
- Recruitment/progress: Sponsor+Exec Comm
- Quality of data
 - Sponsor or CRO or both
 - BUT, they are thinking “end of the trial”
- Efficacy – no one else!

No one else monitors efficacy

- Under preplanned monitoring plan: ok
- What is not ok:
 - Medicine, science, and financial circumstances change, frequently prompting desire to change an ongoing clinical trial
 - in the primary endpoint
 - in entry criteria, evaluable population
 - in concomitant medications
 - in size of the trial
 - May be acceptable but NOT if the change is proposed by individuals with knowledge of interim results

Choose the reporter

- NIH, VA, EORTC: member of coordinating center
- Industry
 - In-house statistician (especially big pharma)
 - Contract research organization
 - Independent statistical group
 - Statistician on the DSMB
- All have problems

Define the operations/charter

- Organizational meeting – ideally before recruitment starts
- Review of:
 - Study design – last opportunity for DMC to comment before ‘contaminated’ by access to unblinded data
 - Model informed consent
 - Draft charter
 - Interim analysis plan/report template

The Charter

- Study players – DMC members, sponsor staff, reporting statistician
- Responsibilities-must be study-specific
- Confidentiality, COI
- Communications by DSMB
- Governance: chair, secretary/recorder
- Frequency of meetings; setting them up and quorum
- Decision rules, statistical guidelines
- Data flow and content of the report

Meeting organization

- (Brief closed session)
- Open session
- Closed session
- (Executive session)
- (Open/debriefing session)

Who should attend open session

- DMC
- Sponsor
- Investigators
- Reporting statistician

Open session

- Progress of the trial
 - Report from the Sponsor
 - Report from the Steering (Exec) Committee
 - Report from related trials
- Pooled safety findings
- Sponsor, investigator, & DMC describe concerns
 - BEWARE! People can slip especially on the phone!!!
 - DMC members may open and refer to closed report during open session!

Closed session - who is there?

- The DMC only – ideally all members
 - + the statistician(s) preparing the report
 - + the Study Chair?
 - + the sponsor?
 - + trainees?
- Executive session

Meeting organization

- (Brief closed session)
- Open session
- Closed session
- (Executive session)
- (Open/debriefing session)

Meeting minutes

- DSMB must keep impeccable records
 - What did they know and when did they know it?
 - Did behavior/rules change in response to data?
 - Rationale for recommendations
 - Summary of open and closed session minutes prepared
 - DMC Chair is often responsible for minutes, but drafting the document is frequently delegated to reporting statistician
- Full and honest disclosure of what happened
 - But no names in minutes
- Generally unavailable for external review until after the database lock

Access to efficacy data

- Should a DMC have access to efficacy data?
 - Sometimes efficacy endpoint is also a safety endpoint (e.g., death, visual acuity)
 - Some DMCs feel need to assess potential risk vs. benefit if safety signal observed
- Sponsor concern
 - Maintain control of access to tx effect during trial
 - Regulators may require statistical penalty for safety looks
- Compromise
 - Reporting statistician presents efficacy only upon request – document look in minutes
 - Present a variant of the efficacy endpoint – e.g., proportion of deaths, but not survival curves
 - Small statistical penalty (e.g., $p=0.00001$) assigned to each “look”

Who is masked in DMC reviews

- Different philosophies
 - DMC should know identity of tx that corresponds to labels
 - DMC should only learn identity upon request
 - Rationale: review data and form two sets of opinions – one assuming Group A is active and one assuming Group B is active
 - Sealed envelope maintained by Chair to open if needed
 - Or request to learn identity from reporting statistician
 - Minutes document when DMC chooses to unmask itself
- Some sponsors feel reporting statistician should be masked as well

Masking can be difficult in practice

- Unequal allocation ratios
- Tell-tale side effects
- Efficacy or futility reviews
- “Acrobatics” required to prepare DMC report
 - Report only percentages, without numerators and denominators
 - Use different set of labels (Group A/B vs Group X/Y)
 - Use pseudo subject identifiers in some data listings to prevent unmasking DMC to individual assignments

DMC Confidentiality

- Interim data & DMC discussions must remain confidential
- Leaks can affect
 - Recruitment
 - Adherence
 - Outcome assessment
 - Trial support
 - Scientific integrity
- Message to sponsor & DMC: the DMC is not a steering committee!

