Axio

PARTNERS IN RESEARCH

DMCs and the Teams that Support Them

David Kerr

Director of DMC Services

15 Oct 2018

DMC 101

Too Many Names!

- **DMC – Data Monitoring Committee**
  - DSMB
  - DSMC
  - DMB
  - {I/i}DMC, etc.
- **SDAC - Statistical Data Analysis Center**
  - {I/i}DAC, {I/i}DCC
  - SAC,
  - Reporting / Unblinded / Independent statistician, etc.

Big Picture

- DMC is a
  - group of (independent) experts who
  - periodically receive (by-arm) reports
  - created by (independent) SDAC
  - using interim data from ongoing study(ies) in order to
  - make recommendations about the continuation of the study(ies)
  - based on their best judgment and (sometimes) specified guidelines.

Evolution of Guidance

- **Older:**
  - 'Greenberg Report' – issued 1967 / published 1988 – National Heart Institute
  - DMCs in Clinical Trials – A Practical Perspective (Ellenberg, Fleming, DeMets) – 2002 –updated edition soon?
  - FDA guidance – March 2006 (expires end of 2018)
  - EMA guidance – January 2006
- **Newer:**
  - Clinical Trials Transformation Initiative (CTTI) DMC recommendations – May 2016
  - "Data monitoring committees: Promoting best practices to address emerging challenges" Fleming et al, Clinical Trials 2017, Vol 14(2) 115-123"
  - "Data monitoring committees: Current Issues" Fleming, Ellenberg, DeMets, Clinical Trials 2018

Need For a DMC – per FDA

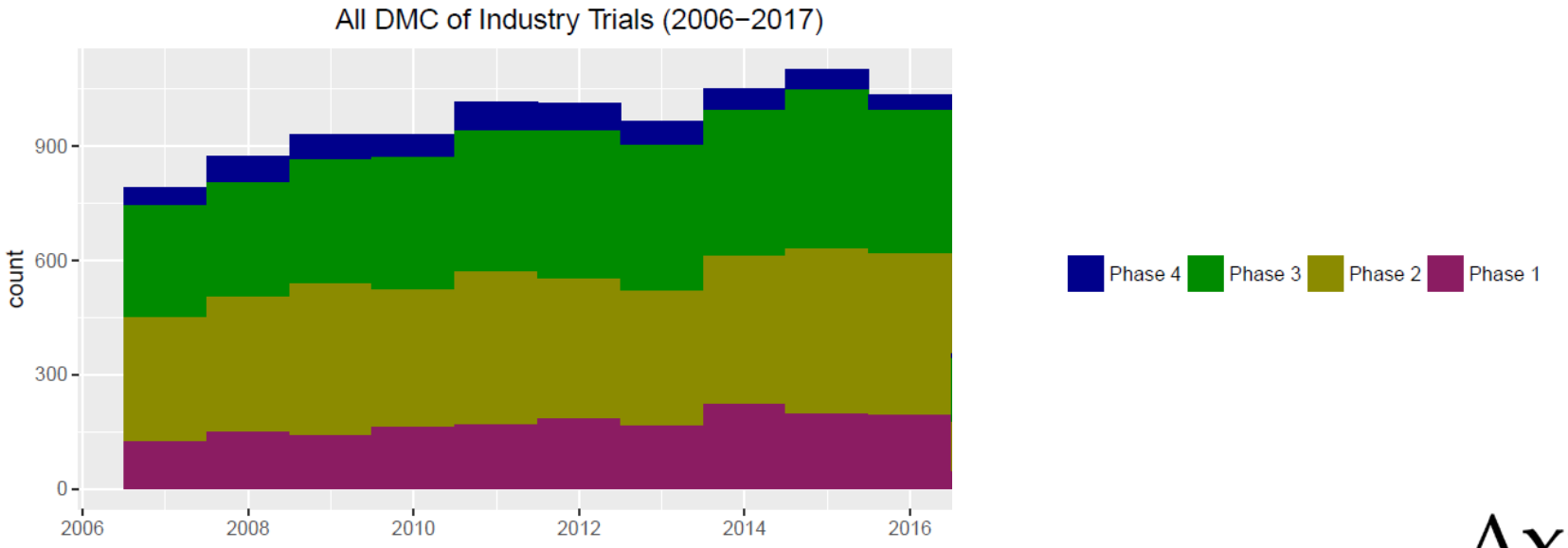
"All clinical trials require safety monitoring, but not all trials require monitoring by a (DMC)… We recommend sponsors consider using a DMC when:"

- Large, long, randomized multi-center study
- Primary endpoint for treatment is to prolong life or reduce major morbidity (or a seriously sick population even if a lesser endpoint used)
- Fragile population (children, elderly, diminished capacity)
- *a priori* safety concerns or possible serious toxicity
- Highly favorable or unfavorable or futility could ethically require termination of study

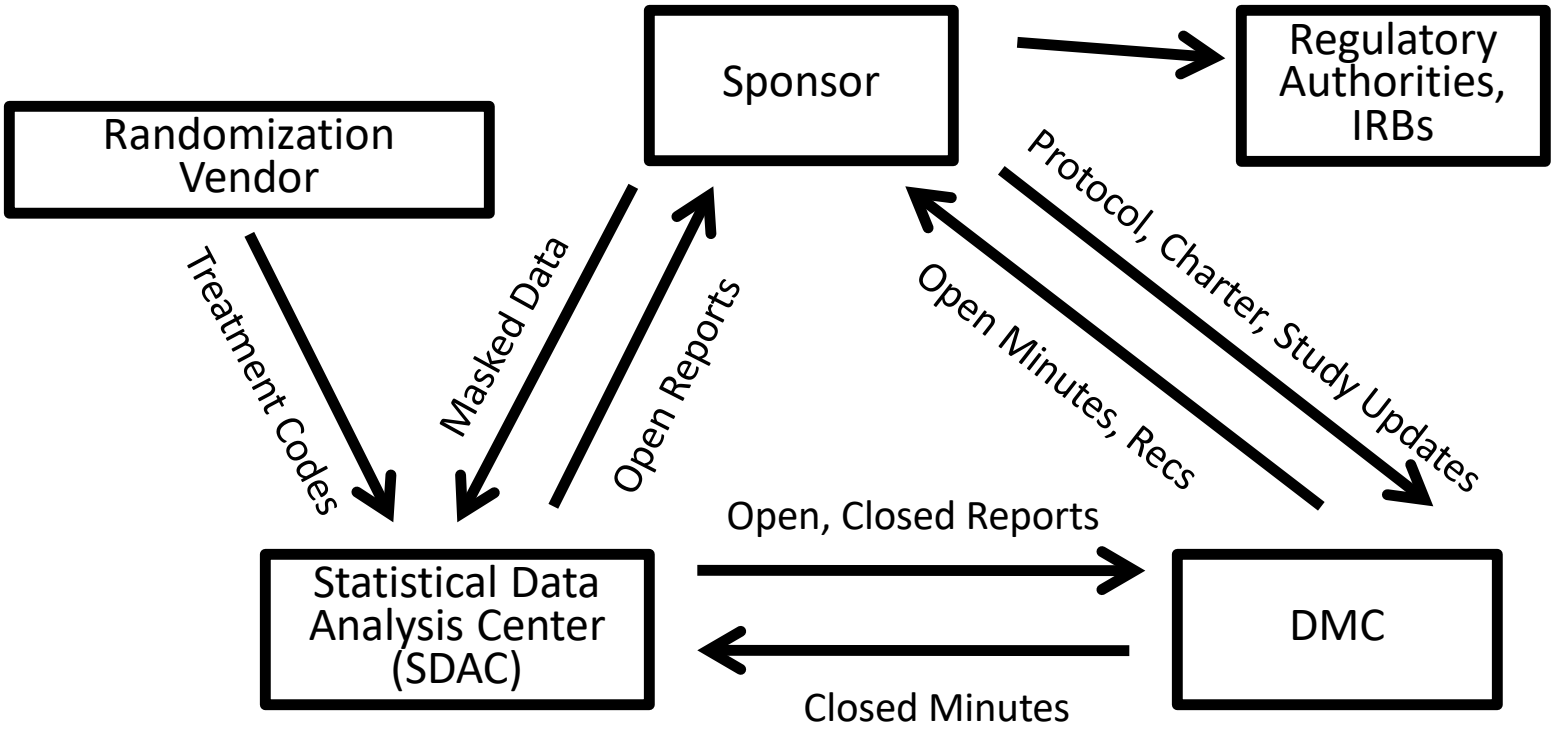
- The most typical DMC situation is overseeing a randomized study that is blinded to the Sponsor (double-blind, or firewalled open-label)
- However DMCs can be involved with single-arm studies or randomized open-label studies where the Sponsor has full access

Use of DMCs is Increasing Over Time

- clinicaltrials.gov database includes a question on whether study has a DMC – we analyzed DMC use in industry-sponsored clinical trials
- One-half of Phase 2 and Phase 3 studies employ a DMC
- One-fifth of Phase 1 and Phase 4 studies employ a DMC
- Number of new DMCs **started each year** increased from 800 a decade ago to 1000 this past year (- lots of DMC members needed!)



