Reasoning and General Guidelines for Data Monitoring Committees

Jody D. Ciolino, PhD
June 18, 2019

1. **Inspiration and Resources**
    a. Poll audience
        i. Has anyone reported to a DMC before? If so, how many?
        ii. Has anyone sat on a DMC before?
    b. The idea of DMCs comes up often. Do we always need one? Why would we/wouldn't we need one?
    c. University of Pennsylvania's 10th Annual Conference on Statistical Issues in Clinical Practice (April 2017): "Current Issues Regarding Data and Safety Monitoring Committees in Clinical Trials"
    d. Challenges and best practices (Fleming TR, DeMets DL, Roe MT, Wittes J, Calis KA, Vora AN, Meisel A, Bain RP, Konstam MA, Pencina MJ, Gordon DJ. Data monitoring committees: Promoting best practices to address emerging challenges. Clinical Trials. 2017 Apr;14(2):115-23. http://journals.sagepub.com/doi/abs/10.1177/1740774516688915)
    e. DMC 'Training' Video: https://videos.ictr.wisc.edu/DMCTraining/story.html
    f. FDA Guidance: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf
    g. Regarding the naming conventions
        i. DMC = Data Monitoring Committee
        ii. DSMB = Data and Safety Monitoring Board
        iii. DSMC = Data and Safety Monitoring Committee
        iv. They are all synonymous

2. **A DMC is an independent group of experts (and potentially patient representative[s]), appointed by a sponsor/investigator to review accumulating clinical trial data on a regular basis**
    - **a.** They are not legally required for any/all studies; exception: studies in emergency settings with waiver of informed consent
    - **b.** *Usually* comprised of three to five members; may be more in several situations
3. **Why are DMCs used?**
    - a. **Ethical** – monitor patient safety
        - i. Monitor for harm or for efficacy
        - ii. It is unethical to withhold potentially efficacious treatments from patients (or to prolong the study if there is clear benefit)
        - iii. It is unethical to subject patients to undue risks of study involvement if there is clearly harm or if treatments are futile early on
        - iv. It is unethical to continue studies that are failing for other reasons (logistical, etc.) such that they will not be able to address initial question
    - b. **Scientific** – monitor study conduct and ensure sound design, operation, analyses
        - i. Independent party that can identify sources of bias and/or protect against operational biases
        - ii. Diverse, expert panel allows for another layer of review to ensure appropriate (sound) methods
    - c. **Economical** – monitor trial progress to ensure time/effort/money/resources are not wasted

5. **History**
    a. 1967 – **Greenberg Report** (Bernard Greenberg): https://sph.unc.edu/files/2013/07/greenberg_report.pdf
        i. NHI (precursor to NHLBI) convened committee to review conduct of clinical trials
        ii. Greenberg Report published in 1988 in *Controlled Clinical Trials*
        iii. Idea: "mechanism must be developed for **early termination if unusual circumstances dictate that…a study should not be continued**"…"on **recommendation** of consultants"
        iv. BUT those involved in the design and conduct a trial may not be fully objective in "reviewing interim data for emerging concerns"
    b. **Coronary Drug Project** (CDP) = one example trial in which precursor to DMC involved
        i. 53 sites, five treatment groups, >8K participants
        ii. CDP became prototype for many other institutes/centers/studies
        iii. Published in 1981
    c. **DHHS in 2000**: all trials must have a **monitoring plan** (may or may not include DMC and may or may not "live" in the study protocol)
    d. **NIH policy (1998)**: all sponsored trials must have a monitoring system (may include safety, efficacy, validity) and a **DMC often mandated for phase III trials**
    e. **FDA DMC Guidelines (2006)**:
        i. **Not binding** *recommendations*
        ii. DMC **only required** per FDA for one type of trial: **emergency setting and waiver of informed consent**
    f. Increased use in 1990s due to **International Conference on Harmonization (ICH)** efforts/documents (https://www.ich.org/products/guidelines.html); increased collaboration between industry/NIH/FDA
    g. Today – many variations of DMCs: some are merited, others are superfluous

