

The DMC Experience in Response Adaptive Learn Trials

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Key Lessons Learned (1)

- **DMC typically had the need to consult with executive management at one or more points during the trial**
 - Required help in trial decision-making, informed management of progress to support business decisions
 - Formal executive steering committee (even if completely sponsor internal), and rules for interaction among various parties, proved helpful
- **Early data processing runs insured that things worked smoothly when decision-making was required**
 - Identify data flow issues (e.g., missing lab data)
 - Alert DMC to the need for supplemental analyses
- **Tools to predict package requirements can minimize extra drug supply costs that potentially arise with an adaptive design**
- **A wide range of scenarios must be considered at the planning stage so we're not surprised by the model's performance**
 - For example, the null scenario might be the worst one considered
 - May not fully appreciate how the model performs when test drug is seen to be worse than placebo



Key Lessons Learned (2)

- **The independent statistical center allowed information to be expeditiously provided (including supplemental analyses) without study team involvement/knowledge**
 - Particularly useful for dealing with non-standard analyses (e.g., relating to the Bayesian approach)
 - May be able to accomplish the same thing with an internal structure (separated from the project team)
- **Still assessing best approach for involving the project team**
 - Should team be involved with making decisions? If so, at what stage? Who from the team should be involved?
 - Does the team always need to be involved in implementation of a decision (e.g., dropping a treatment group)?
- **Best practices are evolving and we're unlikely to have a "one size fits all" approach. Processes for each study must be determined and prospectively documented in the DMC charter.**



Recent Experience with Adaptive Learn Phase Trials

- **We focus on our recent experience with response-adaptive learn phase trials**
 - Experience is illustrated through 3 case studies
 - Infrastructure required to execute the trials and implement the numerous decisions during the trials is described
 - Specific logistical challenges and decision problems are presented for each case study
- **We share some lessons learned during the execution of these three trials**
 - The trials were all run during approximately a 2 year period
 - The DMC members generally had limited formal DMC experience at the beginning of this process; some lessons came with gaining experience
 - We were also faced with situations relating to the response adaptive nature of the designs (frequent decisions to be made) and being in the learn stage of the clinical development process (who should have access to information)



Similarities and Differences Across the Three Case Studies

- **Common design features**
 - placebo controlled
 - dose-ranging (4-7 dose groups of test drug)
 - study could be terminated, or doses could be dropped, for futility and/or intolerability
- **Key design differences**
 - 2 of 3 studies included an active control
 - 2 of 3 studies allowed stopping for success (adequate efficacy/sufficient information)
 - 1 study included all dose groups from the start, the others added dose groups based either on response or the availability of drug supply
 - 2 of 3 studies had response-adaptive dynamic randomization, other was a 2-stage trial where additional groups could be opened in second stage
 - decisions in 1 trial driven by single efficacy endpoint; the other trials focused on an efficacy endpoint plus an additional endpoint (in one case a safety endpoint, in the other a composite endpoint incorporating both efficacy and safety)



Design Overview for the 3 Case Studies

| | Case Study 1 | Case Study 2 | Case Study 3 |
|---------------------------------|---------------------------------|----------------------------------|-----------------------------|
| Placebo Controlled? | Y | Y | Y |
| Active Controlled? | N | Y | Y |
| No. of Test Drug Groups | 5 | 4 | 7 |
| Stopping for Futility? | Y | Y | Y |
| Stopping for Intolerability? | Y | Y | Y |
| Stopping for Success? | Y | N | Y |
| Starting with all Doses? | Y | N (waiting for stage 1 response) | N (waiting for drug supply) |
| Response-adaptive Allocation? | Y | N (could add groups in stage 2) | Y |
| No. (Type) of Primary Endpoints | 2 (one efficacy, one composite) | 2 (one efficacy, one safety) | 1 (efficacy) |



Case Study #1: Design Details

- **Six treatment arms (placebo, 5 dose groups); balanced randomization for first 120 subjects (20/group)**
- **Dynamic response-adaptive allocation from 121st subject onward, based upon emerging data (maximum sample size of 420)**
- **Interim analyses performed weekly to estimate the dose-response; 4 comprehensive interim analyses planned after randomization of 90th, 180th, 270th, and 360th subject**
- **Study could be terminated for safety-related reason anytime, for futility or positive efficacy/sufficient information anytime after randomization of 210th subject**
- **Decision making driven by two endpoints; both were measured as the number of events per week**