Organizational Flow (Simplified)



DMC Responsibilities

- DMC operational aspects are specified in a DMC Charter that should be a set of principles – flexible enough to handle unexpected challenges rather than rigid rules

DMC Responsibilities

- Safeguard trial participants during the study through evaluation of safety and efficacy
- Protect trial integrity
- Address scientific and practical issues
- Perform an advisory role by recommendations
  - Proceed as usual
  - Proceed with changes (minor or major)
  - Trial termination
- Maintain strict confidentiality – no unauthorized information to Sponsor or to external parties – and probably no reason to even declare participation on the DMC unless specifically required
- Duration of term of service should be specified

DMC Chair Responsibilities

- Confirm quorum
- Lead the meeting
  - Make sure all voices heard
  - Generate consensus – tally votes in rare situations consensus is not obtained
  - Keep discussion on track (minimize DMC members trying to update protocol or focusing on management of one patient)
  - For tricky situations, propose ‘out of box’ ideas
- Summarize recommendations
- Set agenda for Closed portion of the meeting
- Approve (sign) recommendations and minutes
- Take lead on *ad hoc* interactions with Sponsor
- Typically Chair has the most DMC experience of the DMC – can be statistical or clinical member

Axio

Statistical Data Analysis Center (SDAC) Responsibilities

- Prepare and distribute DMC reports that are useful to the DMC
- Have independent statistician attend the meetings and present the report to the DMC
- Have general clinical trials expertise and expertise with DMCs and specific knowledge of the study protocol and DMC Charter
- Have knowledge of the data and the programs used to the create the outputs
- Provide DMC with technical support and have flexibility to respond to *ad hoc* DMC requests (perhaps without study team knowledge)
- May provide logistical assistance: meeting scheduling, drafting meeting minutes, reimbursement
- Should NOT participate in discussions of protocol amendments with Sponsor after being unblinded to interim data

Sponsor Responsibilities

- Recognize the DMC as being responsible for the stewardship of the trial and being independent
- Advise/educate the DMC and SDAC on past and present scientific, clinical and statistical issues concerning the study and new treatment
- Take responsibility for determining response to external information (e.g. protocol amendment, updated ICF) – DMC response could be seen as biased once unblinded to interim data
- Promptly provide any relevant updates (e.g. amended protocols)
- Promptly respond to DMC recommendations and follow-through on any commitments

DMC Membership

- Experience in clinical trials
  - One statistician
  - Two to five clinicians from the disease area or in areas of suspected safety concerns
- Range of DMC experience (not all pros, not all rookies)
- Geographic representation if international
- Must be flexible and responsive to attend meetings and review documents, minutes, etc.
- “Free of apparent significant conflicts of interest (CoI), whether they are financial, intellectual, professional or regulatory in nature”
- Key: disclosure of “significant” CoI
- CoI should be periodically re-assessed
- Have process for member replacement

Potential Conflict of Interest

- Nothing to report
- Something to report to other members of DMC but not necessarily an official conflict of interest
  - Serving on other DMCs (Sponsor or competitor)
  - Site investigator for competitor's study
  - Colleague serving as investigator for study
  - Consulting for Sponsor or competitor in limited scope
- Genuine potential conflict of interest
  - Change in employer (working at Sponsor or competitor)
  - Site investigator for study
  - Principal Investigator for competitor's study
  - Major consultant or investor in Sponsor or competitor

Finances

- Not *pro bono*, should represent normal rate
- Paid per meeting or by hour? (If by hour, hopefully somewhat comparable between DMC members)
- If per meeting, differential cost for TC vs. in-person
- If by hour, travel time for in-person meeting at full rate or half rate?
- Each member negotiates separately – rates may be identical or not (especially for DMC Chair)
- Preferable to use contracts that differentiate DMC services as different than services which are designed to assist the Sponsor in product development, i.e. “independent scientist” which emphasizes DMC independence rather than “product development consultant”

Logistics – How Much Time to Spend?

- Depends on specifics of study but guidelines could be:
  - Before the meeting
    - 1-2 hours reviewing protocol and charter and previous minutes
    - 1-2 hours reviewing open session materials
    - 2-4 hours reviewing closed report
  - During the meeting
    - 1½ - 4 hours teleconference
    - 3 - 6 hours in-person (plus 8-16 hours travel time)
  - After the meeting
    - 1-2 hours reviewing minutes and post-meeting follow-up and responses to action items

Axio

PARTNERS IN RESEARCH

Liability

- During contracting, strongly consider making sure you are indemnified by company, not *vice versa* – refer to DeMets et al "Liability issues for data monitoring committee members", Clinical Trials 2004; 1: 525-531:

The Company [i.e., sponsor] will defend, indemnify and hold harmless the Consultant from any liability, loss, damage, costs and expenses of claims and suits (including reasonable attorneys' fees, costs and expenses of handling such claims and defending such suits) resulting from the participation of the Consultant on the Data Monitoring Committee as part of the Services, except that the Company will not be required to defend, indemnify and hold harmless the Consultant where any claim or suit arises from:

- (i) the failure of the Consultant to comply with any applicable laws or regulations or to adhere to the terms of the Data Monitoring Committee Charter for the clinical trial; or
- (ii) a judicial finding of willful misconduct of the Consultant.

Axio

DMC 102

Meeting Structure, Timing and Purpose

Organizational Meeting

- Review pre-clinical and clinical studies
- Review near-final protocol and eCRFs and IB and ICF and SAP
- Review near-final DMC Charter (and iSAP or DMC SAP)
- Review report ToC and/or mock tables

Meeting Structure, Timing and Purpose

Organizational Meeting

1) What are the important outcomes to assess safety and efficacy
2) Have anticipated AEs been defined and how are AEs collected/coded
3) What happens if a patient discontinues treatment – still continue to be followed for safety, efficacy and other outcomes
4) Will primary or other event data be adjudicated, and how long will it take for primary event data to be available
5) Are there monitoring guidelines for efficacy or futility and are they clear and reasonable

Meeting Structure, Timing and Purpose

Safety looks

- Review safety data (and non-inferential efficacy data) and recommend whether study is ethical to continue in face of risk/benefit evaluation

Formal interim evaluations

- Use pre-specified monitoring guidelines to assess efficacy data
- Discuss in advance:
  - Are the guidelines clear and reasonable
  - Both efficacy and futility or just one - If not both, provide rationale to DMC to explain why neither or just one direction will have monitoring guidelines

Meeting Structure, Timing and Purpose

- (Brief closed session – with DMC and SDAC)
- **Open Session (review ‘total-only’ results - with DMC and Sponsor and SDAC and possibly Steering Committee, PI, other vendors)**
- **Closed Session (review ‘by-arm’ results - with DMC and SDAC)**
- (Executive session – with DMC)
- (Open Debrief – with DMC and SDAC and Sponsor subgroup)
- (Open Debrief – with DMC and SDAC and full Sponsor team)

Meeting Structure, Timing and Purpose – Open Session

- Proposed protocol modifications
- Regulatory updates (in real time also, if appropriate)
- Status of ‘sister’ studies not covered by DMC
- Response to action items made at previous DMC meeting
- SHORT review of interesting, new SAEs/deaths/unblindings
- Prompt answers and cooperation from Sponsor – DMC should feel free to literally or figuratively set the agenda of the Open Session

Meeting Structure, Timing and Purpose – Open Session

- Report discussed in Open Session should focus on issues concerning trial conduct
- Study quality metrics vs. expectations (and, if issues, then provide reasons and proposed solutions)
  - screen failure rate and enrollment rate,
  - discontinuation from treatment rate,
  - withdrawal from study rate,
  - protocol deviation rate,
  - endpoint rate,
  - visit completeness and timeliness (including adjudications)
- Demographics and baseline disease characteristics and other important prognostic factors – are these the expected patients?

Meeting Structure, Timing and Purpose - Recommendations

DMC trial recommendations and proposed modifications should be provided to a Sponsor Liaison or leadership group authorized to act on those recommendations, and not to those directly involved with implementation of the trial. Therefore propose:

- Open Session followed by Closed Session
- No ‘Recommendations/Recap/Reconvene/Debrief’ Session
- Recommendations and detailed Action Items go directly from DMC Chair to only Sponsor Liaison (outside of study team)
- This approach very helpful if DMC has non-trivial recommendation that may require additional analysis or back-and-forth discussion between Sponsor and DMC – Liaison may be provided unblinded reports and may counter-propose another way to account for DMC concerns

Meeting Structure, Timing and Purpose

- Meeting frequency generally described, more specific for formal efficacy looks
- Generally no more than 6-9 months between meetings
- Every 4-6 months seems to work well for most
- In-person once a year (3 - 6 hours), telecon (1½ - 4 hours) for others
- Balanced between ‘information time’ and ‘calendar time’ (depends on enrollment and event rates – both safety and efficacy events)

Structure of DMC Meetings and Recommendations

- All attempts should be made to hold the first DMC meeting in person, before initiation of patient recruitment, to allow DMC members the opportunity to get to know one another, and to review the DMC Charter, trial protocol, and planned SDAC report templates

- Annual face-to-face meetings should be held; other meetings can be held via web- or teleconference.
  - Preferably organizational meeting and 'formal efficacy' meetings are held in-person and preferably annually also
  - Current trends are for very few meetings to be held in-person

Structure of DMC Meetings and Recommendations

- **Teleconference – Pros**
  - Clear cost and time efficiencies for all concerned
  - Less time commitment required
  - Easier to schedule

- **Teleconference - Cons**
  - Lessened involvement and focus during meetings
  - Inability to communicate non-verbally
  - Potentially more difficulty successfully collaborating with non-native English speaking DMC members
  - Loud voice can dominate the meeting
  - Technological issues
  - DMC Chair can help offset potential Cons

Structure of DMC Meetings and Recommendations

- DMC members should have minimal sponsor interactions outside the formal DMC meeting open session
- DMC meetings should be held at a neutral location (e.g., not at the trial sponsor or particularly luxurious locations)
- DMC members should not have discussions about the trial outside of DMC meetings
- No Sponsor/DMC dinner (especially with wine and lobster) before or after DMC meeting – reduces chance of DMC revealing potentially unmasked information and increases appearance of impartiality
- Lunch or breakfast between Sponsor/DMC acceptable – but caution must be taken by DMC to be careful with what is discussed

Recommendations and Documentation

- Quorum needed for meeting – described in DMC Charter
- Consensus is strived for rather than up-and-down vote, although voting is described in DMC Charter
- DMC Charter describes plan if Sponsor disagrees with DMC recommendation – challenging situation if DMC recommends study stop for safety concerns and Sponsor refuses (bring in outside adjudicator?)

Recommendations and Documentation

- Written documentation:
  - Open minutes
    - Discussion of the open session
  - Closed minutes
    - Discussion of the closed session
    - Action items for SDAC whose very request should be kept confidential from Sponsor
  - Brief continuation form / top-line recommendation
    - Suitable for Sponsor to send to IRB or regulatory agencies
  - Detailed action items
    - Specific about who will do it, and by when (immediately, within a few weeks, or for the next DMC meeting)
    - Only include action items which are suitable for Sponsor (or at least Liaison) to know about, e.g. more protocol training needed in a certain country, etc.

Axio

Program-wide DMCs

- **Pros:**
  - Can really focus on giving the one single DMC a solid education on the investigational product
  - Globally consistent *ad hoc* requests for tables, listings, and figures (TLFs) or protocol amendments – as opposed to if multiple DMCs overseeing
  - Earlier recognition by DMC of global trends in safety patterns of potential concern, even if unofficial 'meta-analysis'
  - Cheaper - Fewer unique meetings across the program

Program-wide DMCs

- **Cons:**
  - Larger DMC to cover all different disease indications
  - Intense prep work from study team to get data to SDAC
  - More time needed at SDAC to prepare multiple reports
  - More time needed by DMC to review – slightly ‘staler’ data
  - Less thorough review and discussion of DMC on each individual study
  - Longer, more complex, more frequent, and potentially confusing DMC meetings

How Clean and Current Should Data Be?