7. **Determining Need for DMC**
    a. *Usually* for large, randomized, multisite studies in which **outcome is time-to-death** or **major adverse health outcome** (cardiovascular, recurrence of cancer, etc.)
    b. Generally **not needed** at **early** stages of intervention development
    c. Generally **not needed** for trials with **"lesser" outcomes** (e.g., relief of symptoms) **unless population studied is at elevated risk for more severe outcomes**
    d. **FDA guidance recommends *considering*** a DMC when:
        i. Study result may be such that highly favorable or unfavorable results (or even futility) at an interim analysis might ethically require termination of the study early
        ii. Predetermined reasons for safety concerns (e.g., invasive procedure)
        iii. Possibility of toxicity/severe side effects
        iv. Fragile population (children, pregnant women, elderly, terminally ill, etc.)
        v. Large, long duration, multicenter studies
        vi. NOTE: it also needs to be *practical*
8. **Membership** (*usually* at least three people: two clinical members + one biostatistician)
    a. Clinical expert in relevant field(s)
    b. Biostatistician
    c. Basic scientist
    d. Regulatory specialists
    e. Ethicist
    f. Patient representative
    g. NO conflicts of interest: financial, clinical involvement, intellectual investment

9. **DMC Review Process**
    a. Beginning to end of study
    b. The DMC Reviews…
        i. Design/initial protocol
        ii. Data quality/timeliness/completeness
        iii. Adherence to protocol – procedures, clinic visits, treatment allocation
        iv. Early data summarizations: baseline characteristics, comparability of groups, design assumptions, etc.
        v. Interim analysis results – evaluate risk/benefit profile
    c. Meeting schedule = study/DMC dependent
        i. Pre-study initiation
        ii. Interim trial fractions (e.g., 25%, 50%, 75%, 100%)
        iii. Usually at least once/year
        iv. As needed; may require ad hoc meetings
        v. Flexibility = key
    d. **Meeting format** – usually dictated by a **charter** (important, living document that guides DMC procedures; plan of operations for DMC)
        i. **Open session**: all parties involved present (site, CRO, sponsor, DMC, reporting statistician); review data in aggregate
        ii. **Closed session**: just DMC + unblinded statistician; review unblinded data by study arm
        iii. **Executive session**: DMC only
        iv. **Debrief session**: involves sponsor/team representative(s) + DMC
        v. Minutes/recommendations communicated after meeting in writing
    e. Recommendations the DMC generally makes…
        i. **Continue as planned** with no modifications – most common
        ii. **Continue as planned** with protocol **modifications** – less common
        iii. **Termination of the study** – usually guided by pre-specified stopping rules (there are separate, statistical methods that are often used here) – least common
        iv. These are *recommendations*, not decisions

10. Reasons for Early Termination
    a. Unequivocal evidence of treatment benefit or harm (group sequential methods, stopping bounds, spending functions)
    b. Unexpected, unacceptable side effects
    c. No emerging trends/no reasonable chance of demonstrating benefit (futility; conditional power)
    d. Overall progress/conduct of trial – not enough patients at a sufficient rate, lack of compliance in large numbers, poor follow-up, poor data quality
    e. Based on external information – other studies answer questions, other studies or data illustrate risks
    f. Caution – do not use statistical tools as “law”; they are *tools* (i.e., guidelines)

