Creating a Better, Shorter DMC Report: A Stack of Needles, Not a Needle in a Haystack

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Abstract
Data Monitoring Committees (DMCs) are now standard for Phase 2 and Phase 3 clinical trials. A DMC is a group of 3-4 independent clinicians and statisticians who meet regularly during the course of the study to ensure the study is still ethical to continue by focusing on protecting the safety of trial participants, the credibility of the study, and the validity of study results. Ellenberg, Fleming, and DeMets’ provide an excellent overview of the DMC process.

Based on 15 years of experience with the production of DMC reports, we would like to share our insights into what distinguishes an effective DMC report from an ineffective one. Because DMC members have a limited time to review the report prior to the DMC meeting, the tables, listings, and figures (TLFs) should be designed to focus on safety signals or to establish the lack of safety signals as briefly as possible. The DMC can request additional follow-up material if the abridged report shows a signal or appendices can be provided in a searchable format along with the report.

Additionally, there are aspects of DMC monitoring that are intrinsically related to the real-time nature of reviewing a live database where data are still being actively entered and where the data have not been fully cleaned. For all trials, and especially for those with formal interim analysis, computation of ‘days overdue for next visit’ and Kaplan-Meier plot of time for next scheduled visit, and Kaplan-Meier plot of time overdue for next scheduled visit (2 pages).

What to Include in a DMC Report

Data Monitoring Committees’ primary evaluation is for safety. But the DMC also needs to review disposition data and, if specified in the DMC Charter, efficacy data.

Our philosophy is to start small, but make sure that all potential issues have some avenue to become apparent at a high-level. In the case that a potential issue emerges the DMC would, at their discretion, request from the Independent Statistical Center additional TLFS that provide further insights into the nuances of the issue.

The report is not a subset of the Final Statistical Report. It has to address issues specific to the DMC review. We follow the Goldilocks principle “not too big, not too little” and “The Airplane Rule” (should be able to be reviewed in the time spent flying to the meeting).

We advocate:
• More reports on disposition and study integrity
• More thought to the ‘real-time’ nature of the data
• More figures
• Including SAEs both from CRF and from Pharmacovigilance sources
• Including efficacy data as the critical counter-point to potential safety concerns
• Particular attention if a Clinical Events Committee / Events Adjudication Committee is part of the endpoint process.

What Not to Include in a DMC Report

We advocate:
• Exclude listings (generally include only SAEs / Deaths and abnormal labs)
• Exclude numeric summaries by visit
• Exclude ‘traditional’ lab shift tables
• Exclude TLFS not directly relevant to the responsibilities of the DMC

Proposed Table of Contents for a DMC Report

Executive Summary / Compare with Earlier Results
Summarize key results, and results at previous meetings for comparison to see if previous imbalances have increased or decreased (1 page)

Baseline and Disposition Summaries
• CONSORT Diagram
• Figure of cumulative enrollment (1 page)
• Demographics and baseline characteristics including stratification variables and summaries by region, country or site (5 pages)
• Major protocol violations, including eligibility violations (1 page)
• Time on treatment and of withdrawal from treatment including reasons, and Kaplan-Meier plot of time to withdrawal (2 pages)
• Time on study and of discontinuation from study including reasons, and Kaplan-Meier plot of time to discontinuation (2 pages)
• Time from last visit to clinical cut-off date and time overdue for next scheduled visit, and Kaplan-Meier plot of time overdue for next scheduled visit (2 pages)

• Number of visits seen versus number of visits expected at each scheduled time point, and graphically display (-5 pages)

Adverse Events Summaries
• AE top-line summaries by various classifications and subgroups (1 page).
• Tabulate number of subjects with at least one AE
• AE of grade 3+ severity
• AE of grade 4+ severity
• Treatment related AE
• AE resulting in withdrawal from treatment
• AE resulting in discontinuation from study
• AEs by System Organ Class (SOC) / Preferred Term (PT) (-20 pages)
• AEs by descending frequency of PT where >5% in any arm (-5 pages)
• SAEs from CRF in standard SOC/PT table (-5 pages)
• SAEs from CRF in standard SOC/Fatal AE table (-5 pages)
• (The denominator for this could be larger than for other tables)
• Grade 3+ severity AEs in standard SOC/PT table (-5 pages)
• AE resulting in withdrawal in treatment standard in standard SOC/PT table (-5 pages)
• AE resulting in withdrawal in treatment in standard SOC/PT table (-5 pages)
• Subgroupings of AEs of Interest, from MedDRA or from specific Pharmacovigilance tables
• Summary of Deaths, and Kaplan-Meier plot of time to death (2 pages)

Laboratory and Vital Signs
• Figures of means (-/+. 1SE) of lab parameters over time (-30 pages)
• Table by lab parameter of maximum toxicity across all visits (-5 pages)
• Including Standard Grade 3/4 lab values, including values from other visits (-10 pages)
• Figures of means (-/+. 1SE) of vital signs over time (-5 pages)

Efficacy
• Summary of primary and secondary endpoints, and p-values as appropriate and specified in the DMC Charter (-5 pages)
• Kaplan-Meier figures or other graphics as appropriate (-5 pages)
• If relevant, information on the concordance between site-proposed events and committee-confirmed events, and how many events are still to be adjudicated and timelines of adjudication (1 page)

Non-Traditional Outputs (Disposition)
These data are from a sample study comparing two treatments for patients at high-risk for heart failure. The primary endpoint is a composite of CV death, myocardial infarction, and stroke.

• CONSORT diagram: Allows the DMC to quickly understand the patient populations that follow and how many are still on treatment and on study.
• Figure of cumulative enrollment: Actual vs. projected enrollment helps the DMC determine if the study will have difficulty accruing the expected number of patients (and events) in a reasonable amount of time.

• Time from last visit to clinical cut-off date and time overdue for next visit
• Kaplan-Meier plot of time overdue for next scheduled visit
• Number of visits seen versus number of visits expected at each scheduled time point, and graphically display (-5 pages)

• AE of grade 3+ severity
• AE of grade 4+ severity
• Treatment related AE
• AE resulting in withdrawal from treatment
• AE resulting in discontinuation from study
• AEs by System Organ Class (SOC) / Preferred Term (PT) (-20 pages)
• AEs by descending frequency of PT where >5% in any arm (-5 pages)
• SAEs from CRF in standard SOC/PT table (-5 pages)
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• AE resulting in withdrawal in treatment standard in standard SOC/PT table (-5 pages)
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• Subgroupings of AEs of Interest, from MedDRA or from specific Pharmacovigilance tables
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Non-Traditional Outputs (Laboratory Data)

• Figures of means (-/+. 1SE) of lab parameters over time and counts of abnormal values: invaluable for quick review of data, and shows both global trends and individual toxicity results. Example: ALT (U/L)
• Table by lab parameter of maximum toxicity across all visits: rather than traditional shift tables that require summing the triangle of values that increase from baseline to post-baseline, we provide a simplified approach of maximum toxicity across all post-baseline visits.

• Kaplan-Meier plot of time overdue for next scheduled visit: Identify patients who are de facto ‘lost to follow up’. Overdue patients should receive extra attention from the study management team.

References

Conclusions
A well-laid out DMC Report includes only results critical for DMC evaluation, but can grow as data are seen that requires more investigation. This initial approach allows the DMC to more quickly review the material and focus, knowing that every table is providing valuable information.

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