Managing conflicts of interest

- DMC members may not gain financially depending on trial outcome
- But any qualified DMC member will have potential conflicts (or perceptions of conflict)
 - For example, work on competing trials
- How ‘broad a net’ should be used when fishing for potential conflicts?
- Different models
 - When contracting with DMC members, sponsor questions about potential conflicts
 - DMC Chair reviews potential conflicts of other members and judges whether they preclude membership
 - Periodic queries during DMC tenure about new conflicts

How current are data?

- Tension between data currency and accuracy
- Easiest way to aggravate DMC is to show them data that they judge as unacceptably ‘stale’
- Opt for currency and program defensively
- One approach is to have 2 tiers of data
 - For read-ahead report, all data presented with a certain cut-off
 - Important data (e.g., deaths and SAEs) refreshed right before report for an update at meeting
- Working backwards from the DMC meeting
 - DMC receives report at least 1 week before the meeting
 - Reporting statistician has data in house 2-3 weeks before sending report
 - Why so long? Need to react to the data and program ad hoc summaries if study modification is a possibility

Sponsor approaches (a.k.a. what exactly is a data cut-off date?)

- For safety reports
 - Data provided to reporting statistician is a snapshot of database, warts and all, OR
 - Sponsor draws a line in the sand and strives to have all visits in DB as of a certain date
 - often this date is 2-4 months before meeting
 - Sometimes sponsor excludes data that happen to be in database after this cut-off date
 - Preferred approach: include all data with understanding that data included after the cut-off date is a convenience sample of visits
- For efficacy reports
 - Have as close as possible to the milestone number of pts or events for the report
 - Does not need to be exact!
 - Endpoint data cleaned as best as possible – other data dirtier

Where people go wrong in monitoring

- They forget that theory assumes no selection
 - They take the first k *reported* events
 - Should take order of randomization & then count
- They rely on their processes for end of study
 - Monitors go out when a patient has finished
 - Early events & withdrawals get counted too early
- They understand ordering, so are very delayed
 - Study: 150 randomized; we see data for the first 30
- Only present data if entire patient CRF complete

What data are sent to reporting stat?

- Enrollment/randomization data
- Data from clinical database
 - Sometimes receive analysis datasets programmed by sponsor
 - Always want to also receive CRF datasets
 - Full database, even if some datasets aren't planned to be used
- Pharmacovigilance/regulatory database: More current than clinical database
- Central labs
- Reading center/adjudication committee database
- Protocol deviations

Handling the DMC report

- Hardcopy sent ~ 1 wk before meeting with return mailer
- Sometimes also distributed electronically
 - Available sooner and helpful for 'mobile' DMC members
 - Helpful for 'late-breaking' analyses
 - Electronic archive allows editing of minutes to be more interactive
 - Concern regarding security?
 - Access to assistants for luddites?
- Requests to retain reports
- MedWatch reports – to include or not? How helpful
- DMC reports are numbered and accounted for
- Archive copy for surrender to sponsor at trial end

Conveying DMC recommendations

- Who receives recommendation?
 - Sponsor executive
 - Steering Committee Chair
- Generally not a member of the study team
 - Why not?
 - Recipient serves as a firewall in case sponsor does not accept DMC recommendation outright
- This means that ‘debriefing’ or open session following DMC deliberations may be ill advised
 - At the very least, discussions in debriefing sessions need to be particularly guarded

Conveying DMC recommendations

- Timing of recommendations
 - Varies greatly between DMC charters
 - Good model: conveyed verbally following meeting, with formal written recs following within 5 days
 - Recommendations may take extended time to reach study team
- Sometimes two versions prepared
 - Abbreviated set for distribution to IRBs by sponsor
 - More complete set that may contain guidance or requests from the DMC

Conveying DMC recommendations

- All meetings generally have corresponding recommendations
 - Possible exception are unscheduled (i.e., unplanned) DMC reviews
- Sponsor should communicate acceptance of recs to DMC via reporting statistician

