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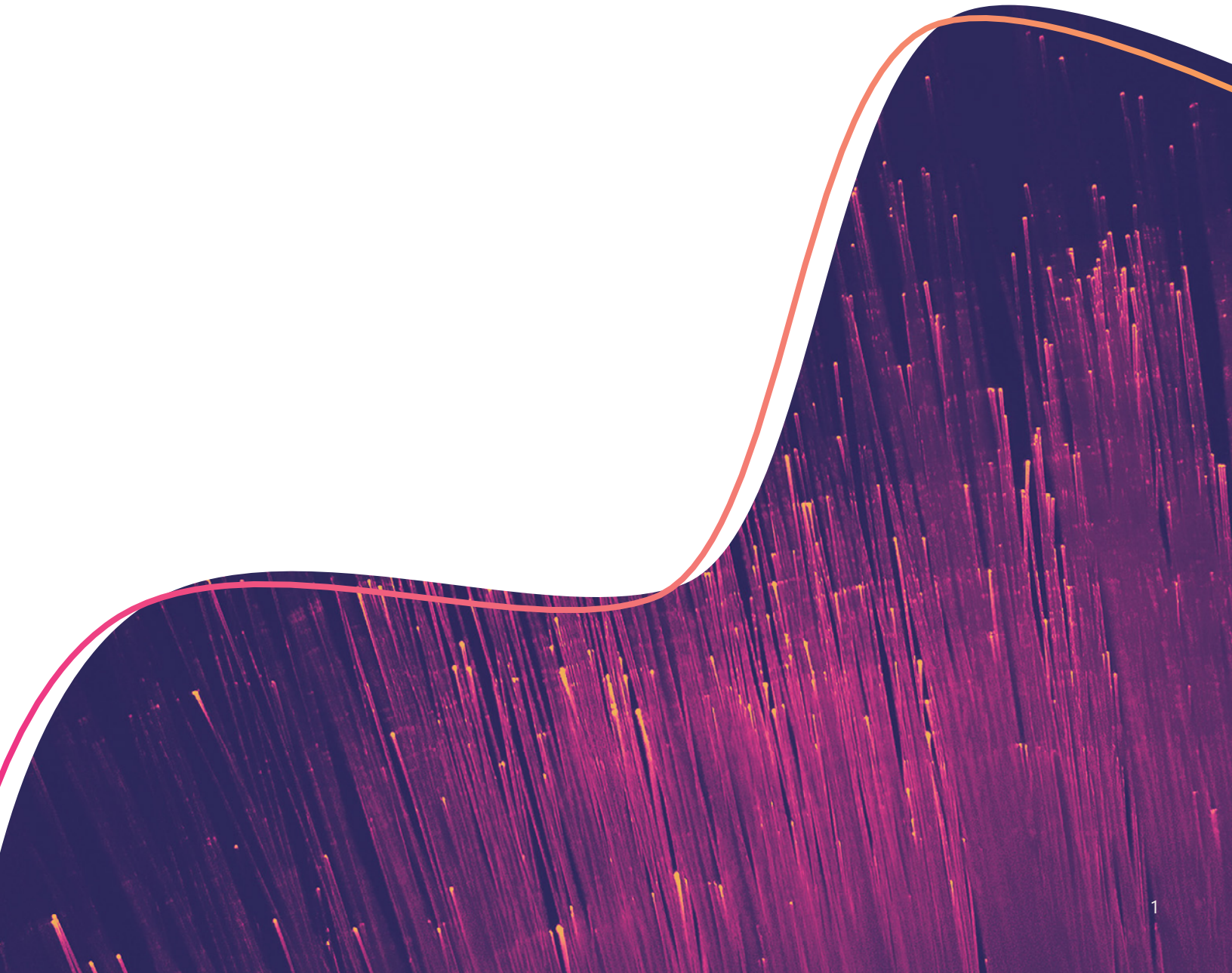
DMCs for Oncology Studies

By David Kerr and Bill Coar



Introduction

Data monitoring committees (DMCs) review data from ongoing clinical studies to make recommendations regarding study conduct based on risk-benefit. They are an essential component to ensure the integrity and safety of clinical studies. When DMCs were first introduced, they commonly oversaw large cardiovascular studies. Over the past few decades DMCs have shifted to the oversight of trials in other therapeutic areas, predominantly oncology. This change stems from the general increase in oncology research and the specific aspects of oncology studies that necessitate the involvement of a DMC.