- Perfectly clean, but no data from past 3 months?
- Data snapshot from 2 weeks before DMC meeting?
- Somewhere in between?

Typical Timeline (for DMC meetings after first meeting)

- **T -8 Weeks – 'clinical cut date'**
  - Strong efforts by sites and study team data management that data expected prior to this data will be entered and reasonably clean (focusing on AEs, disposition, and efficacy)
- **T -3 Weeks – 'snapshot date'**
  - Clinical data extracted and sent to SDAC
  - All data expected prior to T -8 weeks should be present
  - All data entered prior to T -8 weeks should be reasonably clean
  - Should include data collected between T -8 weeks and T -3 weeks, even though not necessarily complete or clean
  - Send other data (IxRS, specialty lab, central reviewer, etc.)
- **T -1 Week – distribution to DMC (open/closed) and Sponsor (open)**
  - Include study team update on study status and any safety updates based on blinded study results or from other information outside of study

Typical Timeline (for DMC meetings after first meeting)

- Note that current CTTI guideline is that data for the SDAC should always be available ‘on demand’ or on a frequent periodical basis (at least monthly)
- Download of this data should be invisible to the core study team
- Should include ALL data used for DMC reporting – safety, efficacy, IxRS, central laboratory data, specialty laboratory data, ECG, etc.
- Purpose is that if the DMC wants confidential *ad hoc* summaries or more frequent periodic looks based on by-arm results that this request can be accommodated invisibly by SDAC

Data Format

- Common nowadays for SDAC to receive SDTM files from study team
- But note the difficulty if the first DMC meeting occurs only 3-6 months after first patient randomized
- Will SDTM be ready in time for SDAC to get test transfers to complete programming in advance of the first DMC meeting?
- For a variety of reasons, the first data review may be subset of key tables
- Note also the hazards of study team changing SDTM formatting mid-study without proactively alerting the SDAC of these updates in advance of transfers for production of DMC reports

Who Programs?

- SDAC logs directly into firewalled area of **Sponsor environment** and creates TLFs after swapping in real randomization and running code
- SDAC receives **Sponsor code** that creates TLFs and simply merges on real randomization in own environment and runs code
- SDAC receives **Sponsor's ADaM (-like) datasets** and merges on randomization code and programs TLFs
- SDAC receives **SDTM (-like) datasets** and creates analysis datasets that are merged on randomization and creates TLFs
- SDAC receives **'raw' datasets** and creates analysis datasets that are merged on randomization and creates TLFs

- Increasing level of ability of SDAC to reply intelligently / confidentially to DMC *ad hoc* requests in these different models

Structure and Format of DMC Reports

- A DMC report is NOT just a subset of clinical study report (CSR)
- Dynamic of focusing on key results but not missing any unanticipated safety signals – comprehensive and comprehensible
- Start with shorter, tailored, focused report and expand if needed
- Preferably just 100-200 pages
- Distributed electronically and easily navigated as a single .PDF with bookmarks and a hyperlinked table of contents
- Outputs are labeled for easy comprehension of what is presented – e.g. counts are number of events vs. number of patients
- Thoughtful use of populations (ITT vs. Safety)
- Thoughtful use of how missing vs. 'not yet available' data is handled for denominators of percentages

Real-time Analysis

- Real-time analysis has particular issues
  - Missing visits entirely, missing data within visits
  - Clearly incorrect data (outliers, lab data with bad units)
  - Inconsistencies between IxRS and CRF data (stratification, treated)
  - Inconsistencies within data, e.g. patient who discontinues treatment for reason of AE does not correspondingly have an AE with action of discontinuation from treatment
  - Uncoded AEs and unadjudicated events (how to handle those still ‘in the queue’ for adjudication)

Real-time Analysis

- DMC should aware of these issues if they exist, but not necessarily be overly alarmed
- DMC should focus on robust analyses – medians, not means
- In some cases outliers may need to be a focus, e.g. abnormal lab results may be looked at in detail to see if truly extreme vs. potential unit issues
- SDAC can present data ‘as is’ but additionally provide some analyses that are robust or remove/adjust likely outliers (particularly for baseline characteristics that don’t represent safety issues)
- SDAC can present data in ways to help accommodate missing/inconsistent data
- Analyses used by SDAC for safety may be simplified compared to what is used at the end of the study – e.g. don’t use advanced date imputation or visit windowing

Structure and Format of DMC Reports

- Typically explicitly show unmasked treatment groups (“Active” vs. “Placebo” for example) rather than masked treatment group (“Arm A” vs. “Arm B” or “Purple” vs. “Gold”) - especially if more than two arms
- If “Arm A” vs. “Arm B”, DMC Charter will explain process for DMC to obtain full information
  - Could be provided by default as first course of business
  - Could be provided upon request of DMC –
    - some may ask that it be done immediately
    - some may ask only if an imbalance is seen
    - need to be thoughtful – an imbalance of 5 vs. 15 deaths could be a nice trend or a very worrying safety signal – and DMC should not assume this signal is in the expected, positive direction

Axio

Structure and Format of DMC Reports

- Report Elements
  - Key tables
    - Demographics and baseline disease characteristics – implications if groups are not balanced
    - Exposure – implications if one group discontinuing treatment more than another group
    - Disposition – implications if one group withdrawing from the study more than another group
    - Safety - AEs, labs, vital signs, etc.

Structure and Format of DMC Reports

- Report Elements
  - Key tables
    - Avoid long, long tables of continuous data summarized at each time point
    - Better reporting of lab data – avoid baseline toxicity vs. toxicity grade at every visit
    - Better reporting of AEs – SMQs or AEs of Special Interest or HLT (not PT) or other constellations of terms
    - Typically downplay investigator-assigned AE relationship to treatment
    - Focus on Grade 3+ AEs (severe, life-threatening, fatal), Serious AEs, AEs leading to discontinuation of treatment
    - p-values as a way to help filter for further thought?

Structure and Format of DMC Reports

- Report Elements
  - Few listings (traffic-lighting for new events relative to previous)
    - SAEs
    - Deaths
    - Extreme labs
  - More graphics
    - CONSORT diagram
    - Kaplan-Meier time to treatment discontinuation
    - Kaplan-Meier time to withdrawal from study
    - Kaplan-Meier time to first SAE
    - Innovative visualization of AE data
    - eDISH plots for LFTs
    - Box plots combined with dot plots for labs over time

Study Integrity and Conduct?

- Should DMC focus on just safety?
- Or should DMC work with Sponsor to ensure study is still viable and will be interpretable in a reasonable period of time?

Contents of DMC Reports

- DMC should be interested in not just safety and efficacy, but study integrity and conduct
  - Recruitment progress,
  - Quality and timeliness of data collection,
  - Adherence to the protocol (e.g., missing data).

Presentation of Study Metrics

- Enrollment over time vs. projected
- Enrollment by region (unexpectedly high rate of ex-US?)
- SAE rates by country (unexpectedly low in some countries?)
- Received vs. Expected visits at each visit
- Time overdue for next visit for those still on study
- Inclusion/exclusion criteria violations
- Major protocol deviations
- Timeliness of central adjudication/review progress
- Rate of accrual of endpoints
- Rate of withdrawal from study follow-up

Efficacy Data

- Should DMC focus on just safety?
- Or should DMC have efficacy data available as well?

Presentation of Efficacy Data

DMCs must periodically review the accumulating **unmasked** safety and **efficacy** data **by treatment group**, and advise the trial sponsor on whether to continue, modify, or terminate a trial based on benefit-risk assessment, as specified in the DMC Charter, protocol, and/or statistical analysis plan.

- Need efficacy to assess benefit-risk (more relevant if efficacy represents how patient feels, functions, survives – rather than if efficacy is a biomarker)
- May be a close 'proxy' to formal efficacy (e.g. local assessment of disease progression instead of central review)
- Not necessarily inferential – may be enough to have table or figure showing a promising trend in efficacy to offset a safety concern
- If concern about 'alpha spending' then allocate alpha=0.00001
- At minimum, SDAC has as 'back-up' material available to DMC on immediate demand

Buhr, et al, Therapeutic Innovation & Regulatory Science 1-10

Table 1. Sample Content and Organization of Open and Closed IDMC Reports.

Section	Open	Closed	Sample of questions answered in section:
Recruitment	×	×	• Is enrollment meeting projections?
	×	×	• Are a few clinical centers dominating enrollment?
		×	• Is treatment roughly balanced within region and country? Are stratification factors balanced?
Availability of data	×	×	• How much follow-up data are available?
	×	×	• Are sites entering data in a timely fashion?
	×	×	• Are there endpoint events that occurred before the last report's data cut-off but are only first reported in the current report?
	×	×	• Do any sites have anomalously low (or high) AE reporting rates?
Baseline characteristics		×	• Is treatment roughly balanced by baseline prognostic factors? Could baseline differences account for safety or efficacy findings?
	×	×	• Do the distributions of baseline characteristics match those expected in the study population?
	×	×	• Is there evidence of errors when specifying stratification factors at randomization?
Disposition	×	×	• In what phase of the study (eg, screening, treatment, follow-up) are participants? (For particularly complex study designs, a diagram of disposition may be useful.)
		×	• Are discontinuation rates and reasons comparable between the study arms? Does the timing of discontinuations differ between study arms?
	×	×	• Are both treatment discontinuations and study discontinuations clear?
Treatment exposure	×	×	• What proportion of participants fail to receive study treatment?
		×	• Is the intensity of received treatment similar by study arm?
Protocol adherence	×	×	• Is the study being conducted in a manner that will allow it to answer the research questions?
	×	×	• Do any sites have particularly high rates of deviations?
Adverse events		×	• Do the groups differ with respect to AE findings?
		×	• Do the observed safety data match the expected safety profile of the intervention under study?
	×	×	• Are the observed safety data consistent with the expected background event rates in the study population?
Laboratory, ECG, and/or vital sign parameters		×	• Do the groups differ with respect to safety findings?
		×	• Are the laboratory findings consistent with findings from the AE data?
	×	×	• Are particular events, like cases of Hy's Law, easily identifiable in the data (eg, via listings, patient-profile plots, tables/plots of specific labs)
Efficacy		×	• Are the preliminary efficacy data consistent with the possibility of a favorable risk: benefit profile of the agent under study? (Recommend evaluating this question at each safety review, not just interim efficacy reviews)
		×	• Have predefined efficacy or futility criteria been met?