The DMC archive

- What is in archive?
 - Reports
 - Minutes
 - Open session powerpoints
 - Substantive communication
 - Data used for each report
- Our view: Most chairs should not maintain archive

The DMC report

- Goldilocks principle: not too big, not too little
 - Use the airplane rule
 - Part of job description of reporting statistician is to be a good editor
- Guide: only material the DSMB can use for decisions
 - Depends on the charge
- Not a subset of final tables
- Purpose of interim monitoring \neq purpose of final analysis
 - Changing the study during the trial \neq what does the study show
- Don't be locked into rigid rules!
- Report evolves over time
 - First report with small N may be listing based
 - Presentations added and dropped with subsequent reports

Preparing DMC Reports

- Data freeze 4-6 weeks (or ASAP) prior to meeting
- Prioritize cleaning important data
- Deliver reports to DMC members ~1 week before meeting
- Bring recent updates (accrual, deaths, SAEs) to meeting

Labeling groups (A, B etc)- don't use real names

- Reports get lost
 - In the magazine holder in the plane
 - Side of street after falling off of FedEx truck
- Identify labels at meeting if DMC requests
- Send DMC sealed envelope they may open
- If many doses, keep in order
- Don't change labels btwn reports
- SCI's view: DMC should be unmasked

Report contents

1. Summary of protocol, charter, & outstanding issues
2. Executive summary - one page summary of data
3. Recruitment and follow-up
4. Baseline data
5. Check of randomization
6. Significant protocol deviations
7. Timeliness of data & adjudication of endpoints
8. Dosage of study medication
9. SAEs & deaths from the regulatory database (greater currency)
10. Adverse events with study-specific coding (beyond MedDRA)
11. Vital signs and laboratory parameters
12. Outcome data
13. Previous minutes
14. Informed consent document

Contents

High-level overview of good and bad

Crocus Tulip

Deaths (p.23)

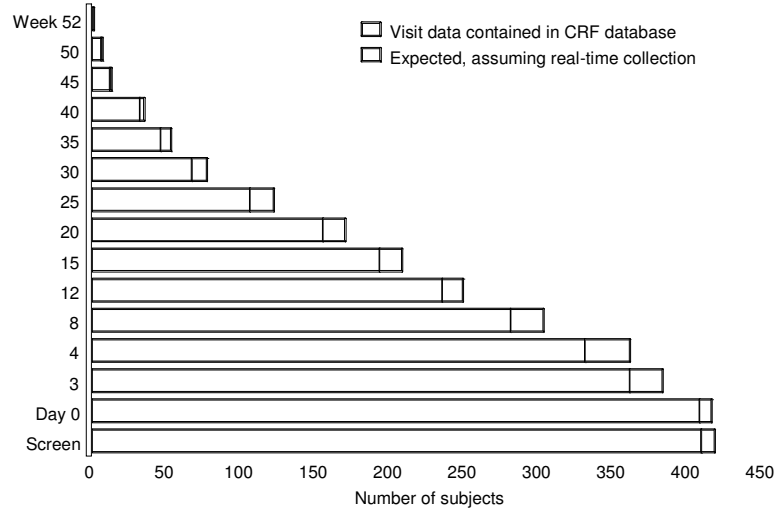
Major bleeds (p.30)

Primary outcome (p.54)