Case Study #1: Design Details (2)

- **Primary endpoint expressed as number of events per week during a 4-week double-blind treatment period**
 - Events per week for test drug dose groups compared to events per week for placebo
 - Events per week also anticipated to be primary endpoint for any subsequent phase 3 trial
- **Secondary endpoint also measured as events per week during a 4-week double-blind treatment period**
 - Anticipated dose-limiting toxicity expected to result in diminished response for secondary endpoint (but not for primary endpoint)
 - Secondary endpoint used to facilitate identification of optimal dose by incorporating efficacy and dose-limiting toxicity into a single measure
- **Distinct dose-response models employed for the two key endpoints, along with longitudinal model to ensure full use of accumulating data**



Case Study #1: Design Details (3)

- **The two primary goals of the trials were to**
 - Identify dose with the maximal response on the secondary endpoint
 - Determine whether that dose could demonstrate superiority over placebo on the primary endpoint in a phase 3 trial of a fixed maximum sample size (specified by the team, based on practical considerations)
- **Following an initial “burn in” period (20 subjects/group), adaptive allocation kicks in conditioned on the available data**
 - Goal was to preferentially allocate to treatment arms that provide best learning about dose-response (keeping at least 15% assigned to placebo)
 - Specific learning goals were to identify dose with maximal response on secondary endpoint and to determine whether that dose could beat placebo on the primary endpoint in a phase 3 trial
 - Operationalized by minimizing variance functions related to these goals
 - Tends to allocate preferentially to efficacious and well-tolerated doses



Case Study #1: Design Details (4)

- **The study could be stopped, or a dose group could be dropped, for safety concerns at any time (not driven by a formal decision rule)**
- **Once 210 subjects had been randomized, the DMC would receive a weekly recommendation based on a computer algorithm regarding whether or not the trial should continue**
 - Stopping for “success” based on having identified optimal dose with high degree of assurance and having a sufficiently high likelihood of phase 3 success with that dose
 - Stopping for futility based on a sufficiently high likelihood that the drug did not have a clinically meaningful advantage over placebo (considering posterior probability estimates)
 - Doses were not dropped for futility, although the allocation probability for a dose could be (temporarily) set to 0



Case Study #1: Drug Supply Considerations

- **The drug supply requirements were less predictable than with a traditional design**
 - Large number of dose groups
 - Dynamic centrally-randomized treatment allocation
- **To ensure availability of the required treatment, more than the usual number of double-blind packages were required**
 - Overall cost of drug supply was approximately twice what it would have been with a traditional design
 - This needs to be considered as part of the business case
 - Steps were taken to minimize the extra drug supply costs
- **Model developed to predict drug supply demands**
 - Considered screen failure rates and updated allocation probabilities
 - Provided predicted requirements based on 95% and 99% assurance of having needed supplies (avoiding “forced randomization”)
 - Generated list of supplies needed for each site
 - One week delay built in to resupply sites before updating IVRS



Case Study #1: The DMC Charter

- **Trial overseen by DMC consisting of a physician, clinical pharmacologist, and biostatistician**
 - Affiliated with the sponsor, but with no day-to-day trial role
 - Key results relating to primary and secondary endpoints provided weekly (4 more comprehensive data reviews were scheduled)
- **The weekly information included current estimate of dose-response curve for the two key endpoints (observed means and model-based estimates)**
- **DMC also provided with several probabilities key to the decision process (based on a Bayesian approach)**
 - Posterior probability of having identified the best dose
 - Posterior probability of any dose being better than placebo by the pre-specified minimal clinically significant degree
 - For each dose, the posterior probability of it being the best dose and the second best dose
 - The predicted probability of phase 3 success



Case Study #1: The DMC Charter (2)

- **DMC also provided with summary results by study week**
 - Primary focus on results across the entire 4 week double-blind period
 - Weekly results facilitate investigation into possible time effect or treatment-by-time interaction, allow performance of longitudinal model to be assessed
- **Analyses generated by an independent statistical center and provided to the DMC through sponsor-internal statistician not affiliated with the project**
- **The DMC consulted with executive management as required**
 - Any such interactions were documented
 - There was no formal executive steering committee structure