Abbreviations: AE, adverse event; ECG, electrocardiogram.
Note: Open reports do not present any data by treatment group.

DMC 103

The Plan – Closed Session

1. Get all members to the meeting, or at least establish quorum
2. Check for and discuss potential conflicts of interest
3. Review minutes and action items from previous meeting(s)
4. Review and discuss the tables, listings, and figures (TLFs) in the Closed report
5. Discuss and answer any outstanding questions from the Open session
6. Enumerate action items for the Sponsor and the SDAC (including when to meet next)
7. Make a formal recommendation (continue or not)

The Closed Session really begins

- The Chair leads the DMC through the TLFs or
- The Chair defers to the independent statistician to lead the DMC through the TLFs or
- The Chair solicits items of focus from the DMC, shares her own, and these are visited in turn
- Executive summary – helpful or ‘enabling’?

The Closed Session in Progress

- Items of interest or concern are noted, discussed, and documented
- Action items are identified and timeline for resolution are agreed upon
  - Sponsor to provide information at next meeting or ASAP
  - SDAC to provide information at next meeting, soon after meeting, or during meeting
- Equipoise still maintained?
  - Would you accept your ill mother being enrolled on this study?
  - Would you accept your ill mother being treated on placebo arm?
  - Would you accept your ill mother being treated on active arm?

The Closed Session Finale

- Recommendation to continue the study without modification to the protocol
- Recommendation to continue the study with modification to the protocol or other change or sharing of information
- Recommendation withheld pending receipt of additional information
- Recommendation to stop the study for safety (and futility and/or efficacy – if formally part of DMC job)

Fears of a DMC – How to Handle These?

- There may be a safety signal but the numbers are too small to be certain
- There may be a safety signal but the DMC is missing it completely
- The DMC wants to alert the sponsor to a potential concern but the risk of unmasking or damaging trial integrity is too great
- The study looks futile (but safe), but there is no official futility boundary - a waste of patient and sponsor time and resource?

Stopping a Study Early

- Most studies run to completion
  - 70% run to normal completion as expected by protocol
  - 10% stop early due to logistics
  - 10% stop early due to safety concerns
  - 5% stop early due to overwhelming statistical efficacy as defined in protocol
  - 5% stop early due to statistical futility as defined in protocol

Stopping a Study Early for Logistics

- Study is limping along – low enrollment and/or few events being observed. Should the DMC recommend a major change?
- Study has large number of withdrawal of consent or lost-to-follow-up (perhaps imbalanced by arm). Should the DMC recommend a major change?
- Study has large numbers that are enrolled that failed eligibility criteria and there are excessive number of protocol violations. Should the DMC recommend a major change?

Stopping a Study Early for Safety

- The hardest decision of the DMC – why there are experts and not just a computer
- A naïve p-value < 0.05 on a single safety event (other than death) is not typically sufficient in and of itself to recommend stopping for safety
- 2 vs. 0 on PML might be enough
- 60 vs. 20 on neutropenia or pruritus (across all severity) might not be enough

Stopping a Study Early for Safety

- Is the signal robust? Consistent across dimensions (AEs and lab results correlate)?
- Can we combine similar AEs for more informative analysis (e.g. combine ‘LDL increased’, ‘Lipids increased’, ‘Hyperlipidaemia’, ‘VLDL increased’)?
- Is the signal known from preclinical results or as a class effect? Or is the signal novel – and therefore needs to be more compelling in order to be believed?
- Is the signal clinically relevant to the patient?
- Is the imbalance increasing from meeting to meeting?
- Is the safety concern offset by trends for positive efficacy?

Stopping a Study Early for Safety

- Are there baseline imbalances that have caused the active arm to be more prone to having these events?
- Is there an imbalance on average follow-up which means that safety is biased towards reporting more events on the active arm?
- Does the nature of the visit schedule of the (open-label) study have more assessments on the active arm so more chance to have spontaneous events captured?
- If program-wide DMC with the same DMC, do the other studies show a similar trend or not?
- If there is a different DMC reviewing a similar study, can a communication pathway be established so that the DMC Chairs can discuss whether studies show similar trends?

Alternatives to Stopping a Study Early for Safety

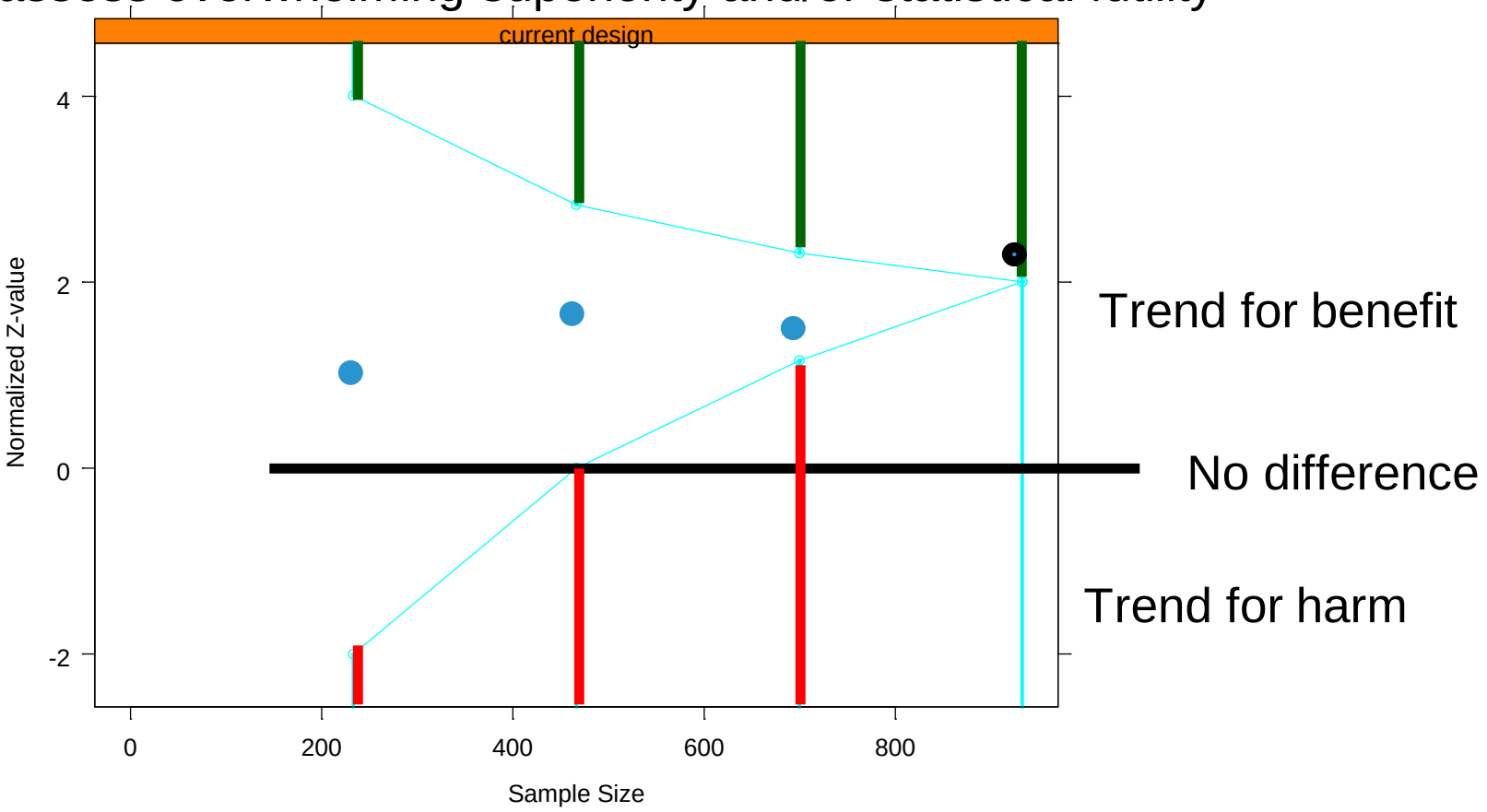
- Review efficacy data to see if it counterbalances safety
- Reinforce site training to be vigilant of specific safety issue
- More frequent DMC reviews
- Add different DMC analyses to confirm results are consistent across various dimensions
- Mitigation strategies that could be employed before or after the event is seen (tighten eligibility criteria to remove those at higher likelihood of event or enforce dose adjustment strategies if precursor event is seen)?
- Halt enrollment, keep treatment going
- Halt enrollment and treatment, but keep follow-up going

Stopping a Study Early at Formal Review of Efficacy

- Can be stopped for overwhelming superiority
- Can be stopped for statistical futility (not necessarily harm)
- Boundaries are prospectively put into place
- Greater use of boundaries is encouraged, but for variety of reasons are currently underemployed
- These are guidelines, not ‘rules’
- Assess entire context of the data provided
- Use only adjudicated events, or supplement with local assessment (for endpoints with adjudication)?
- Force cut-off of events at protocol-specified number, or allow for slightly more or less (and accordingly update monitoring boundaries)?