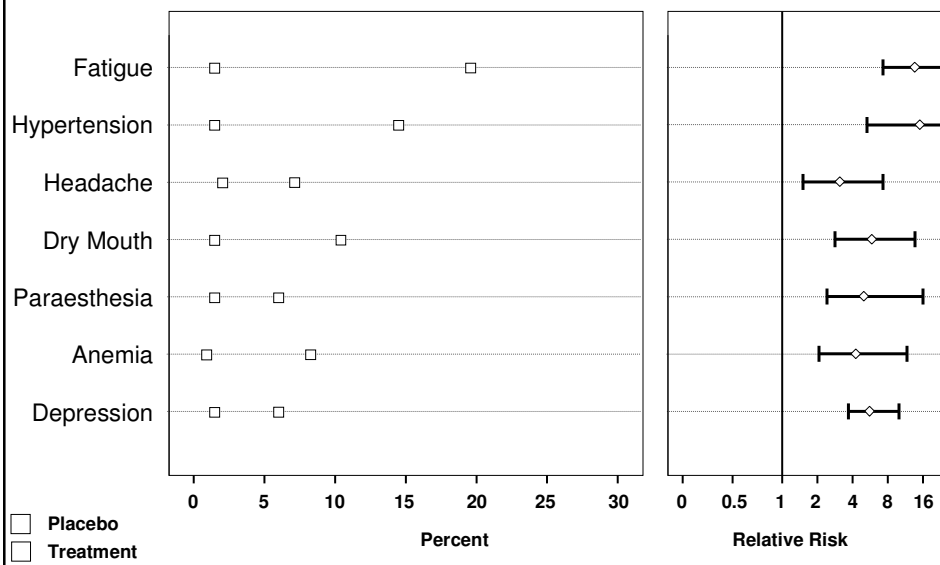
Safety

- Deaths, SAEs, and targeted AEs
- AEs (?)
- Lab values (clinically significant changes)
- MedWatch forms (?)
- Line listings
 - SAEs
 - clinically significant changes
- Graphs for laboratory parameters
- (Not so much that DMC ignores information)

Currentness of data



AE Summary



Efficacy analysis

- Primary
- Secondaries
- If DSMB is thinking about stopping
 - Analyses by subgroups of interest
 - Covariate-adjusted analysis

How report helps DMC ensure integrity

- Fidelity of randomization process
- Speed of recruitment
- Representativeness of population
- Adherence to protocol
- Consistency of data

DMC role in safety assessment

- Assess safety at several levels
 - Individual patient (usually not the DMC)
 - Aggregate and subgroups
 - Must be sensitive to multiplicity
- Stop development of toxic treatments
- Drop unsafe arms; make dose adjustments
- Does assessment of safety require info on efficacy?
 - Many DMCs: Yes
 - Many sponsors: No

Known vs. unknown signals

- Quantification of known harms
 - Better to do at end of trial
- Identification of new concerns
 - Protocol amendment, information
- Stopping because of safety concerns

Lousy reports to DMC members

- Reporting statistician
 - Not present
 - Doesn't understand the study
- Reams (literally) of paper
- Most tables have
 - Lots of zeros
 - False precision

Horror stories

- Study of dread disease: miscount deaths
- Some events by person; some by episodes
- Report arrives just before meeting
 - Hot off the fax
 - Over email, many separate files
- No text; no interpretation

Who is the boss?

- What if DMC asks for analysis and the answer is:
 - “The program won’t let me do that”
 - “My budget won’t allow that”
- Many CROs don’t do analyses that DMCs request

Which is to be master?



- **HD:** When I use a word, it means just what I choose it to mean - neither more nor less.
- **Alice:** The question is, whether you can make words mean so many different things.
- **HD:** The question is: which is to be master - that's all.

Safety report sample

• Time Point	A [N= 150]	B [N= 148]	Total [N= 298]
•			
• SCREENING	0	0	0
• RANDOM	0	0	0
• WEEK 2	0	0	0
• WEEK 3	0	0	0
• WEEK 4	0	0	0
• WEEK 5	0	0	0
• WEEK 6	0	0	0
• WEEK 7	0	0	0
• WEEK 8	0	0	0
•			

But wait! You also get:

• Time Point	A [N= 150]	B [N= 148]	Total [N= 298]
•			
• SCREENING	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• RANDOM	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 2	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 3	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 4	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 5	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 6	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 7	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
• WEEK 8	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
•			

What to do?