These aspects, associated more commonly with oncology studies, include:

- The inability to conduct a blinded study
- The significant morbidity or mortality associated with the underlying disease
- The use of adaptive designs
- The potential for long-term safety monitoring after the primary analysis is performed

The DMC, the sponsor, and the Statistical Data Analysis Center (SDAC) facilitating the DMC's efforts must thoroughly understand these aspects.

Breakthroughs in oncology and the role of DMC

In recent decades, there have been remarkable advances in developing anti-cancer treatments. Immunotherapies, including CAR-T and CAR-NK cell therapies, checkpoint inhibitor anticancer drugs, and combination therapies, along with treatments focusing on genetic biomarkers like HER2+, EGFR, and PI-1 pathways, have given patients new hope. These advances are the direct result of the efforts of sponsors and patients in previous clinical studies that evaluated the efficacy and safety of these treatments. While the disease significantly impacts the patient's quality of life, the treatments themselves can be toxic. DMC oversight is crucial in these clinical studies to ensure patients do not experience excessive harm in the absence of a clinically meaningful benefit and perhaps have the option of stopping early for the overwhelming benefit or futility.

Understanding the FDA guidance and the implications for oncology studies

The FDA guidance on DMCs[1] notes that while all studies require monitoring, not all require a DMC.

Key considerations for a DMC:

1. Large, long, randomized multi-center studies
2. Studies where the primary endpoint is to prolong life or reduce major morbidity (or a seriously sick population, even if a lesser endpoint is used)
3. Studies involving vulnerable populations, such as children, the elderly, or those with diminished capacity
4. Studies with a priori safety concerns or potential serious toxicity
5. Instances where highly favorable, unfavorable, or futility outcomes could ethically require the termination of the study

We firmly believe that many, if not all, of these five considerations are relevant for oncology studies. The populations involved are generally seriously sick, and the treatments often cause or could potentially cause serious toxicity. In many situations, clear evidence of benefit or lack thereof could motivate early termination of the study. Additionally, many studies are late-stage (i.e., Phase 3) or involve vulnerable populations, such as a high proportion of elderly patients, or pediatric participants many of whom have exhausted standard chemotherapy options and are turning to immunotherapy studies as a last resort.

1: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees

Use of DMCs in oncology studies

Data monitoring committees (DMCs) are crucial in safeguarding the integrity and safety of clinical studies, particularly in the high-stakes field of oncology. As oncology research continues to expand, the unique complexities of these studies necessitate vigilant oversight to balance the potential benefits of innovative therapies against their risks.

We researched historical data on clinicaltrials.gov, the repository of information for clinical studies conducted in the United States. Among the data collected for each study is the phase and the use of a DMC. Our research shows that approximately 23% of studies started in the past 15 years focus on cancer treatment. Clinicaltrials.gov also provides information on the use of DMCs for these studies. Given the FDA guidance on the use of DMCs, it is not surprising that oncology studies have a higher rate of DMC use than non-oncology studies.

Our research shows that 41% of oncology studies use a DMC compared to 34% of non-oncology studies. When looking at Phase 3 studies alone, the overall rates and the imbalance are even greater — 78% of Phase 3 oncology studies employ a DMC compared to 43% of Phase 3 non-oncology studies. Given the high prevalence of DMCs in oncology studies, it's critical to consider the key differences in the DMC process for these studies.