Case Study #1: The DMC Experience

- **From early in the study until the eventual termination due to futility, the dose-response curve was essentially flat (no dose separated from placebo)**
 - Never a suggestion that any dose was better than placebo by the clinically significant degree targeted during the design stage
 - End of study predictions consistently showed that demonstrating efficacy was highly unlikely
 - However, the formal futility criterion was never satisfied
 - Although the mean responses for all doses fell in a narrow range, a slight advantage for the higher doses led to a shift in allocation proportions once the trial moved beyond 120 subjects enrolled
- **The futility criterion was quite stringent**
 - Requirement was that the best dose have less than a 1% chance of a clinically meaningful advantage over placebo
 - Based on a relatively small – easy to achieve – value for the meaningful advantage
 - DMC became concerned that the futility criterion was overly stringent



Case Study #1: The DMC Experience (2)

- **The decision guidelines are assessed through a simulation exercise during the planning stage**
 - There is a trade off between the desire to stop early for an ineffective drug vs. the concern that we will (incorrectly) kill a good drug
 - While our rules didn't lead to type 1 errors, we were fairly likely to reach the end of the trial before recognizing an ineffective drug
 - During the design discussions with the team (who thought the drug would work), the main concern was that we would kill a good drug
- **The DMC was faced with a consistent pattern of a flat dose-response curve; while very likely headed to declaring the drug ineffective, the futility criterion was not yet met**
 - DMC had the latitude to overrule the formal decision rules, considering a variety of factors including pharmacokinetic data
 - The DMC requested posterior probability estimates for a clinically meaningful advantage over placebo based on alternative criteria for clinical significance (and associated end-of-study predictions)
 - Requests were implemented within 24 hours without involvement of project team, confirming low likelihood of meaningful treatment effect



Case Study #1: The DMC Experience (3)

- **The DMC recommended terminating the trial for lack of efficacy before the formal futility criterion was satisfied**
 - The consistency of results over many weeks, always indicating little chance of a meaningful advantage over placebo, made the DMC comfortable with the decision
 - Further support for the decision was provided through pharmacokinetic analyses
- **Although the investigational drug failed to demonstrate efficacy, we feel that the adaptive design was beneficial**
 - The modeling and adaptive allocation facilitated efficient learning about the dose-response curve
 - The wealth of information provided to the DMC enabled decision-making (posterior probability estimates, end-of-study predictions)
 - The infrastructure allowed supplemental analyses to be efficiently provided, without involvement of the study team
- **The DMC was able to consult with executive management as required; however, we recognized that having a formal steering committee (and rules for interaction) would be preferable**



Case Study #2: Design Details

- **Six treatment arms (placebo, active comparator, 4 dose groups)**
- **Two stage design**
 - Stage 1: Equal allocation to placebo, active comparator, and the two middle doses of investigational drug (“low” and “medium”), to a maximum of 240 subjects
 - Stage 2: Subjects allocated to placebo, active comparator, and up to four different doses of investigational drug (“very low” and “high” groups added), to a maximum of 500 subjects (stages 1 and 2 combined)
- **Decision criteria based on posterior probabilities applied to determine**
 - Whether and when to make the transition to stage 2
 - Whether and when to terminate the trial for futility or safety
 - Decisions based on investigational drug being very likely (or very unlikely) to have an advantage over the active comparator
 - If stage 1 enrollment reached 240 without a clear recommendation to terminate the trial or move early to stage 2, stage 2 would be initiated



Case Study #2: Design Details (2)

- **Interim analyses performed weekly to estimate the dose-response; 3 comprehensive interim analyses planned after randomization of 100th, 240th, and 375th subject**
- **Study could be terminated for safety-related reason anytime, for futility after 100th subject treated for at least 4 weeks (that was also earliest point for transition to stage 2)**
- **Two stage design implemented to obtain early read on efficacy and safety**
 - Maximize allocation to efficacious and well-tolerated treatments
 - Minimize exposure to potentially harmful doses
- **Maximum enrollment was 500 subjects; if trial progressed to stage 2, subjects allocated in proportions intended to lead to equal enrollment at the end of the trial**



Case Study #2: Design Details (3)