11. Topics for Further Discussion

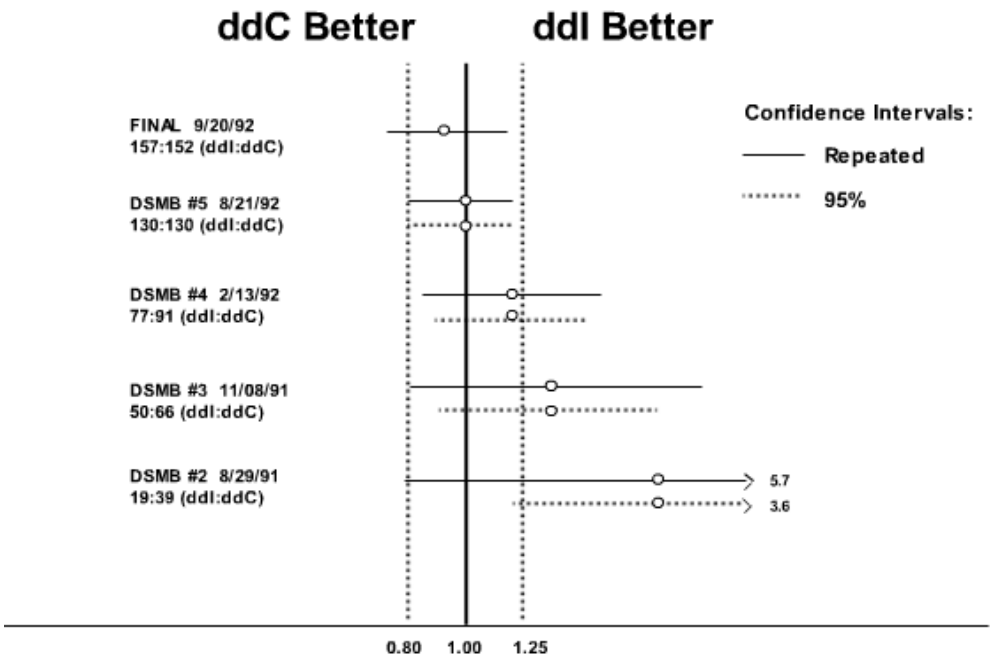
a. **Training** issues
   i. An MD, MS, or PhD is *not* enough: must have more than "classical" training
   ii. Also true for sponsor/PI/funder other study team members and DMC members – DMC chair = vital in taking ownership and dictating the demands/needs of DMC
   iii. "Apprenticeship" model – this seems like a good idea in my opinion

b. On reporting
   i. Report and charter are living documents, subject to change per needs of DMC
   ii. Concise reporting
   iii. Be thoughtful, anticipate questions
   iv. Will need to involve a clinical expert and/or obtain feedback from DMC regarding needs
   v. Unblinded data in closed report (include codes 'A' or 'B' in case the report is sent to the wrong person/people, but reporting statistician should have these codes available during the meeting)
   vi. Open report and closed report do not need to overlap so much
   vii. May not always be appropriate to report aggregate event rates to sponsor or investigators
   viii. Should highlight/report new findings since last time
   ix. Always include protocol synopsis
   x. Number pages, number tables, make it simple, report denominators
   xi. Allow ample time to review reports (at least a week?) – allow for walking through report as a team and generate/pose questions in advance of meeting

c. DMC Myths (DeMets)
   i. DMCs should be blinded
   ii. DMCs meetings must be held precisely as scheduled and be limited in number
   iii. Review must be on clean, adjudicated data only
   iv. DMC reports can be pre-programmed
   v. Each AE/SAE must be reviewed by DMC

Examples (see online video)

- **Example: ddI/ddC Trial (HIV network trial)**
  - AIDS/death = primary outcome
  - Event target =243 events, 467 randomized (1:1) 12/1990 – 09/1991
  - ddI approved while trial in process
  - Early trend of ddI efficacy when compared to ddC, but due to large error bounds, decided to continue



Fleming TR, Neaton JD, Goldman A, et al, *J. AIDS*, 1995.

  - DMC needs to be flexible; meeting schedule adapted according to results and need
  - Final results:

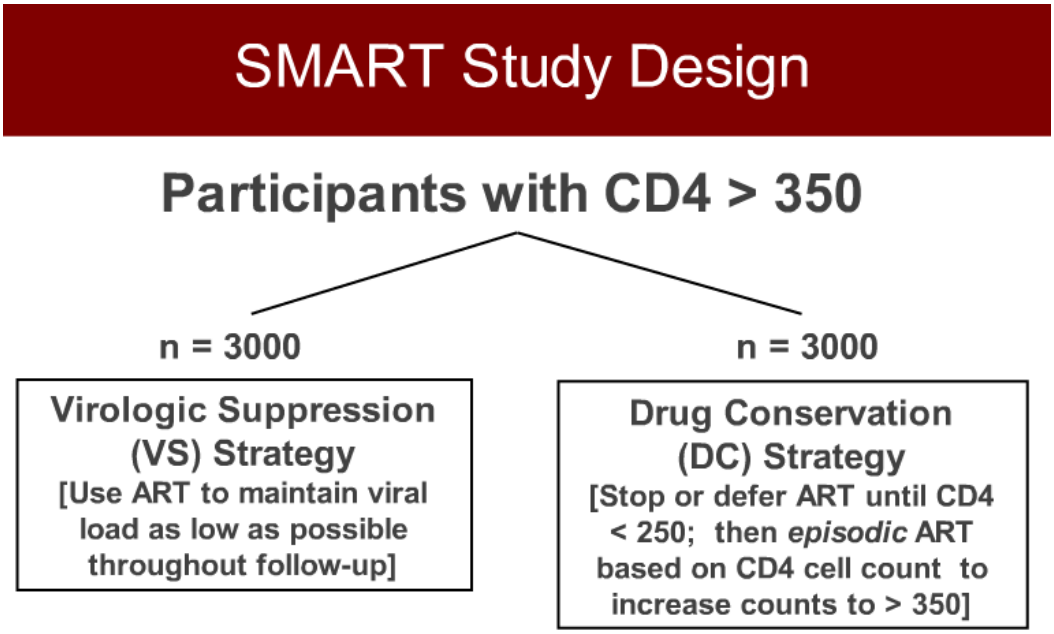
ddI/ddC Final Results

	ddI (N=230)		ddc (N=237)		
	No.	Rate+	No.	Rate+	P-value
AIDS or death	157	93.3	152	87.7	0.56
Death	100	42.8	88	35.1	0.09
ΔCD4+ count at 2 months	+8.6		+5.9		0.009
+ per ICC person years					

"zacitabine was found to be as efficacious as didanosine… neither treatment offered substantial long-term benefit."

- Early findings can be unreliable; importance of restricting interim results to DMC may be relevant as well here
- Ultimate conclusion: "neither drug very good"

- **Another Example: INSIGHT SMART trial**
  - Another HIV treatment trial in 2001
  - ART = antiretroviral treatment: side effects, difficulty with adherence; concerns re: HIV drug resistance; "drug holiday"



N Engl J Med 2006; 355:2283-2296.

  - Primary endpoint = AIDS or death; secondary composite endpoints (major cardiovascular endpoints, renal events, etc.)

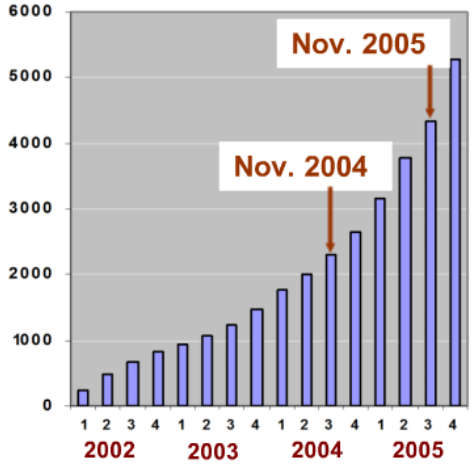
Secondary Outcome: Major CVD or Metabolic Disease

Outcome:	Justification:
Cirrhosis	Composite outcome:
CAD (requiring surgery)	• expected ART toxicities
Myocardial infarction	• occur with a similar incidence as AIDS events
Stroke	• more serious than most AIDS events
Kidney failure	

- DMC: NIH appointed (10-12 members)
  - Interim review at least one time per year
  - Clinical endpoints reviewed for safety, clear evidence of benefit, clear evidence of harm too
  - Futility as well
  - "Clear and substantial evidence of benefit or harm"