Stopping a Study Early at Formal Review of Efficacy

- At pre-specified time points, formal interim evaluations can be done to assess overwhelming superiority and/or statistical futility



Stopping a Study Early at Formal Review of Efficacy

- Example – study needs 400 progressions or deaths (note – number of actual subjects enrolled is irrelevant)
- Sponsor interested in assessing futility early, and both futility and benefit with data that is more mature
- Endpoint is log-rank test of time to progression or death (censored for those still alive without progression), stratified, with hazard ratio < 1 indicating reduction in hazard in favor of experimental arm, overall alpha is 1-sided 0.025
- Possible formal monitoring boundaries for DMC:

Look	Events	% Info	Futility if HR	Futility if 1-sided p-value	Benefit if HR	Benefit if 1-sided p-value
IA #1	200	50%	HR>1.0	P>0.50		
IA #2	300	75%	HR>0.9	P>0.30	HR<0.7	P<0.003
Final	400	100%			HR<0.8	P<0.024

Stopping a Study Early

- Expect a lot of *ad hoc* discussion (especially if stop for safety)
- DMC may be asked to run subgroup/sensitivity analyses or these may be done by small unblinded group at Sponsor
- Small or inexperienced Sponsor in particular may be desperate to find some hope rather than stopping for futility or safety

End of the Study

- Sometimes DMC duration is not so clear (if study has long-term open-label extension, or if DMC monitors until PFS events seen, but continued follow-up for OS events)
- DMC members should destroy all materials after each meeting but certainly after end of study
- There may be a final DMC wrap-up meeting after study team has top-line analysis or ‘first interpretable results’ – no recommendations, just informative
- Final wrap-up is mutually beneficial – DMC learns final results and how those will be presented to medical community and regulatory agencies, and Sponsor learns why DMC made specific recommendations and also learns how group of experts (DMC) will interpret this final data

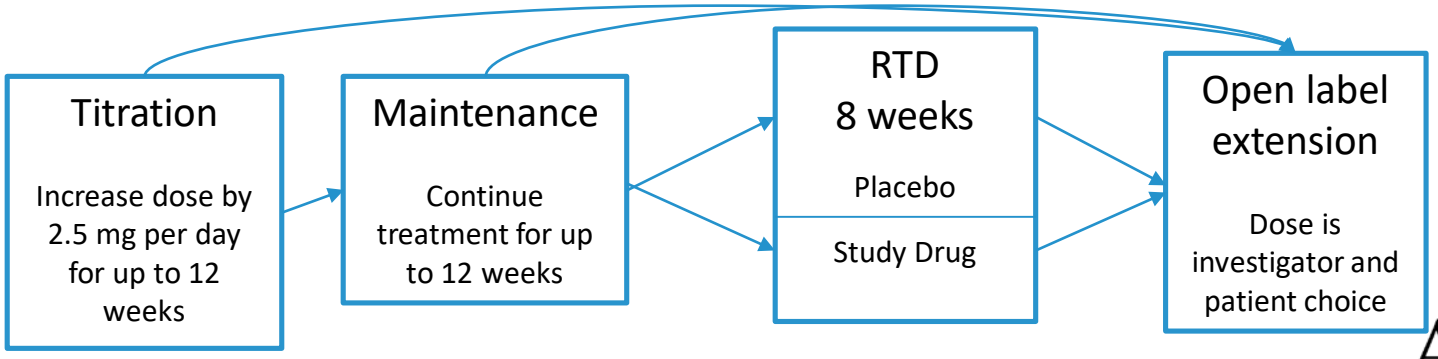
Example #1

Background

- Biologic therapy for an inherited metabolic disorder with limited therapeutic options
- Hypersensitivity and injection site reactions seen in phase 2 studies
- In phase 2, sponsor determined best dosing method to reduce these AE was for patients to take frequent low doses of the investigational product

Study Design

- Randomized discontinuation trial (RTD)
  - Open label study
    - Subjects titrate up to target dose over a 12 week period
    - Continue treatment for at least 12 weeks
  - Blinded randomized discontinuation study
    - Subjects are randomized to either continue study drug treatment or take a placebo for 8 weeks
    - If metabolite rises after discontinuation, this would demonstrate efficacy



Self Administration Guidelines

- First doses administered in the clinic to ensure competency
- Self-administration training manual included the following:
  - Instructions for at-home use of a non-sedating anti-histamine
  - Anaphylaxis and hypersensitivity reaction symptoms and instructions on when to contact the investigator
  - Workbook to document the time of study drug injections and any suspected AE
- Clinic staff contacted subjects weekly to monitor subjects for problems with self administration and for any AEs.

DMC Monitoring

- The following stopping rules were provided by the sponsor to the DMC
  - If ≥ 8 subjects report at least one severe AE, dosing of all active subjects may be stopped and further enrollment in the study may be halted as determined by the DMC or sponsor
  - If ≥ 4 subjects develop the same severe AE, dosing of all active subjects may be stopped and further enrollment in the study may be halted as determined by the DMC or sponsor
  - If ≥ 1 subject develops a life-threatening AE, dosing of all active subjects may be stopped and further enrollment in the study may be halted as determined by the DMC or sponsor

What Happened

- After 4 months, a patient experienced a life-threatening hypersensitivity reaction, triggering a stopping rule
  - 4 other patients had experienced a severe hypersensitivity or injection site reaction
- An Ad Hoc meeting was called to discuss the events.
  - The sponsor brought an expert on anaphylaxis to consult.
- Ultimately, the DMC recommended that the study could continue per protocol

What Happened Next

- 1 month later, the stopping criteria were triggered again by:
  - 9 subjects had at least 1 severe AE
    - 6 were types of hypersensitivity reaction
  - At least 4 subjects had the same severe AE
- The DMC requested additional information from the sponsor to track the frequency of these reactions
- Allowed the study to continue per protocol

What Happened Next

- 1 month later, the stopping criteria were triggered again by a patient with a life-threatening AE, assessed as related to the study drug by the investigator
- At this point, the DMC has had 3 Ad Hoc meetings in 2 months due to study stopping criteria being met

Outputs Requested by DMC

- Kaplan-Meier figure of time to first severe or worse AE
  - Flat after first 10 weeks
- Deaths
  - None
- Figure of mean blood concentration over time
  - Showed some benefit of IP over time
- Subject incidence of anaphylaxis per patient year
  - Higher in patients without premedication

DMC Conclusions

- The IP was associated with serious risk for hypersensitivity reaction – however…
    - No deaths
    - Risk seemed highest early in dosing of after dose reduction or discontinuation, although events could occur at any time
    - Risk could possibly be ameliorated with premedication and training patients on how to handle reactions
    - Unmet patient need
    - IP solid trend for efficacy
- The stopping rules were not appropriate
- The DMC recommended that the study could continue – with some updates to the protocol

Axio

DMC Recommendations

- Agreed to update stopping rules
  - An ad hoc DMC meeting would be held if there was a life threatening, treatment related hypersensitivity reaction.
- Updates to Self Administration Guidelines
  - Subjects are given 2 epi pens and should carry one with them at all times
  - If a subject stops treatment, the following must be done for the first week of reintroduction of study drug:
    - Premedication prior to dosing
    - Competent trained will observe the subject for hypersensitivity during study drug administration and for a minimum of 1 hour afterwards

DMC Recommendations

- Additional monitoring of hypersensitivity reactions
  - DMC should be notified of all anaphylactic events within 7 days and reviewed monthly listings of all hypersensitivity reactions
  - Requested the sponsor provide additional information on frequency of events during regular DMC meetings

Conclusion

- After updating the administration guidelines, the study continued for 4 years without a life-threatening anaphylaxis or hypersensitivity reaction.

Example #2

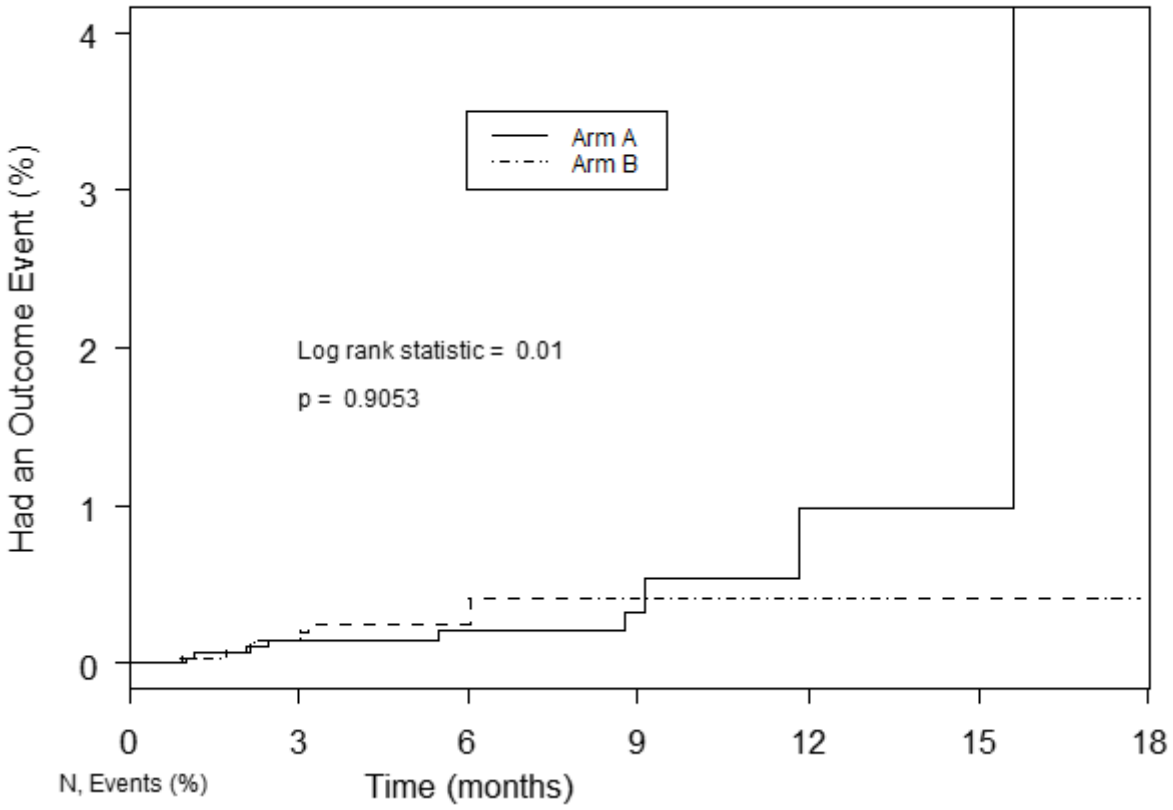
Background

- Drug approved for diabetes and taken by millions of people
- However, concerns over cardiovascular risk
- Post-marketing study mandated by regulatory agencies
- Endpoint was time to first CV death, nonfatal MI, and nonfatal stroke
- Needed 2000 events – to get that the study enrolled high-risk patients who were contra-indicated from the drug(!!!)
- Review for harm at $p<0.01$ at each meeting
- Review for benefit at $p<0.001$ at three looks (25%, 50%, 75%)
- Arm A is ‘Active’, Arm B is ‘Placebo’