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Key differences in how DMCs operate in oncology studies

Open-label studies

Open-label studies are common in oncology research. Even in later-phase randomized studies, the treating physician and the patient know which treatment regimen the patient has been randomized to (e.g., investigational product vs. standard of care) simply due to the mode of treatment required. While this approach makes the clinical operations of the study much more feasible to implement, DMCs may have concerns including:

Interpretation of immediate withdrawal

Immediate withdrawal from treatment or study is increasingly common. This may happen because subjects, not fully comprehending the study and randomization plan, choose to stay only if they're assigned to the novel intervention. We have seen subjects immediately withdraw from the treatment or the study if randomized to the control arm, especially when similar treatments are already available. This can lead to differential average treatment exposure and follow-up for safety and efficacy, making it difficult for the DMC and the sponsor team to interpret comparisons between the randomized arms.

Subjects who withdraw immediately or after just one treatment may not have efficacy endpoints collected, which leads to differential populations among those with endpoint data. For example, if only the 'frail' patients immediately withdraw when randomized to the control arm, the remaining subjects on the control arm might be the 'sturdy' patients and artificially appear to have better responses as a group because of that differential dropout. Safety imbalances may also develop due to longer follow-up in one arm, but this can be mitigated by summarizing safety events per 100 patient-years of follow-up, rather than per subject.

Review of investigator-assessed data

The DMC may need to view investigator-assessed data, such as the relationship of an adverse event (AE) to the treatment or proposed disease progressions. While the DMC may still review these results, they often downgrade their importance due to potential bias from investigators aware of the treatment arms. To address this possible bias, most oncology studies have a blinded independent review committee (BIRC) to assess possible disease progressions. The BIRC uses strict criteria and evaluates data without any knowledge of the treatment arm.

Firewall within the sponsor team

Determining who, if anyone, within the sponsor team can access specific data. For example, there could be a firewall so that only a few people at the sponsor can access the exposure data detailing which treatment each patient received. Similarly, the investigator-assessed relationship of treatment to AEs may not be included in an open report listing provided to the sponsor. These decisions must be made early to ensure clear communication about which information is available to different sponsor team members for discussion. Although some early phase studies may allow sponsor teams to see full details (e.g., in single arm or dose-escalation cohort studies), this is less common in randomized studies. The SDAC must be aware of these firewalling measures to avoid inadvertently unblinding any members of the sponsor team. While implementing a blinding plan may be outside of the DMC's responsibilities, it is incredibly important for everyone to understand the levels of unblinding at the sponsor, including the DMC.

Endpoints

Co-primary endpoints

Co-primary endpoints are common in oncology studies and require more advanced statistical techniques to analyze while preserving type-1 alpha, both at the study's conclusion and potentially during interim analyses by the DMC. These endpoints can have differential timing, such as final progression-free survival (PFS) data being available two years after the study starts, while final overall survival (OS) data may not be available until four years after.

The timing differences in co-primary endpoints raise the question — "Should the DMC stay involved until the final OS data is available or just until the final PFS is complete?"

Different sponsors and DMCs have their perspectives on this. We think it would be useful for sponsors to consider firewalling the final PFS and interim OS results from active study team members and the public. We suggest that the DMC continue monitoring the long-term OS data. There is a concern that unblinding the larger study team to final PFS and interim OS could introduce bias within the sponsor, impacting the acquisition and interpretation of OS data.

Public disclosure of the final PFS and interim OS data could also alter physician and patient behavior, introducing bias into the long-term OS data. For example, if there is public release and there is benefit of the novel treatment on PFS (and if the novel treatment is available for off-label use), many subjects on the control arm might immediately switch to the novel treatment, potentially attenuating an OS difference between the treatments that otherwise would develop with the capture of additional long-term OS data.

These concerns have been discussed in various Oncologic Drugs Advisory Committee (ODAC) meetings at the FDA, where PFS was used for accelerated approval, but the anticipated OS benefit was underwhelming. While we understand the sponsor's desire to move forward with regulatory activities and submissions, we believe there should be a balance between business needs and the desire to have statistically sound and interpretable results.

