How to Construct an Optimal Interim Report: What the DMC Does and Doesn't Need to Know

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Disclosures

Over the last 20+ years for multiple trials of HIV treatment strategies, influenza treatment and the prevention and treatment of Ebola, I have remained blinded to outcome results by treatment group and prepared open reports with protocol co-chairs.

During this same time period, I have reviewed open and closed reports as a DMC member for several NIH, CDC, pharma and device trials.

I have not prepared a closed report for a DMC for a long time!

Some Gripes as DMC Member

Closed reports are frequently prepared by statisticians who are not familiar with the trial data collection plan.

As a consequence, reports are diffuse, often based on pre-programmed, “validated” tables and figures, and questions from the DMC cannot be addressed.

Closed reports do not include a description of methods or an executive summary that point the DMC to key issues.

Closed reports often include safety summaries that lack focus and do not consider event severity or events that might be targeted based on earlier studies.

Open reports are not concise and often include information that the DMC does not need to know.

What I Want to Know as DMC Member

Are the data up to date?

Are major outcome data complete?

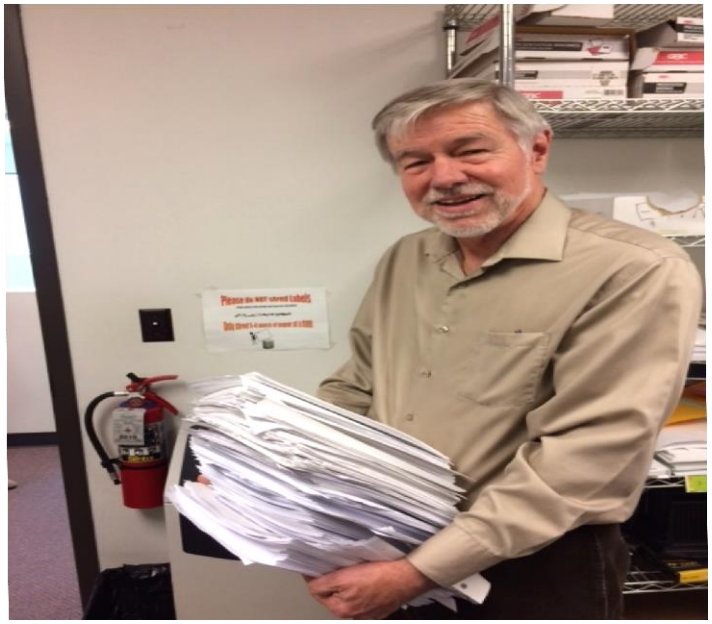
Do the open and closed reports do a good job of conveying strengths and limitations of the data?

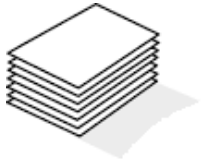
Do the tables and figures allow me to assess risk/benefit?

Is there consistent evidence of benefit or harm?

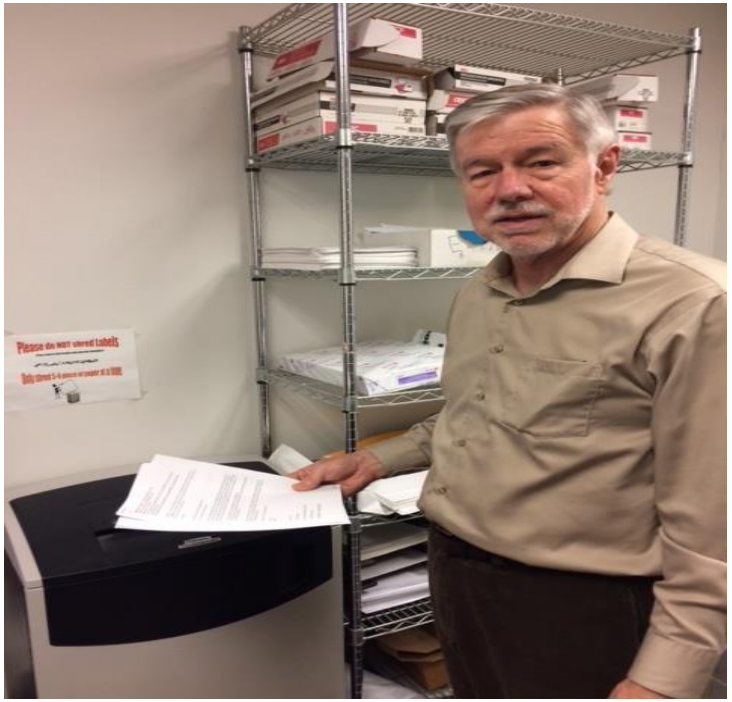
Am I missing the forest for the trees?