- **Enrollment to additional dose groups in stage 2 conditioned on stage 1 results**
 - Opening high dose required evidence of safety at doses used in stage 1
 - Opening very low dose required evidence of efficacy at the low dose
- **Doses could be dropped in stage 2 based on emerging safety or efficacy trends**
- **Decision making driven by two endpoints (one efficacy, one safety)**
 - Primary efficacy assessment at week 12; primary safety assessment at week 24
 - Earlier assessments of these endpoints were also made and longitudinal models applied to obtain most information possible from subjects with incomplete data
 - In stage 2 (with >2 investigational drug dose groups), dose-response models would also be applied



Case Study #2: The DMC Charter

- **Trial overseen by DMC consisting of two physicians and a biostatistician**
 - Affiliated with the sponsor, but with no day-to-day trial role
 - Key results relating to primary and secondary endpoints provided weekly (3 more comprehensive data reviews were scheduled; an additional run could be requested at any time)
- **The weekly information provided to the DMC included**
 - Current estimate of dose-response curve for the two key endpoints (observed means and model-based estimates)
 - Posterior probabilities required for decision-making (conditional probabilities that the test drug was superior to the active control)
- **In addition to the sponsor-affiliated DMC members, two nonvoting external members with therapeutic area expertise were appointed**
 - Participated in the review of the more comprehensive data packages
 - Advised voting members regarding the transition to stage 2 or a decision to terminate the trial



Case Study #2: The DMC Charter (2)

- **DMC also provided with summary results by study week**
 - Focus was on results at the primary time points (week 12 for efficacy, week 24 for safety)
 - Weekly results facilitate investigation into possible time effect or treatment-by-time interaction, allow performance of longitudinal model to be assessed
- **Analyses generated by an independent statistical center and provided to the DMC through sponsor-internal statistician not affiliated with the project**
- **The DMC recommendations were presented to key members of the project team and ultimately to executive management for approval**
 - Any such interactions were documented
 - There was no formal executive steering committee structure
- **This approach differs from that used in first case study**
 - Best practices for a learn study are still evolving
 - Who is in the best position to make decisions?



Case Study #2: A Data Availability Issue

- **Key data elements had been identified up front**
 - Essential for the required interim report packages
 - Drivers of the algorithmic decision recommendations
- **It became apparent that the anticipated amount of data was not available in the sponsor's database (only had 20% of what we expected)**
- **One of the primary endpoints was a laboratory assessment**
 - Original contract with central lab stipulated that data transfer for a patient would occur only when all lab test results were available
 - One of the analytes (of secondary importance) was taking a long time to run and holding up everything else
 - Contract restructured to allow partial data transfers, giving us what we anticipated/needed in our database
- **Issue was particularly critical because of the adaptive design; early data processing runs (before decision-making is required) can help to identify problems**



Case Study #2: The DMC Experience

- **There was never a suggestion of an unacceptable effect on the primary safety endpoint during the DMC reviews**
 - No other safety issues arose
 - DMC deliberations focused on the efficacy side
- **When examining the emerging efficacy data during stage 1, the test drug was seen to fall short of the active control**
 - Noted even before 100 subjects were enrolled (before action could be taken)
 - Occasionally crossed the threshold for futility
 - DMC began to review efficacy data in depth to search for supplemental analyses that might guide upcoming decision
- **Model-based efficacy estimate and observed data at week 12 showed poorer response for test drug than active control; interestingly, the test drug matched the active control at the earlier observation times (before falling behind)**



Case Study #2: The DMC Experience (2)

- **This pattern suggested one of two possible explanations**
 - The observed pattern was actually occurring in our study population
 - Early study entrants with complete data demonstrated poorer efficacy for the test drug, but later study entrants with incomplete data were doing better on the test drug
 - If the latter were true, we would anticipate that with more complete data the test drug would eventually reflect the improved response at week 12
- **To investigate this issue, the DMC requested a report for the cohort of week 12 completers**
 - This allowed us to follow this cohort over time, and to compare the early data from this cohort with that from subjects who entered subsequently
 - The DMC also examined whether any of the modeling assumptions might be unduly influencing the conclusion
 - The supplemental information was expeditiously provided without study team involvement; it failed to demonstrate that a turnaround favoring the test drug was likely to occur



Case Study #2: The DMC Experience (3)