Assessing co-primary endpoints becomes particularly challenging for the DMC if discrepant trends are observed. A common scenario involves the DMC observing favorable (mature) PFS results during a data review meeting, while simultaneously noting adverse (less mature) OS results. Alternatively, the DMC might find a statistically significant benefit in PFS at an interim analysis but observe neutral OS outcomes. The DMC needs to decide how to synthesize these results and make appropriate recommendations for the study, considering the level of unblinding for the sponsor and the possible eventual regulatory pathway.

Dealing with immature data can be very challenging for the DMC, particularly if there are discrepancies in endpoints and/or the possibility of 'late-developing' or 'crossing curves' benefit with further follow-up. Oncology treatments frequently have the theoretic possibility of short-term toxicity accompanied by long-term benefits, making these early evaluations even more complex.

Secondary endpoints

Multiple secondary endpoints are also common in oncology, including:

Overall response rate (ORR) | Complete response (CR) | Duration of response (DOR)

These endpoints may not be fully consistent with primary or co-primary endpoints and need careful consideration. For example, DOR includes only a subset (perhaps a small subset) of the population — only those who had a response. One treatment might have a higher ORR (e.g., 10% vs. 5%), but the length of remission (DOR) among those who had that ORR is shorter (e.g., 2 vs. 4 months). It is not clear what order of preference the DMC would give the two treatments in the example above. It is also not clear how much emphasis should be placed on evaluation of a secondary endpoint on a (small) subset of patients with interim data.

The DMC can consider reviewing endpoint proxies, such as investigator-proposed PFS, if there is an excessive delay in obtaining the 'official' endpoint of PFS from a BIRC. But the DMC would also need to consider the implications of interpreting these results if there is poor concordance between these two sources, especially considering that the investigator-proposed PFS is from a source that is aware of the treatment taken by the patient. In some cases, assessing concordance may even be misleading. For instance, consider a study where only investigator-assessed events are sent in real time for BICR review. Non-events are typically sent in batches at fixed points in time. It is important for the DMC to fully understand this process where the (investigator) event data is far more current than the non-event data, simply by design. The DMC sometimes serves as an extra voice, encouraging sites and the BIRC to accelerate the adjudication process if there is an excessive delay in the BIRC process.

Efficacy assessment

Should the DMC be provided with efficacy outputs at each meeting? If so, should they include inferential statistics? These questions are contentious and should be addressed at the DMC's organizational meeting. Ad hoc efficacy and futility assessment by the DMC is not specifically an oncology issue but is seen more frequently in these studies. There are instances where the DMC observes overwhelming benefit in OS and alerts the sponsor, even in the absence of formal statistical guidelines, believing it may be unethical to delay access to such an efficacious treatment. Conversely, there are cases where the DMC observes toxicity and neutral PFS or OS and recommends stopping for futility, even in absence of formal statistical guidelines. A recent FDA draft guidance on DMCs[2] notes that efficacy endpoints reflecting significant morbidity or mortality, like most oncology study endpoints (such as PFS or OS), would have safety implications if their directionality was contrary to what was anticipated. Therefore, these should be considered safety domains and provided to the DMC as part of standard safety monitoring. We advocate that the SDAC have outputs of the endpoint(s) available to provide to the DMC if requested, at minimum without any inferential statistics, and perhaps using proxy data (e.g. investigator assessed PFS) if needed to help the DMC in their decision-making.

Censoring due to subsequent therapy

Another challenge for the DMC is interpreting data when there is an excessive rate of censoring due to patients receiving other anti-cancer therapy (perhaps based only on investigator assessment of PFS rather than BIRC assessment) or withdrawing from the study. While many statistical analysis plans suggest censoring PFS and/or OS events after the start of subsequent anti-cancer therapies, DMCs often want to see these events to assess whether the study treatment could impact the safety of subsequent therapy. Clearly everyone involved in clinical studies hopes for minimum censoring, but sometimes it is unavoidable. A particular concern arises when a site assesses that a progression has occurred and quickly starts the patient on a new anti-cancer therapy, only for the BIRC to later reject the supposed progression. At this point, the subject is typically considered censored and will not be able to provide the statistical information to help the study reach its minimum number of PFS events.