1st Review – 21 Months into Study

17 Events – Arm A: 9 vs. Arm B: 8

Table 13: Kaplan-Meier plot of time to first CV outcome event confirmed by EAC



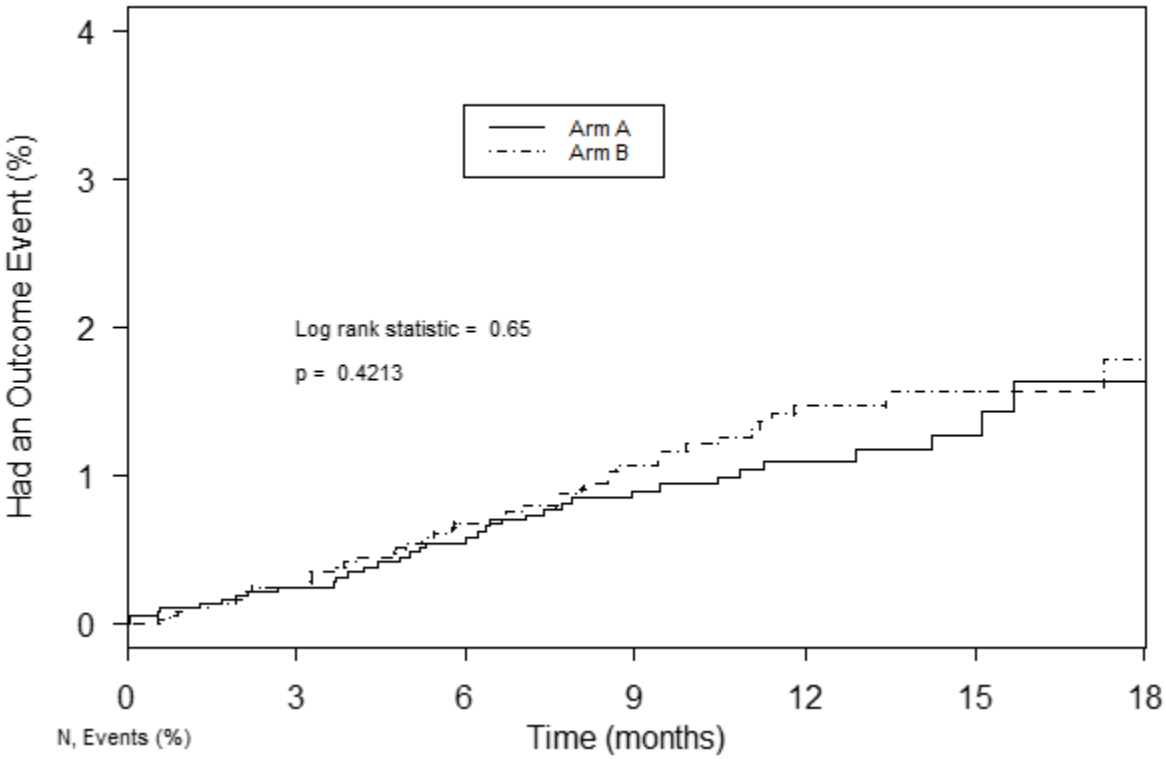
Axio

PARTNERS IN RESEARCH

2nd Review – 30 Months into Study

77 Events – Arm A: 35 vs. Arm B: 42

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



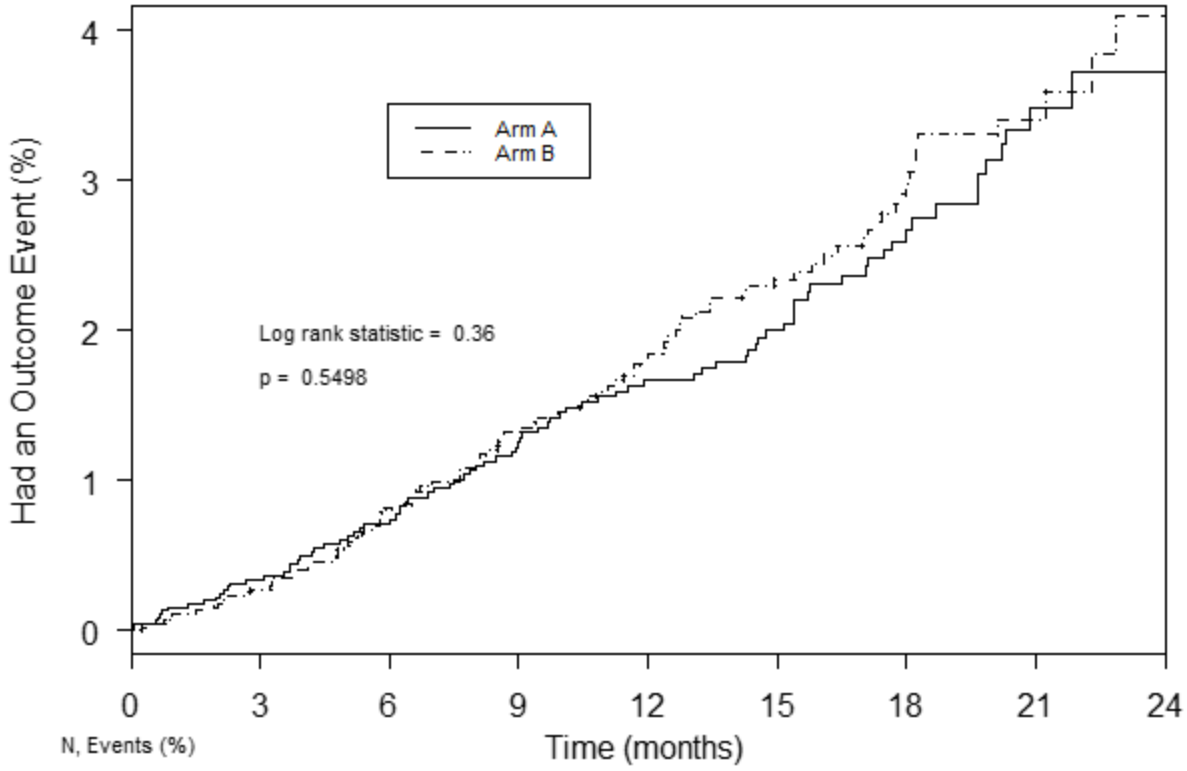
Axio

PARTNERS IN RESEARCH

3rd Review – 36 Months into Study

184 Events – Arm A: 88 vs. Arm B: 96

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



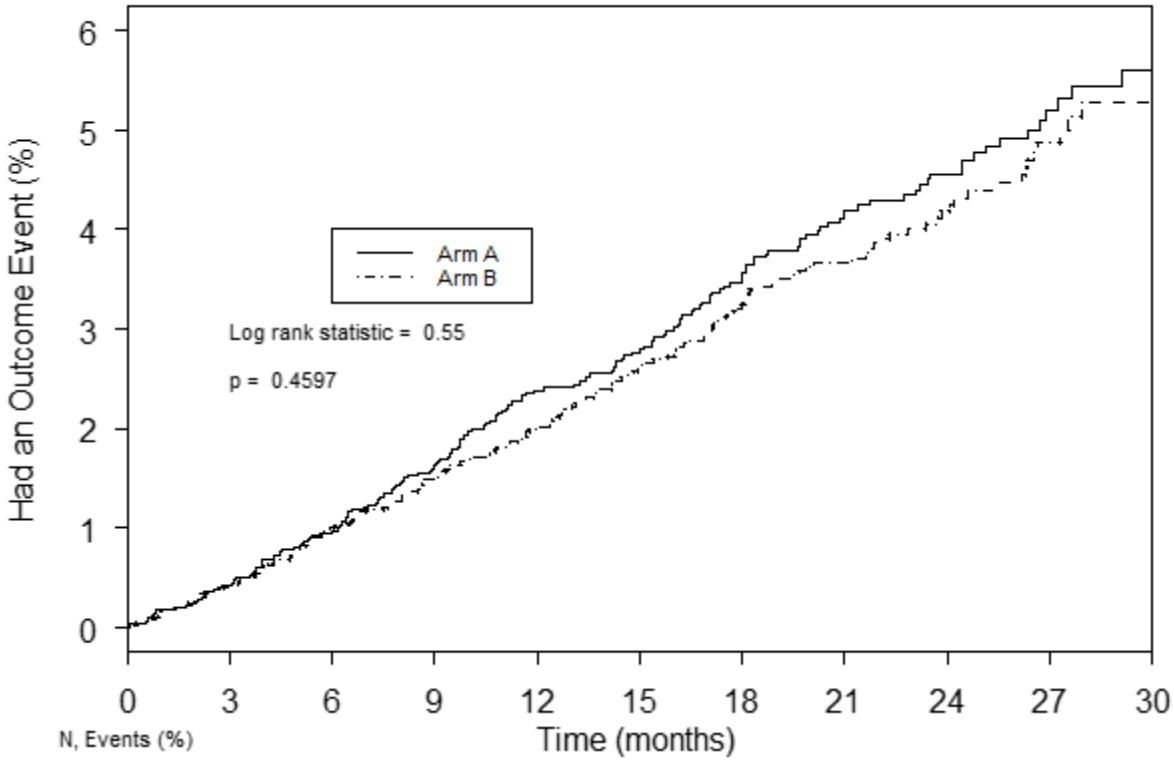
Axio

PARTNERS IN RESEARCH

4th Review – 42 Months into Study

342 Events – Arm A: 178 vs. Arm B: 164

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



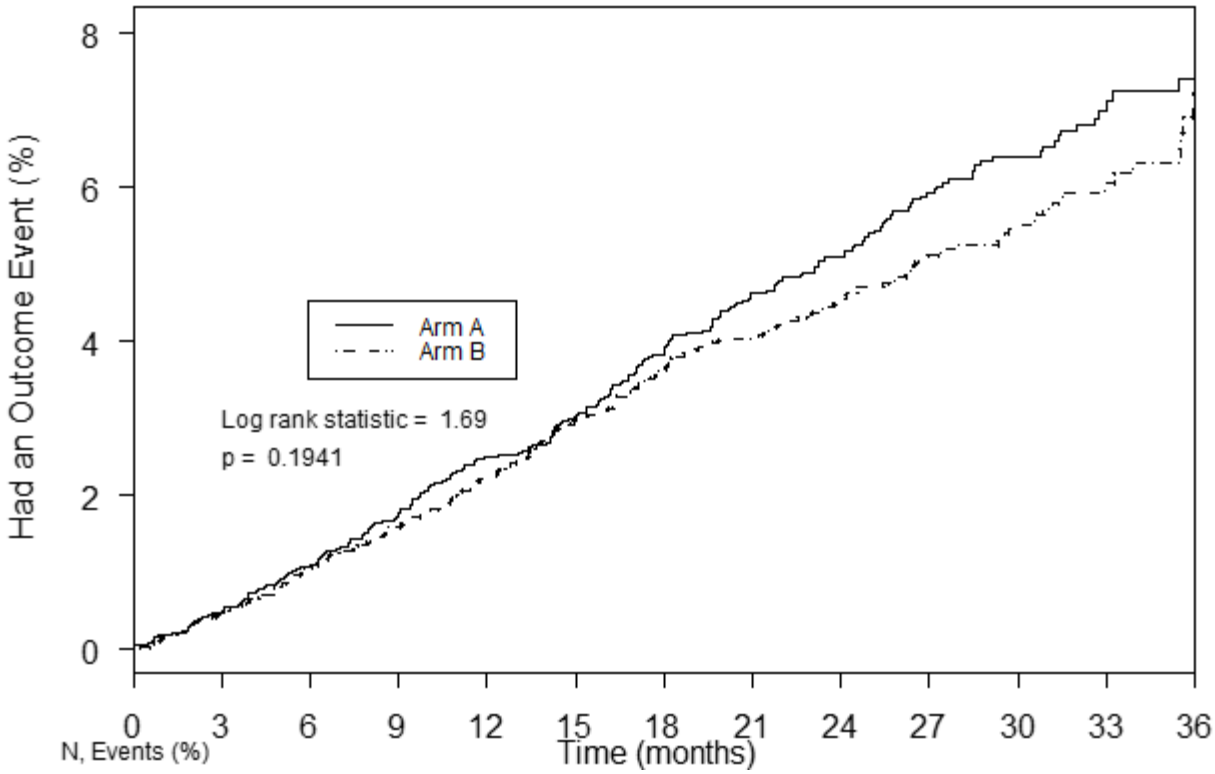
Axio

PARTNERS IN RESEARCH

5th Review – 48 Months into Study

478 Events– Arm A: 253 vs. Arm B: 225 ('official' look at 25% events)