You Can’t Judge a Book by Its Cover





Big reports are not necessarily more informative.



Small reports can be informative.

Outline of Presentation

Background: Generally accepted standard operating procedures.

Key components of open reports, including external information

Key components of closed reports.

Key role of unblinded statisticians in preparing an optimal closed report.

Summary

Focus is on phase 3 (pivotal) trials and strategic trials (typically trials with clinical outcomes).

Background: Standard Operating Procedures (for the most part)

DMC review of protocol, charter and statistical analysis plan (SAP).

Open (sponsor, DMC, unblinded statisticians) and closed (DMC and unblinded statisticians) sessions with separate reports.

Data in closed reports is by treatment group (but not in open reports)

Coded treatment groups (e.g., A and B), but DMC knows what A and B are.

Safety and efficacy summaries in closed report to assess risk/benefit.

Reports distributed 1-2 weeks before meetings.

Recommendations at the end of each meeting (continue as planned, modify, stop) to sponsor and protocol leadership.

Caution: Some Details in Protocol and SAP May Be Missing or Unclear

How are major safety and efficacy endpoints defined and collected?

- Event- or visit-driven
- Checklist or open-ended
- MedDRA terms of importance
- Severity grading
- Event reports irrespective of causality assessment
- Collection of safety and efficacy after treatment discontinuation
- Adjudication procedures

Whether you are preparing a report or reviewing it, understand this.

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Open Report: Key Components

Response to previous DMC recommendations

Protocol history of amendments

Enrollment progress

Missing data

Timeliness of event reporting and adjudication

Protocol violations

Treatment adherence

Major safety concerns (e.g., safety reports, SUSARs, or “unanticipated problems”)

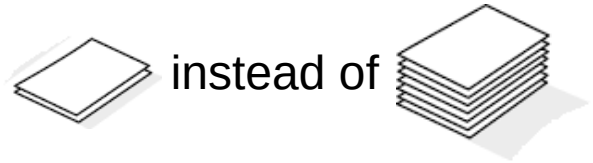
Assessment of design assumptions

Sample size re-estimation

New information from other studies

Open Report: What Not To Include

Open reports should be short and informative



Do not include:

Detailed summaries of baseline characteristics (share with trial investigators instead).

Safety and efficacy data combined across treatment groups (DMC will see data by treatment group; if shared at all, only do so for a small group of the study leadership).

Open Report: Preparation, Discussion and Dissemination (Case Example)

Blinded statistician (protocol statistician) prepares or requests data summaries from unblinded statisticians.

Blinded statistician prepares written report with protocol co-chairs.

Unblinded statisticians distribute open report with closed report.

Blinded statistician and protocol co-chairs discuss open report with DMC during open session.

Open report posted to study website along with DMC recommendations.

Reports to DMC of Relevant External Data

Considerations, whose responsibility and examples.

General Requirements for Informed Consent

Significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided.

WHAT IF THERE ARE NEW FINDINGS?

You will be told about any new information learned during the study that might cause you to change your mind about staying in the study.

Code of U.S. Federal Regulations Part 46, Subpart A, Section 46.116

External Information: FDA Guidance

"A DMC may be asked to consider the impact of external information on the study being monitored. Release of results of a related study may have implications for the design of the ongoing study, or even its continuation."

"The role of the DMC in considering interim changes to a study protocol or other aspects of a study conduct in response to external information **raises additional issues that merit consideration**."

FDA Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees.

Types of New External Information

A finding from a randomized study with the same or similar treatments.

A non-randomized study.

Changes in labeling due to adverse events (e.g., a modification to RISKS and/or DISCOMFORT section of consent).

Animal or laboratory studies.