- DMCs are
 - Paid by the sponsor
 - Responsible to the participants!!!
- If the report is inadequate
 - Doesn't look like harm: train the reporters
 - Looks like harm: stop the study or resign
- The FDA will ask why a DMC has resigned

Ensuring safety

- DMC's job: make sense of the data
- Ind't statistician's job: make that possible.
 - Combine like with like
 - Read narratives
 - Speak to experts

Monitoring for safety

- Searching for the unknown
 - Rare events; unexpected
- “I make no mockery of honest ad hockery”
I. J. Good
- Extreme problem of multiplicity

Taxonomy

- Expected events – balance risk to benefits
- Unexpected, but not serious
- Unexpected, serious
- Unexpected, very serious
- Not credible, but scary if true

Enhancing safety data

- Spontaneous reports notoriously ambiguous
- Formal data collection
 - Diaries
 - Endpoint committees
 - Ongoing reporting of prognostic factors
 - Special data collection forms

Reporting safety data

- Don't rely on coding systems
- Classify and reclassify
- Look at relevant lab data
- Look at:
 - Means (remember the CLT)
 - Extreme percentiles (but not min and max)

Data from a coxib

Cardiac disorders	Placebo	Coxib
• Angina	2	2
• Angina aggravated	0	2
• Angina unstable	0	3
• ...		
• Cardiac arrest	0	1
• Cardia failure congest	2	0
• Coronary artery disease	4	7
• ...		
• Myocardial infarction	5	10

True data from a coxib

	P	C
Respiratory		
• Dyspnea	3	1
Vascular disorders		
• Cerebral infarction	0	1
• Pulmonary embolism	2	0
• TIA	2	0

Combine these...

Placebo

16

Coxib

27

Recommendations

- Pluck events aggressively
 - E.g., a death anywhere in the dataset counts for monitoring as a potential death
- Lots of interaction with sponsor & DMC
 - Many sponsors: Guidance forbids that

Goal is to tell a story

- What happened to the patients?
- How is group A differing from Group B?
 - Is the difference real?
 - Will it continue?
 - Are other harms emerging?
 - How worrisome are the harms?

Warning

- What DMC wants \neq what sponsors provide
 - DMC starts after recruitment has begun
 - Sponsor doesn't respect independence of DMC
 - Data are very late
 - Sponsor selects a date without asking members
- Limit # of DMCs; support those established

Problems for industry

- Most relevant staff have never attended closed session of DMCs
 - Industry
 - FDA
 - CROs
- Industry/CRO SOPs focus on end of study
- FDA worries about leakage of data
- Too much concern about clean data

Problems: culture clash

- DMC feels responsible for participants
- Industry acts as if the DMC is beholden to it
 - Doesn't schedule early enough (assumes DMC will jump)
 - Doesn't start DMC early enough in trial
- Industry assumes DMC report is a mini-final report
 - Many tables in a final report are irrelevant
 - Many others irrelevant to final but needed by DMC
- Industry assumes DMC knows its SOPs
 - DMC doesn't care

FDA's Role (p. 33 guidance)

- Planning the DMC – Sponsor and FDA
 - Sponsor should tell DMC about regulatory context
- Sponsor should speak to FDA
 - If it wants interim data
 - If DMC recommends early termination
- Sometimes FDA and DMC will speak
- Question: what if FDA wants minutes?
 - My advice - resist

The reporting statistician

- FDA Guidance: “independent statistician”
 - Protect the blind, thus avoiding potential bias
- NIH and industry not completely convinced:
 - Independent statistician = Ignorant statistician
 - Presenting statistician must understand trial & data
 - DMCs often ask questions & require additional analyses
 - Significant problem with the today's DMC process

Protocol (study) statistician

- Remains blinded
- Does not prepare DMC report

“Independent” statistician

- Unblinded – but not always!
 - My appeal to FDA-tell sponsors: ind’t statistician **MUST** be unblind
- Prepares open report for protocol team
- Prepares closed report for DMC
- Presents results at DMC meetings
 - **must be present!!!**

Who serves as independent statistician?

- Often contracted to CROs, academics, or others
- May be unblinded Sponsor statistician
- Paid by the Sponsor, but works for the DMC
- Ideally, contracted entity is independent of:
 - Sponsor
 - Protocol statistician
 - But may need to ask questions to for clarification
- Many sponsors prefer to do the programming

Independent statistician: must be engaged & knowledgeable

- Capable of leading DMC
 - Interpreting data
 - Answering questions
 - Shouldn't have "opinions"
- Discusses safety issues with Sponsor before analysis
- Understands DMC roles
- Anticipates DMC questions

How people interpret independence

- Independence = lack of interest
- Independence = ignorance
- Independence = masked

What independence is not

- Independence \neq lack of interest
- Independence \neq ignorance
- Independence \neq masked

These follow letter of guidance, but not the spirit.