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



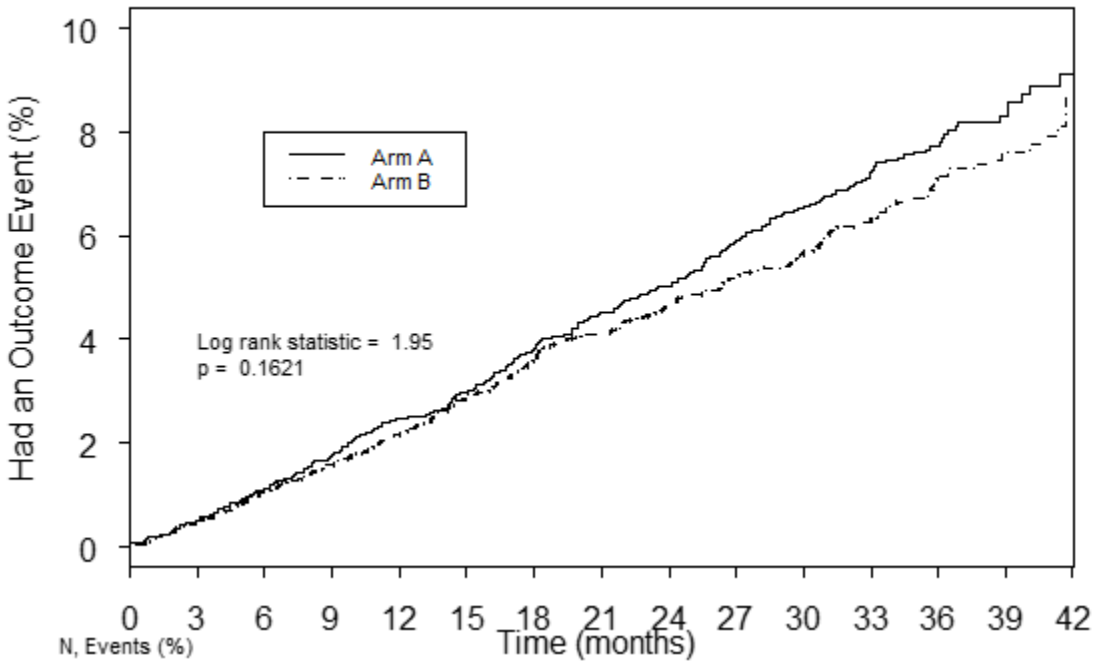
Axio

PARTNERS IN RESEARCH

6th Review – 54 Months into Study

596 Events– Arm A: 315 vs. Arm B: 281

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



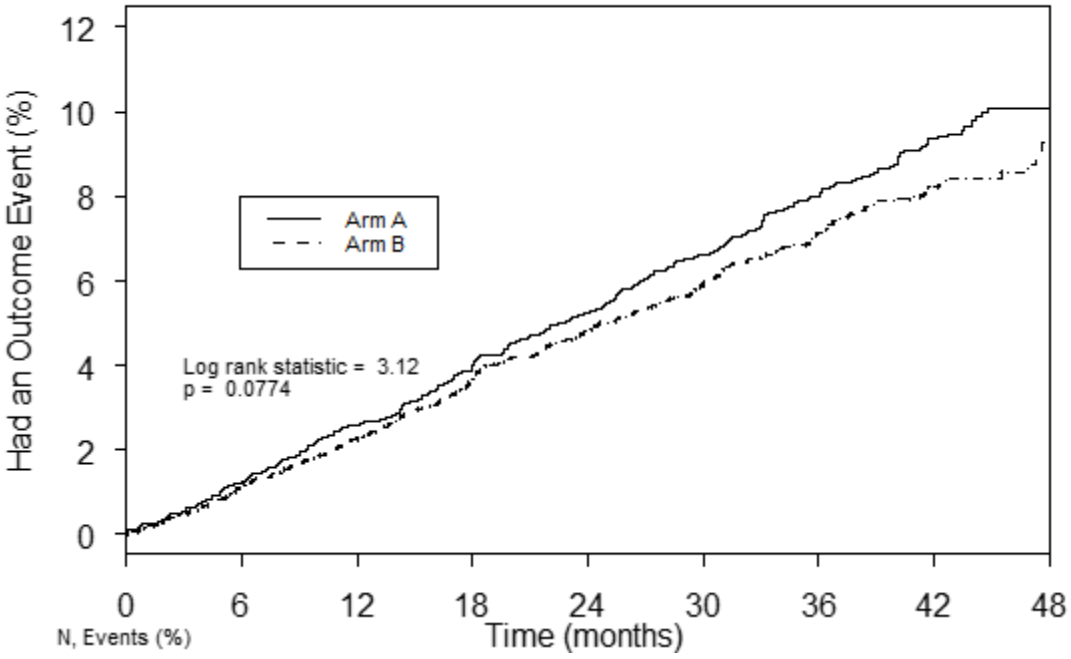
Axio

PARTNERS IN RESEARCH

7th Review – 60 Months into Study

721 Events– Arm A: 384 vs. Arm B: 337 (DMC uneasy, but continue)

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



Axio

PARTNERS IN RESEARCH

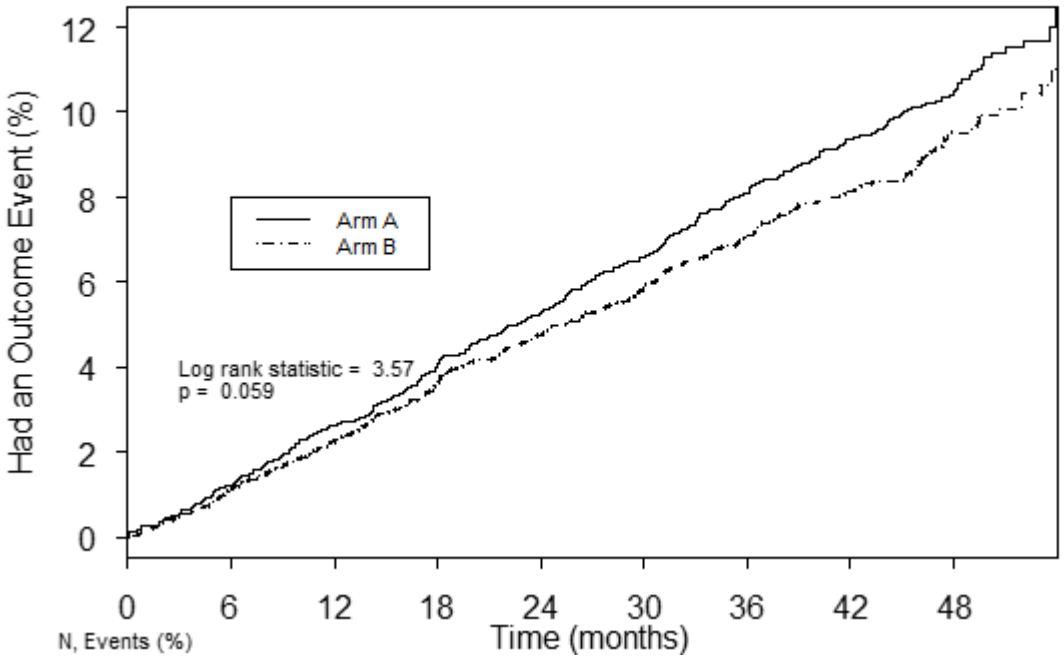
Prior to Next DMC Meeting

- After five years, less than half the needed events seen
- Many subjects off treatment, thereby attenuating useful long-term event data
- Therefore decision was made by sponsor based on **blinded** data to stop study within a year or so after 1000 events seen – one-half the original expectation