2: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-data-monitoring-committees-clinical-trials

Populations

Given that many participants in oncology studies are in advanced stages of their disease, having exhausted standard treatment options, the role of DMCs becomes even more critical. These committees not only protect the participants from undue harm but also ensure that the studies are conducted ethically and with the utmost consideration for the patients' circumstances.

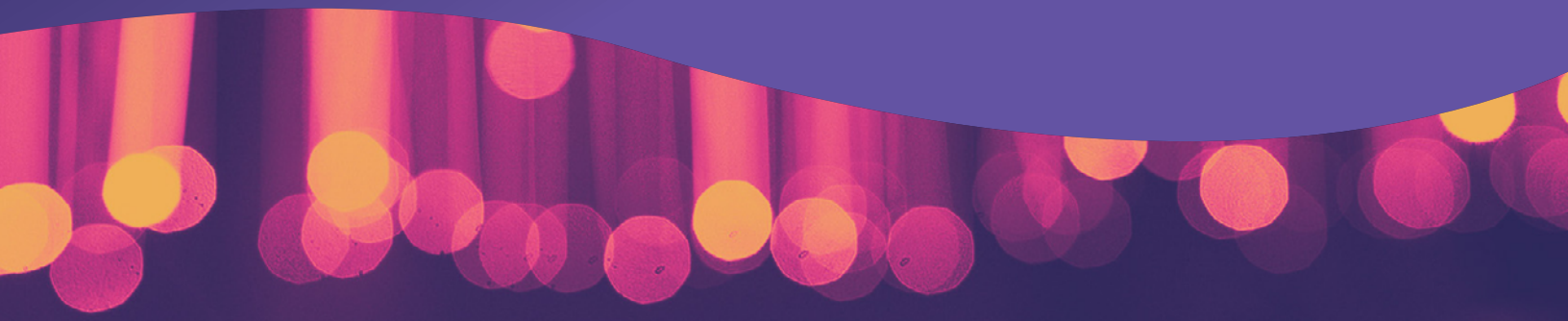
It is common for DMCs to make decisions based not just on multiple endpoints but also on multiple populations, which is difficult when results within those populations are inconsistent. For example, a study might have primary interest in analyzing the all-randomized population while also having a key secondary interest in analyzing the PD-L1<5% biomarker population or the squamous population, where the novel treatment is suspected to be particularly effective. Analyzing both groups naturally leads to a discussion about the dangers of over-interpreting subgroup results.

Another interesting and uncommon aspect is that the subgroup(s) of interest in oncology studies could change during the study based on information gained from other studies using the treatment or from studies of treatments with a similar mechanism of action. In the example above, a protocol amendment made by those with no knowledge of the current by-arm results of the study could change the key secondary population from the PD-L1<5% to PD-L1<1% biomarker population instead.

It is also common for oncology studies to have more than two treatment arms, such as new treatment plus standard of care (combination therapy) vs. new treatment alone (monotherapy) vs. standard of care. In such cases, the DMC has additional comparisons to review, possibly evaluating all three pair-wise combinations of these three treatment regimens. This raises concerns about multiplicity — performing more comparisons increases the chances of (spuriously) finding an apparent effect.

In other studies, particularly early phase studies, there is just a single arm or a process allowing dose escalation within specific cohorts. In these cases, both the sponsor team and DMC likely have access to the same information. The DMC is brought on as an independent voice, even though there is no data specifically created only for their review. It is valuable to have their insight when deciding to escalate to the next dose cohort or determining which dose is suitable for the subsequent Phase 2 study. The DMC may even be required by an IRB or country-specific regulations.