Independence for DMC and reporting statistician

- Disinterested, not uninterested
- No vested interest in the results
 - No gain/loss by early stopping
 - No gain/loss by continuing
- Intellectual ability to remain neutral

What many sponsors expect (and many CROs do)

- Ingredients
 - Data
 - Programs someone else prepares
- Action
 - Attach treatment code to data
 - Press a button

What many sponsors expect (and many CROs do)

- Ingredients
 - Data
 - Programs someone else prepares
- Action
 - Attach treatment code to data
 - Press a button
- Warning: risky for participants & sponsor

Independent statistician needs

- All the data-preferably regularly
 - Don't fall for "it's expensive to download data"
- Treatment code
- Data analysis plan and data dictionary
- Discussion
- Sense
- Time

And then...

- Ingredients
 - All the data
 - Treatment code
 - Data analysis plan and data dictionary
 - Discussion
 - Sense
 - Time
- Steps
 - Write code
 - Interpret results
 - But have no opinion

When sponsor programs work best

- Few planned DMC reviews –
 - Reporting statistician prepares 1 or 2 reports over time
- Coded clearly
 - reporting stat may need to modify programs
 - (at very least needs to understand program conventions)
 - Minimal use of proprietary macros
- Table programs easier to use than data programs
- Use of sponsor programs is a starting point

Sponsor program surprises

- Deleting data
 - Visit occurred after data cut-off – doesn't count
 - We're not 100% sure the subject was treated, so delete
- Errors in programs
- Assuming data are 100% clean
 - A fatal AE reported only on the AE form and not on the death CRF isn't believed
- Programs don't account for missing data and assume a constant denominator
 - Cancer trial shows that only 70% of study population has cancer at screening!

Interactions with Sponsor

- Periodic calls with sponsor during study
 - Can be helpful
 - Coordinating data availability
 - Understanding monitoring issues and data snafus
 - Just don't expect me to talk that much
 - Watch out for inappropriate questions
 - What is the DMC looking for with that request?
 - Who asked for that?

Dummy programming

- Suggest subset of most important presentations
- Perform before 1st or 2nd report and before milestone report(s)
- Make dummy output easy to distinguish from actual output
 - Risk accidentally sending real output to sponsor or using dummy output in DMC report
- Before comparing results with sponsor, try to identify areas of likely disagreement
 - e.g., convention for handling partially missing data

Sponsor correspondence with DMC

- Should be limited during trial
 - Possibility of misrouted communications
 - DMC payment through reporting statistician
 - Reporting statistician in loop so archive is maintained
- Beware email correspondence

Why open reports?

- To inform study team about recruitment etc.
- To check accuracy of the reporting group
- Dangers
 - Extra expense
 - Get in the way of more important activities
 - Potential to unblind
 - May no longer reflect what DMC is seeing in closed report

Open Reports

- Be very wary of anything that can create operational bias
 - E.g., gives away information regarding treatment effects (efficacy or safety)
- Try to avoid pooled endpoint data summaries (particularly efficacy)
 - Even aggregate data can be informative regarding treatment effect
 - Safety data are generally accepted but can sometimes unblind treatment

Open report recommendation

1. Limit what is in open report
 - Pretty minimal: Baseline characteristics
 - Supplement with dummy tables of other content
 - BEWARE when DMC report content changes
 - Open and closed report content may diverge greatly
2. Have firewall to review report before wider distribution
3. No hardcopy of open reports (e-copy only)

Summary

- Think about DMCs in design stage
 - Plan early
 - Start the DMC before randomizing the first participant
- Protect trial integrity
 - Develop a DMC Charter
 - Give careful thought to details that need to be covered in organizational meeting
- Report preparation
 - Requires solid statistical knowledge
 - Concise
- Choose reporting statistician and DMC carefully
- Respect your DMC and its needs