- **The analysis based on 100 subjects reaching 4 weeks fell just short of crossing the futility threshold**
 - Based on deliberations of the full DMC, the study was allowed to continue although we recognized that futility would likely be declared in the near future
 - Various secondary endpoints/supplemental analyses were identified, to continue digging into the data to give the test drug every possible chance to succeed (especially since no safety concerns had emerged)
- **Futility was, in fact, declared soon thereafter**
- **Although the investigational drug failed to demonstrate adequate efficacy, we feel that the design performed well**
 - The active control performed as expected
 - The investigational drug appeared to be safe and pharmacologically active, but fell short of the profile needed to warrant further development
 - The futility guideline, developed through an extensive simulation exercise, was beneficial during the DMC deliberations
 - The DMC requested supplemental analyses to increase their comfort with the futility decision, efficiently provided within our infrastructure



Case Study #3: Design Details

- **Nine treatment arms (placebo, active comparator, 7 dose groups); only 3 of the test drug dose groups used at start of the trial (drug supply constraints); balanced randomization for first 50 subjects (10/group for the 5 groups used initially)**
- **Dynamic response-adaptive allocation from 51st subject onward, based upon emerging data (maximum sample size of 450)**
- **Interim analyses performed weekly to estimate the dose-response; 4 comprehensive interim analyses planned after randomization of 100th, 200th, 300th, and 400th subject**
- **Study could be terminated for safety-related reason anytime, for futility or positive efficacy/sufficient information anytime after randomization of at least 5 subjects to each dose group**
- **Decision making driven by an efficacy assessment at week 4**



Case Study #3: Design Details (2)

- **A dose-response model was employed for the primary endpoint, along with a longitudinal model to ensure full use of accumulating data**
- **The randomization allocation was designed to identify**
 - The MED (smallest dose with the minimum desired advantage over placebo)
 - The dose with the maximum effect (MaxD)
- **Allocation to placebo and active control kept at 20% each throughout the trial; remaining subjects allocated to one of the 7 doses of investigational drug**
- **Stopping for success/sufficient information required**
 - MED and MaxD identified with high degree of assurance (based on posterior probabilities)
 - High degree of assurance that MaxD achieved clinically meaningful advantage over placebo



Case Study #3: Design Details (3)

- **Stopping for futility required a high degree of assurance that no dose achieved a clinically meaningful benefit over placebo (based on posterior probabilities)**
- **Doses were not dropped for futility, although the allocation probability for a dose could be (temporarily) set to 0**
- **The allocation algorithm and the stopping rules for both futility and success were based on comparing the investigational drug with placebo**
- **The comparison between placebo and active control was also critical to the DMC assessment**
 - Therapeutic area is known to have a high placebo response and a substantial proportion of trials have failed to separate an approved drug from placebo
 - Assessment of assay sensitivity internal to the trial (active control vs. placebo comparison) facilitated interpretation of results and helped to guide the DMC decision



Case Study #3: The DMC Charter

- **Trial overseen by DMC consisting of two physicians and a biostatistician**
 - Affiliated with the sponsor, but with no day-to-day trial role
 - Key results relating to primary endpoint provided weekly (4 more comprehensive reviews were scheduled)
- **The weekly information provided to the DMC included**
 - Current estimate of dose-response curve for the primary endpoint, plus response for the active comparator
 - Posterior probabilities required for decision-making
 - Updated randomization allocation proportions
 - End-of-study predictive probabilities
- **In addition to the sponsor-affiliated DMC members, five external physicians were appointed**
 - Three with therapeutic area expertise, two with expertise in other specialties who could help assess potential safety issues anticipated with the class of drug
 - Participated in the review of the more comprehensive data packages; advised the internal members when called upon



Case Study #3: The DMC Charter (2)

- **An adaptive design implementer, affiliated with the sponsor, was appointed as a nonvoting DMC member**
 - Formalize and expand the role of the sponsor-internal statistician
 - Oversight of system interfaces and data transfers
 - Ensuring that required material is available to other DMC members
 - Communicating any DMC requests for additional reports
 - Manage various logistical aspects (e.g., system validation, setting up contracts with external parties)
- **Executive steering committee established for the trial**
 - Consisted of two physicians and a statistician from sponsor's executive management team
 - DMC charter described when steering committee was to become involved and the processes to be followed
- **A pharmaceutical development and drug supply manufacturing liaison was also identified**
 - Senior manager affiliated with sponsor, with no direct trial involvement
 - Received DMC meeting minutes; done because of potential for emerging data to have major impact on future drug supply production