A cynical outsider might accuse members of the sponsor team of minimizing concerns about toxicity like dose-limiting toxicities or, in a CAR-T study, events such as cytokine release syndrome (CRS) or neurologic toxicity. Having the independent voice of the DMC speaking on behalf of the current and future patients helps alleviate those concerns in an early phase study, even if the DMC does not have traditional randomized comparisons to evaluate. These studies are a challenge for all to interpret without a control arm. There may be a statistical member still brought on to the DMC for these single arm studies (especially if there is a statistical algorithm guiding whether the events seen in a cohort trigger dose escalation, dose reduction, or accumulating more subjects at that dose).



Outputs created for DMC review

Many outputs created for DMC review are similar across all therapeutic areas. However, we have identified specific outputs that are particularly appreciated by DMCs in the oncology studies we worked on, while other outputs (such as lengthy summaries of continuous values by visit) are much less desirable or informative in the DMC setting. The duration of follow-up should be considered, which can be years in an oncology study—longer than in many other therapeutic areas.

Graphics are critical, especially for smaller studies. Some graphics that are particularly useful for early phase studies that look at individual subjects but in quick comparison to all other subjects, include:

Spaghetti or Spider Plot

Percent change in tumor burden over time

Waterfall Plot

Percent change in tumor burden

Swimmer Plot

Key events of dosing and disease assessment over time

Summaries of efficacy (e.g., PFS and OS) are traditionally displayed as **Kaplan-Meier figures**, perhaps after considering both investigator-assessed PFS and BIRC-confirmed PFS. PFS and OS results are frequently accompanied by a forest plot of key subgroups, especially at the time of formal internal analysis.

Tables are the primary source of information for the DMC. In large studies where subjects are very sick, there could be voluminous AEs, which may be due to the underlying disease, the new treatment, or the active comparator. In these cases, a summary of AEs by system organ class (SOC) and preferred team (PT) might run dozens of pages. Hence, the tables and focus of the DMC might be on just filtered outputs such as Grade 3+ AEs and/or SAEs and/or AEs of special interest.

Volcano plots of AEs allow the DMC to quickly assess the preferred terms that are both relatively imbalanced and common. The essence of a 20-page or longer AE table can quickly be distilled into a one-page volcano plot. The DMC can then refer to accompanying tables for more details if needed, based on the small handful of AE terms that stand out in the volcano plot.

Line listings are not typically useful to the DMC in mid-stage and late-stage oncology studies. The DMC will typically focus on by-arm differences, not individual cases. However, it is still common and helpful to have a handful of listings. These include listings of SAEs, deaths, and lab listings of Grade 3+ results (or perhaps even more filtered to just Hy's Law cases, or other specific domains of concern with lab data). If needed the SDAC can provide more information on a small selection of patients for ad hoc DMC review rather than generating hundreds or thousands of pages of listings.

The DMC may review **patient narratives**, particularly in earlier phase studies. These could be CIOMS or MedWatch forms for SAEs, SUSARs, or deaths. The DMC may look closely at dose-limiting toxicities or other major safety events (e.g., CRS) to see if they agree with site assessment and possibly create their own assessment of the relationship with study treatment. Looking carefully at individual cases is less common for later phase studies, particularly for late-stage cancers.

Flexibility of Statistical Data Analysis Center (SDAC)

In our experience, it is especially common in oncology studies to expect extremely rapid turnaround time for interim analyses. The actual data cut-off date may be months earlier, but once the data snapshot that has the final efficacy data is made, the SDAC is expected to create outputs within 2-3 days. The DMC is expected to review in just 2-3 days (or is sometimes given no time to review) prior to the DMC meeting date. This requires a lot of advance preparation to ensure a smooth process in the critical days leading up to the DMC's interim analysis. Conducting numerous test runs in advance with fake randomization can make everyone more comfortable. The exact timing of the meeting itself might not be known until late in the process, which leaves little time for scheduling the DMC meeting in advance. For instance, if the interim analysis is event-based, the clock starts ticking once the BIRC confirms that the exact needed n'th event has indeed been observed. One of the approaches we have used is to schedule multiple placeholder meetings in advance, for example, scheduling three meetings a few weeks apart with one being optimistic, one being per expectation, and one being pessimistic on the timing of the n'th event.