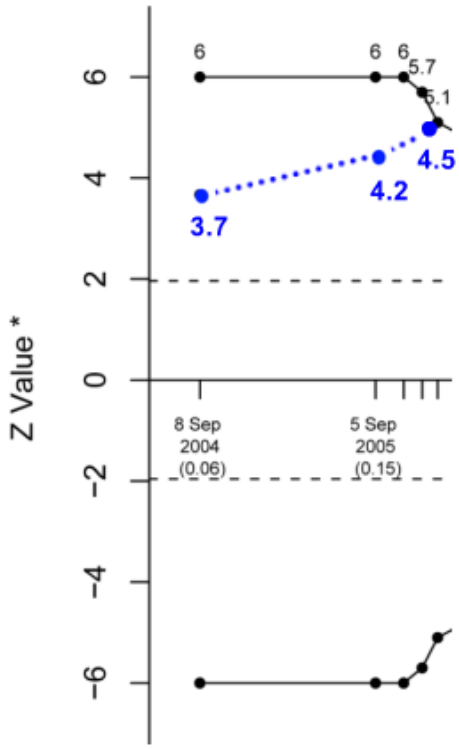
January 2006 DSMB Call

Enrollment



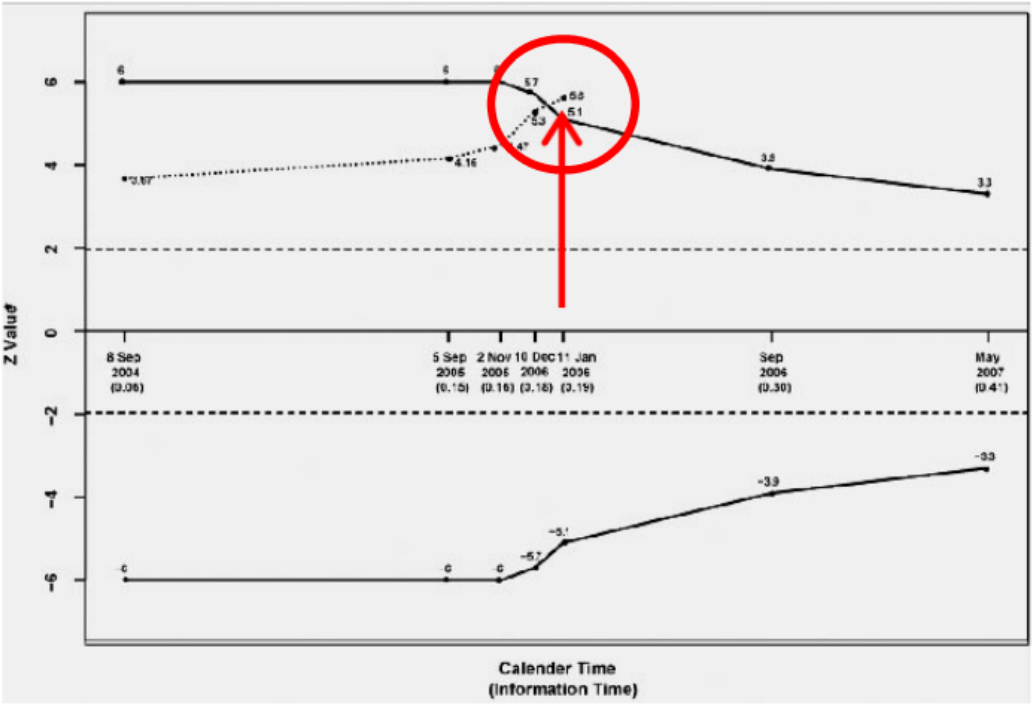
Clinical Endpoints

	Primary	Second.
Events	159 (5800 PY)	110
Rates		
DC	3.6	2.3
VS	1.7	1.5
HR	2.2	1.6
95% CI	1.5 – 3.0	1.1 – 2.3
P-value	<0.005	0.03



- DMC recommends to STOP enrollment
  - Additional follow-up will unlikely demonstrate superiority of DC arm
  - Re-design if can find an ethical/safe way to conduct or stop study
  - Ultimately, after much back-and-forth, enrollment was halted and letter to investigators and participants (2+ times risk of events in DC group)
  - Stopping occurred after just 20% of information planned (roughly 20% of patients/events)

Interim Monitoring: O'Brien Fleming Boundaries For The Primary Endpoint By Cut Date



SMART Primary and Supportive Endpoint Results

	DC Group		VS Group		HR (DC/VS)	
	N	Rate	N	Rate	[95% CI]	P-value
AIDS or death (primary endpoint)	120	3.3	47	1.3	2.6 [1.9, 3.7]	<0.001
Death	55	1.5	30	0.8	1.8 [1.2-2.9]	0.007
CVD, Renal, Liver	65	1.8	39	1.1	1.7 [1.1, 2.5]	0.009
- CVD	48	1.3	31	0.8	1.6 [1.0, 2.5]	0.05
- Renal	9	0.2	2	0.1	4.5 [1.0, 20.9]	0.05
- Liver	10	0.3	7	0.2	1.4 [0.6, 3.8]	0.46

N Engl J Med 2006; 355:2283-2296.