Open Report: New External Information

Blinded investigators, including the funder and sponsor, should bear the primary responsibility for not only informing the DMC of external information, but also of informing the DMC about what they plan to do about it, if anything.

The DMC may disagree.

In some cases the DMC may:

- Recommend some unblinded information be shared with investigators and study participants.
- Request additional analyses of the unblinded statisticians during the closed sessions.

Examples

Concorde HIV trial (Lancet 1994); see Armitage P, Cont. Clinical Trials 1999.

Calcium to prevent preeclampsia (N Engl J Med 1997); see DerSimonian R Stat Med 1996 and JAMA 1997.

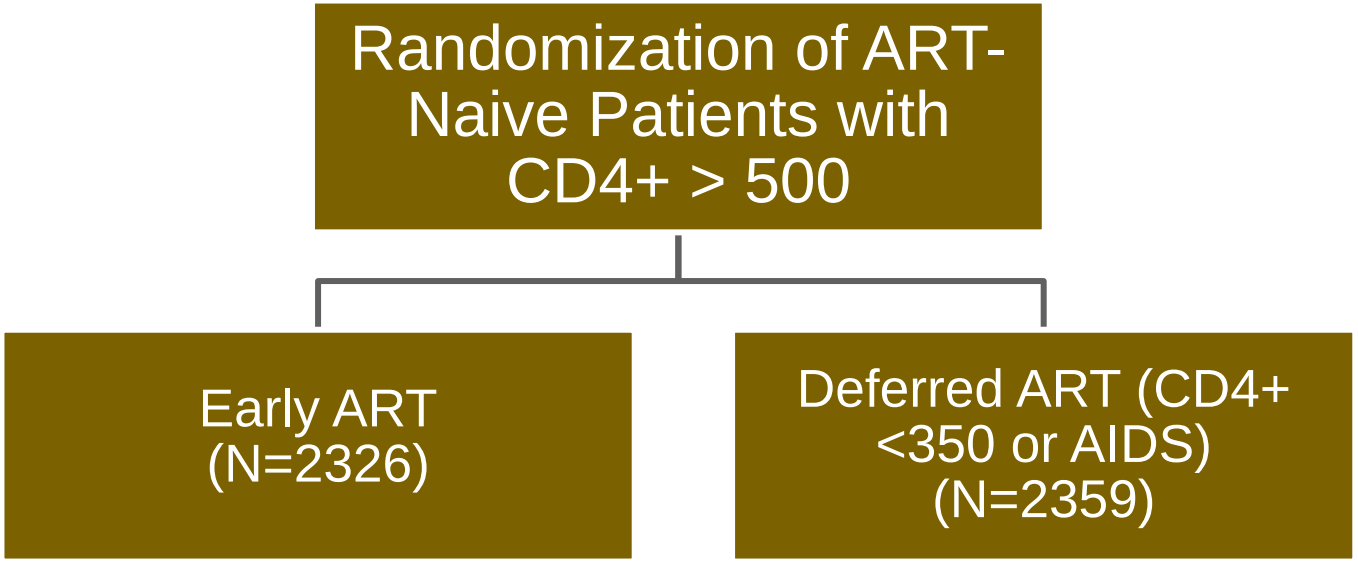
CMV prophylaxis trial (AIDS 1998); DMC recommended sharing some data; see Hillman D Cont Clin Trials 2003.

BEST heart failure trial (N Engl J Med 2001); DMC recommended early termination due to “information…from other studies of beta blockers…and by a concern about the equipoise of the trial”.

Hip protectors in fracture prevention trial (JAMA 2007); OHRP investigation of failure to notify research participants of potential risks. JAMA issues “Expression of Concern” regarding ethical conduct of the study. See Bauchner H (JAMA 2012) and DeMets and Ellenberg (N Engl J Med 2016).

Some of these examples are discussed in a DMC video training https://ictr.wisc.edu/

Handling External Information: An Example Close to Home -- the START Trial



N Engl J Med 2015; 375: 795-807.

START Trial

December 2008: Version 1.0 of protocol; observational study claiming benefit of early treatment cited; meeting with funder

May 2009: Investigators provided with protocol team assessment of observational study following its publication; DMC provided with team response.