Case Study #3: The DMC Experience

- **Reports were generated to test the system shortly before 50 subjects were enrolled**
 - Preceded the point where adaptive randomization was to begin
 - An extremely high placebo response was noted, with placebo showing a better mean response than active control or any of the test drug groups
- **At the first look after 50 subjects had been enrolled, placebo again showed best response on the primary endpoint**
 - Active dose lagged slightly behind, 3 test drug dose groups showed poorer response
 - Of the test drug doses, the highest dose used was the best (that dose was actually 3rd highest of the 7 to be assessed); consequently the allocation generated by the model steered future enrollment towards the high end of dose range
 - Model already predicted that trial was likely to stop for futility although the unusually high placebo response (beating active control) would make interpretation difficult



Case Study #3: The DMC Experience (2)

- **At the next look, placebo continued to show the best response**
 - Eventual termination due to futility appeared very likely
 - Not yet that close to declaring futility, primarily due to the requirement that at least 5 subjects be randomized to each dose group
 - Of the test drug groups, the lowest dose now showed the best response (though still substantially behind placebo) and consequently the model assigned all future subjects to that dose
- **The allocation algorithm was constructed to assign subjects in proportion to the likelihood of a dose having a clinically significant advantage over placebo**
 - Because of the high placebo response, these probabilities were all tiny
 - With the small number of subjects and high placebo response, a minor shift in response had led to a dramatic shift in the allocation proportions
 - The assignment of all subjects to the low dose was troubling, as this dose was not expected to be effective and we would not move toward the 5 subject/group requirement for futility termination
 - The DMC elected to keep the current allocation schedule in place, and also requested additional reports to investigate the placebo response



Case Study #3: The DMC Experience (3)

- **Shortly thereafter the comprehensive analysis based on ~100 subjects was performed**
 - The placebo response remained extraordinarily high; placebo narrowly beat active control, with the test drug groups looking worse
 - The futility condition was not satisfied, although we appeared headed in that direction
 - The full DMC (including external experts) reviewed the safety and efficacy data (primary and secondary endpoints); several further reports were requested to investigate the placebo response
- **Though results were not definitive, it was becoming clear that the test drug was unlikely to show a meaningful advantage over placebo in this trial**
- **It was unclear whether we simply had a failed, noninformative trial with no assay sensitivity (not that rare in this therapeutic area), or it there was also valuable information about the test drug**



Case Study #3: The DMC Experience (4)

- **The pattern of results persisted and a few weeks later the futility criterion was satisfied**
 - There was no good explanation of the high placebo response, although many of the extreme responders were concentrated at a few sites
 - It was agreed that continuing the trial would not reverse the primary finding that test drug could not demonstrate an advantage over placebo
 - There was discussion within the DMC and then with the steering committee about the advisability of continuing the trial
 - Might the “failed trial” vs. “failed drug” question be resolved? Would a fresh start at new sites (different geographic locations) be worthwhile?
 - After a couple of weeks of deliberation, we decided to terminate the trial
- **The DMC and steering committee structures facilitated the data review and decision-making process**
 - An appropriate decision was made, limiting spending on hopeless cause
 - The model and decision rules performed reasonably well, although the extreme placebo response and initial unbalanced randomization raised some concerns (consider extreme scenarios during the planning stage)



Key Lessons Learned (1)

- **DMC typically had the need to consult with executive management at one or more points during the trial**
 - Required help in trial decision-making, informed management of progress to support business decisions
 - Formal executive steering committee (even if completely sponsor internal), and rules for interaction among various parties, proved helpful
- **Early data processing runs insured that things worked smoothly when decision-making was required**
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 - Particularly useful for dealing with non-standard analyses (e.g., relating to the Bayesian approach)
 - May be able to accomplish the same thing with an internal structure (separated from the project team)
- **Still assessing best approach for involving the project team**
 - Should team be involved with making decisions? If so, at what stage? Who from the team should be involved?
 - Does the team always need to be involved in implementation of a decision (e.g., dropping a treatment group)?
- **Best practices are evolving and we're unlikely to have a "one size fits all" approach. Processes for each study must be determined and prospectively documented in the DMC charter.**