The process after the interim analysis meeting also needs to be carefully laid out. A flowchart can help describe the exact process of communication of DMC recommendations in different scenarios. This involves senior leadership receiving the results, independently confirming the SDAC results, perhaps performing some additional analyses (e.g., with the aid of a small group of unblinded supporting statisticians and programmers), and ultimately deciding whether to accept or reject the DMC recommendation and determining the next steps for the sponsor and regulatory agency notification.

The SDAC might assist in event projection or event tracking leading up to the interim analysis or perhaps the final analysis. Although the sponsor can often do this themselves, in some situations, event projection is based on data unavailable to the sponsor. For example, if a study has combination therapy vs. monotherapy vs. standard of care, the statistical analysis might require at least 250 events in each of the two pairwise comparisons: combination therapy vs. standard of care (SOC) and monotherapy vs. SOC. The sponsor team cannot determine this since it's based on randomized treatment. Even if the event projection or event tracking is done entirely by the sponsor, the DMC is often interested in these results. The DMC may be concerned about 'logistical' futility, where the study will finish many years later than originally intended due to low event rate, perhaps compounded by high censoring rate. The eventual clinical relevance of the study is a concern, especially with the comparator arms used if the study has excess delay, and whether the sponsor, sites, and patients have the stamina to continue through the long follow-up process.

Similarly, sometimes there is biomarker subpopulation. Although a baseline variable, the sponsor team may intentionally remain firewalled from it. If a minimum number of events is needed in that biomarker subpopulation, the SDAC would be the logical group to assist in determining the number of current events as well as using statistical methodology to predict when the needed number of events will occur. Some reflection is needed on exactly what is presented back to the study team. Unblinded information could be gleaned from the event projections/tracking provided by the SDAC depending on the rate of events accruing and the frequency of assessments by the SDAC.

It is also not uncommon in oncology to have a 'program-wide' DMC supported by the SDAC. The DMC reviews multiple studies, sometimes with unique protocols or through a platform, basket, or umbrella study as part of a single master protocol. Examples include comparing the novel treatment to different already-approved treatments or looking at the same comparison but in different types of cancers. The SDAC and DMC likely need extra time to respectively create and review the outputs for a 'program-wide' DMC. Additionally, the DMC may need wider representation of expertise for these 'program-wide' DMCs and consider how much informal or formal "meta-analysis" to perform in different studies to assess for common trends across the clinical program.

Conclusion

In conclusion, the oversight provided by DMCs is indispensable in the realm of oncology studies, where the stakes are extraordinarily high. By understanding and addressing the specific challenges outlined in this white paper, DMCs, sponsors, and SDACs can collaboratively ensure that these studies are not only scientifically rigorous but also ethically sound, ultimately paving the way for safer and more effective cancer treatments.

About Axio & Cytel

Axio, with over 35 years of expertise in Data Monitoring Committees (DMCs), became part of Cytel following its acquisition in 2019, and now serves as Cytel's dedicated DMC division.

Cytel is the world's leading provider of cutting-edge solutions, quantitative methods, and statistical software for the life sciences industry, committed to advancing human health. For nearly four decades, Cytel has pioneered adaptive trial design, using data-driven insights to inform strategy across all phases of drug development and commercialization. Cytel continues to drive innovation in clinical research by accelerating drug development, improving success rates, and delivering better patient outcomes. Headquartered in Cambridge, Massachusetts, Cytel has a global presence with more than 2,000 employees across North America, Europe, and Asia. Learn more about how Cytel is harnessing the power of data to transform healthcare, visit www.cytel.com.

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