December 2009: U.S. guidelines changed

December 2009 and January 2010: Investigators and participants notified of guidelines change; sites provided modification to sample informed consent.

May 2010: DMC provided team response to U.S. guidelines

May 2011: Investigators are informed of early release of HPTN 052 results

May 2012: DMC provided team response to HPTN 052 results

May 2013: DMC informed of upcoming changes in WHO guidelines.

May 2015: DMC informed of a recent presentation of a trial in Côte d'Ivoire.

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Closed Report: Key Components (1)

Brief summary of design, data collection and monitoring plans.

Executive summary with references to key tables and figures by page number.

Definitions of numerators and denominators, including key calendar dates (file creation, censoring).

Clear differentiation of missing information from information that has not been collected.

Completeness of event ascertainment; reasons for missing data, and how it is handled.

Baseline comparability.

Items in red are often missing.

Closed Report: Key Components (2)

Completeness of event adjudication and agreement of event adjudication with investigator report.

Adherence to each arm.

Major safety outcomes, including listings with consideration of severity, D/C of treatment, and whether pre-specified based on previous studies.

Major efficacy outcomes, including more clinically relevant components of composites.

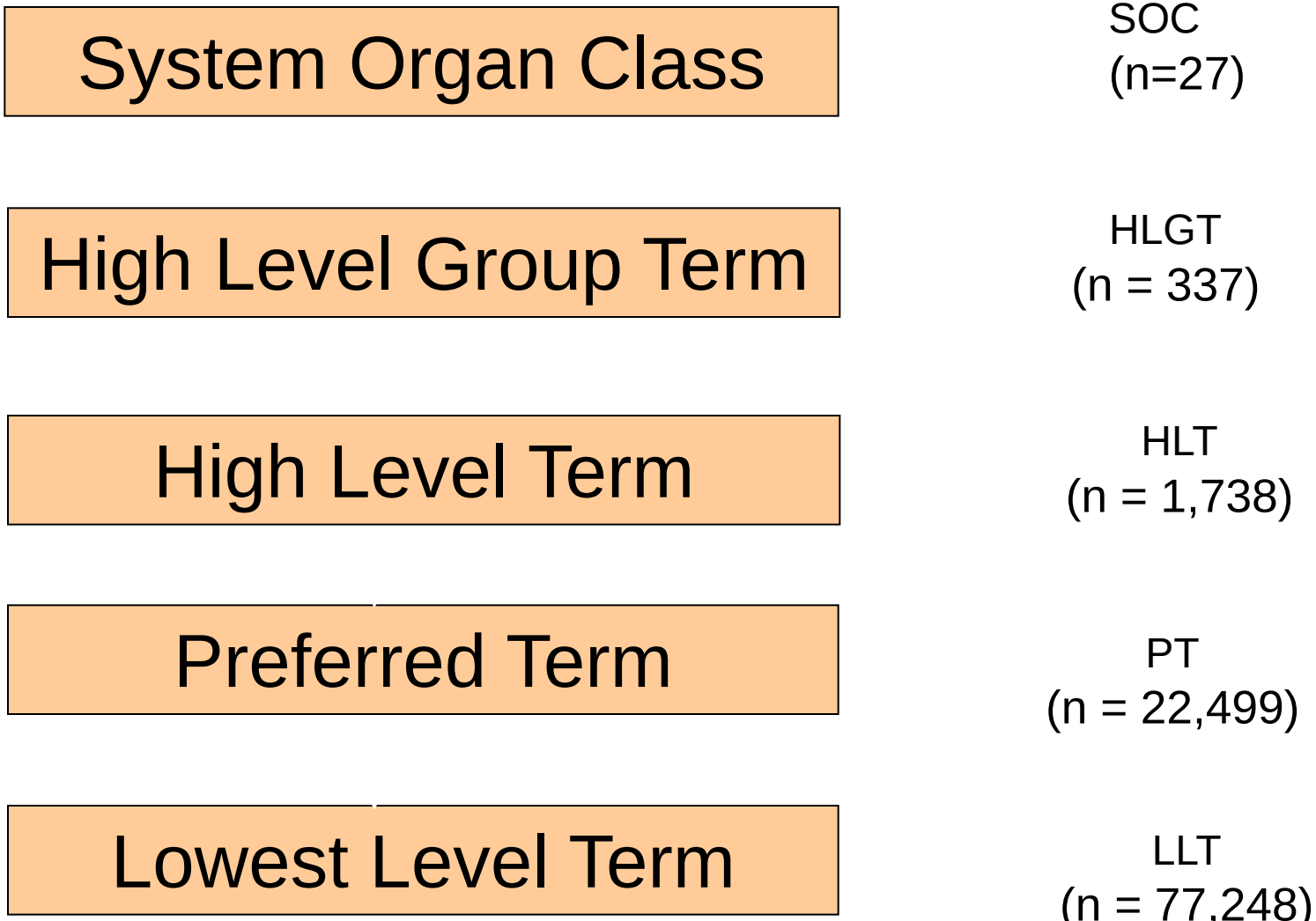
Finding for key subgroups.

Monitoring history with reference to guidelines (e.g., plot of critical values, assessment of completeness of information at each review).

A Simple Safety Summary

- A hierarchy of events and associated composites:
  - Death
  - Death or serious AE
  - Death or serious AE or treatment D/C due to AE
  - Death, serious AE, treatment D/C due to AE, or grade 4 event

How Much Granularity for Safety?



Medical Dictionary for Regulatory Activities (Version 20.0)

There is Risk of Missing Forest for Trees with Reports of Safety Data

Imagine a report by MedDRA Preferred Term (PT) that includes:

All adverse events

All adverse events related to treatment

All adverse events that lead to D/C

All serious adverse events

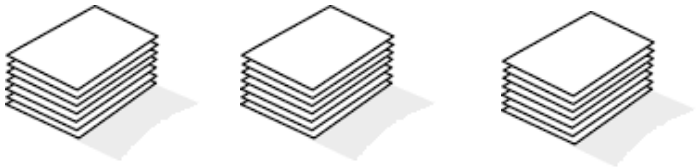
All serious adverse events related to treatment

For which it is unclear whether numerator is events or patients.

With no ability to combine data for several related events.

With no information on time course of events.

With no statistics to gauge significance of differences



A Numerator and Denominator Problem for a Major Endpoint

	Group A (N=aa)		Group B (N=bb)	
Event	No.	Pct.	No.	Pct.
CVD in 30 days	x	x.x	x	x.x
- CVD death	x	x.x	x	x.x
- Non-fatal MI	x	x.x	x	x.x
- Non-fatal stroke	x	x.x	x	x.x

But adjudication is several months behind and “aa” and “bb” are numbers randomized.

A Useful Summary of DMC Reviews: Number of Deaths by Treatment Group and DMC Review

Cutoff Date	File Created	Days dif.	Gp A deaths	Gp B deaths	Net gain
11 Dec 2003	22 Jan 2004	42	26	25	
			26	27	2
31 Dec 2004	9 Feb 2005	40	48	39	
			51	40	4
29 Oct 2005	29 Dec 2005	61	63	52	
			65	55	5
19 Aug 2006	19 Oct 2006	61	68	71	
			70	75	6

Numbers in red are data as of DMC review Nov 2007

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Key Role of Unblinded Statistician

Currently much variability.

Proposed pre-requisites, in addition to knowledge of statistics:

Familiarity with the data collection plan and protocol.

Capable of supplementary analyses without knowledge of sponsor and investigators.

Capable of writing a methods and results section for closed report.

Able to anticipate questions that will arise during closed session and to carry out additional analyses to address them.

Need independent thinkers?

Summary (1)

Open and closed reports should be concise and informative.

Reports should include executive summaries and make use of appendices for detail, including listings.

Open reports should address issues concerning trial conduct, new external information (broad definition), and sample size-re-estimation. Detailed summaries of baseline data or blinded safety/efficacy information should not be included.

Summary (2)

Closed reports should address timeliness and completeness of outcome data, adherence to treatment, findings for major safety (those pre-specified or an event hierarchy) and efficacy outcomes and key subgroups. Detailed summaries of MedDRA PTs should generally be restricted to severe events and included as an appendix.

Unblinded statisticians should be familiar with the protocol and data collection plan and be able to independently carry out analyses for the DMC that they or the DMC consider important.

Thanks