8th Review – 66 Months into Study

829 Events– Arm A: 440 vs. Arm B: 389 (DMC vote 4-2 to continue)

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



Axio

PARTNERS IN RESEARCH

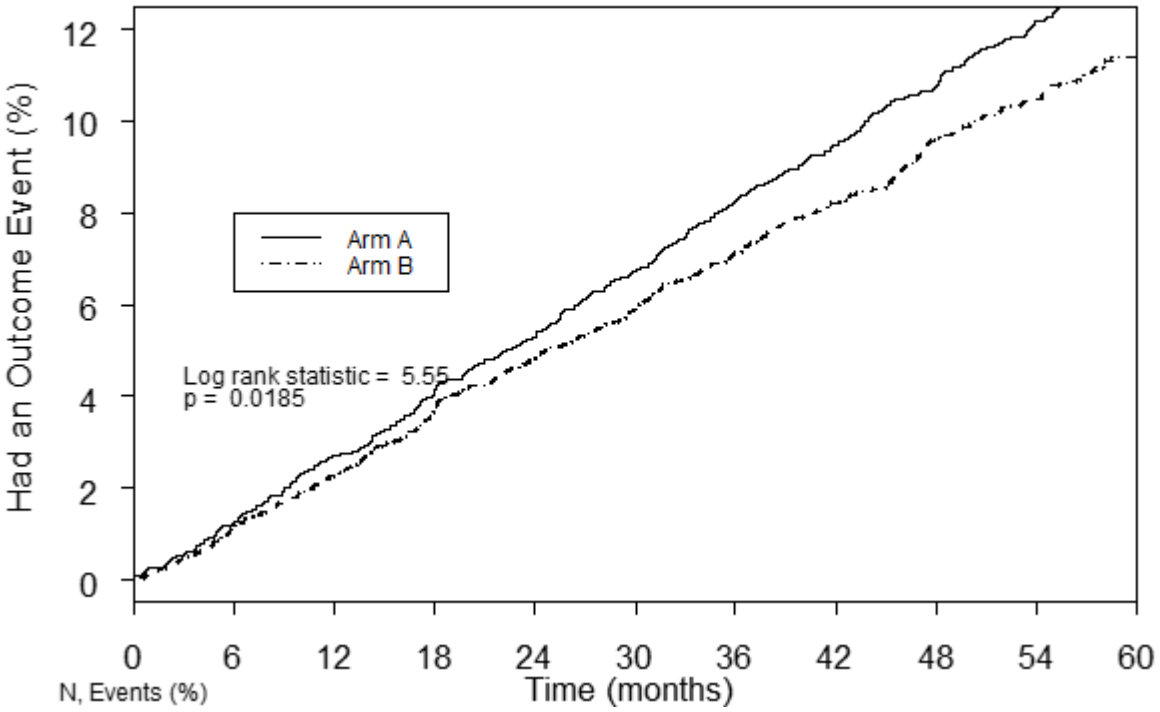
Context of DMC Decision

- Data have not proven harm
- A recommendation to stop study will not appreciably impact trial participants (enrollment completed and the large majority already off treatment)
- A recommendation to stop due to harm may not be compelling enough (yet) for outside parties and the millions taking the treatment
- The majority of the imbalance is in the non-fatal events; deaths are quite similar between arms
- Study will finish anyways within a year and data will become public then

9th Review – 78 Months into Study

1047 Events– Arm A: 559 vs. Arm B: 488 (DMC vote to disclose)

Table 13a: Plot of time to primary outcome event confirmed by EAC during Randomization Phase



Axio

PARTNERS IN RESEARCH

Context of DMC Decision

- Study team was anticipating at least four more months for final data cleaning, plus additional time for internal report generation
- Data were essentially final
- Data was compelling and clear to the DMC that harm was established
- DMC could not recommend stopping study – it was already in process of being shut down
- DMC felt compelled to disclose results to regulatory agencies about this imbalance in a timely way and not wait another half-year for the results be publicly reported

Example #3

Background

- Phase III Open-label Randomized Trial to compare new combined treatment (Investigational product A + on-market drug B) vs. A alone vs. SOC, in oncology setting
- Endpoints: PFS, OS
- Study status at the decision: >90% enrolled, a potential amendment is planed to enroll extra 400 patients
- Monotherapy Arm (A alone) was added about 6 months after starting A+B and SOC arms
- Drug A was known to have delayed treatment benefit

DMC Monitoring

- Meet at least every 6 months
- Descriptive statistics on safety and efficacy were provided at every meeting
- No planned efficacy interim analysis

What Happened

- At the second data review, the hazard ratio of overall death was more than 1.5 times higher in the combined A+B arm vs. SOC
- Hazard ratio of overall death was more than 2 times higher in the combined A+B arm vs. SOC in a specified sub-population of interest (>80% of total population)
- All toxicities were worse in the combined A+B arm vs. SOC
- The monotherapy A-only arm seems comparable vs. SOC
- An accelerated review was called to occur 3 months later

What Happened

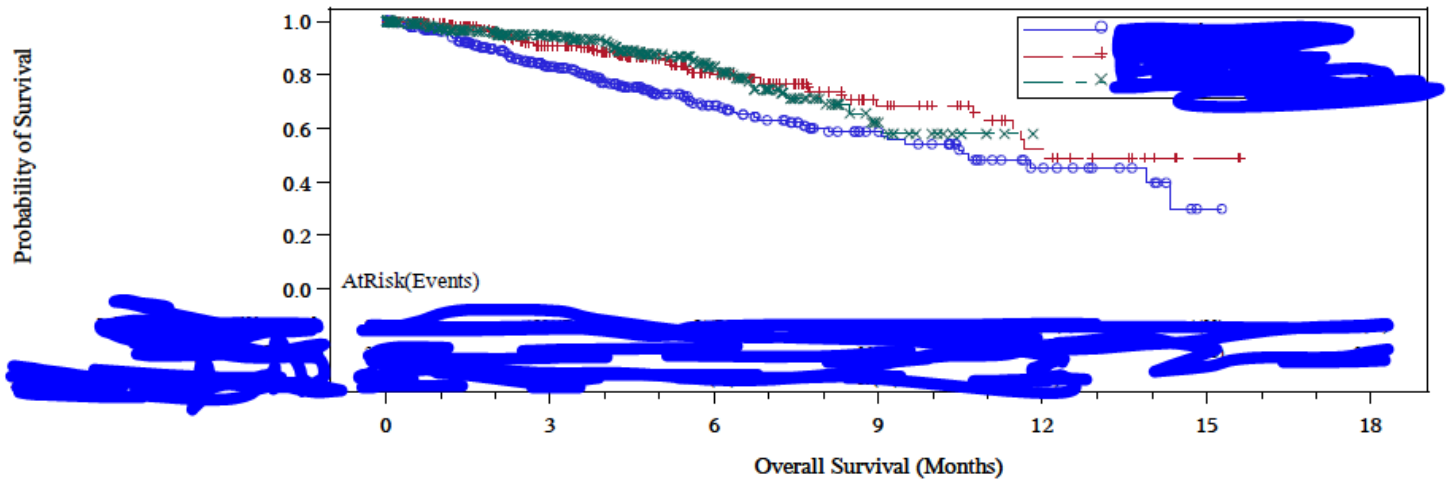
- Three months later, a similar pattern was observed
- Another review was conducted 1 month after the accelerated review and a similar pattern was observed again

What Happened

[redacted]

[redacted]

Figure C.5.1.1: Kaplan-Meier Plot of Overall Survival
All Randomized Subjects



[redacted]

Blue: A+B
Red: SOC
Green: A

Events	Median (95% Confidence Interval)	
90/348	10.6 (9.1,14.3)	A+B
53/344	12.1 (11.5,NA)	SOC
43/311	NA (8.9,NA)	A

Hazard Ratio	
1.83 (1.24, 2.75)	A+B over SOC
1.05 (0.64, 1.71)	A over SOC

[redacted]

Axio

PARTNERS IN RESEARCH

DMC Recommendation

- Stop future enrollment to the combined A+B arm immediately due to safety concern of early death risk
- The current participants continue as per protocol

What Happened

- DMC decision was communicated to the sponsor right after the closed session
- Sponsor accepted the recommendation the following day and stopped the enrollment into the combined A+B arm
- Axio was requested by sponsor to submit DMC report and closed minutes to various regulatory agencies using a carefully laid out process
- DMC continues to monitor the patients on study

Example #4

Background

- Phase III Randomized Trial to compare new combined treatment vs. placebo, for 180-day CV death
- This is the second Phase III study – the first study achieved statistically significant positive results on primary endpoint of short-term symptom relief and suggested benefit in 180-day CV death

DMC Monitoring

- Meet at least every 6 months
- Descriptive statistics on safety and OS were planned to be provided at every meeting (but not CV death)
- One formal evaluation for benefit at 60% of CV deaths – HR<0.738
- No formal evaluation for futility

Meeting #1

- No specific safety concerns, and deaths 11 active vs. 20 placebo using safety population
- Recommend Continue, but…
- Request to see OS for ITT population
- Request to see CV deaths – both investigator and CEC assessments, and concordance table

Meeting #2

- No specific safety concerns, and deaths 67 active vs. 81 placebo using ITT population
- Recommend Continue, but…
- Request to see Kaplan-Meier curves for OS, and CV death (both investigator and CEC)

Meeting #3

- No specific safety concerns, and deaths 147 active vs. 161 placebo using ITT population, and CV deaths show similar pattern (both investigator and CEC)
- Recommend Continue

Meeting #4

- Formal review of efficacy for benefit
- CV Death HR = 1.00 – definitely not <0.738
- No specific safety concerns, and deaths 234 active vs. 246 placebo using ITT population, and CV deaths show similar pattern (both investigator and CEC)
- Recommend Continue, noting…

Meeting #4

- “In summary, the study probably has met statistical futility for CV mortality, however that is not a pre-specified action for the DMC to consider. The formal statistical boundary for declaring benefit has clearly not been crossed. There are no safety concerns compelling enough to recommend any change in study conduct and there is still valuable information being collected by the study. Therefore the DMC agreed unanimously to continue the study and to meet again in approximately six months by teleconference.”

Meeting #5

- No specific safety concerns, and deaths 291 active vs. 310 placebo using ITT population, and CV deaths show similar pattern (both investigator and CEC)
- Recommend Continue, noting…

Meeting #5

- “The DMC considered the possibility of stopping the trial early for statistical futility, as continuing the trial could potentially create ethical concerns by continuing the study and subjecting newly enrolled patients to treatment where the primary endpoint is unlikely to demonstrate superiority. However, the DMC noted that the DMC Charter only specifies the ability to recommend stopping the trial for certain efficacy or for safety concerns. …”

Meeting #5

- "… As a result, the majority of the DMC felt that, lacking a safety risk to the participants, it was not in their charge to recommend discontinuing. Additionally, a minority view was that valuable information may potentially still emerge through continuing the trial. For these two reasons, the DMC agreed unanimously to recommend continuing the study."

Conclusion

- One year later, top-line results were published
- Study did not meet primary endpoints
- Clinical program for the drug effectively terminated

Example #5

Background

- Double-blind, randomized study of active vs. placebo in high-risk patients with Type 2 Diabetes
- Primary endpoint is time to composite endpoint of CV and diabetes outcomes

DMC Monitoring

- Meet at least every 6 months
- Descriptive statistics on safety and OS were planned to be provided at every meeting (but not efficacy data)
- Formal evaluations at
  - 1/3 of events – $p<0.0001$
  - 2/3 of events – $p<0.0060$
- No formal evaluation for futility

Meeting #1

- No specific safety concerns, although some imbalances although DMC maintained masking of “A” vs. “B”
- Recommend Continue, but…
- Request to see blinded version of efficacy outputs – to know if composite endpoint is dominated to some particular (less clinically relevant) component

Meeting #2

- Some safety imbalances emerging (e.g. edema, hyperkalemia, hypotension), with excess on “A”, although DMC maintained masking of “A” vs. “B”
- Blinded version of efficacy outputs were helpful – and DMC wants to see by arm but nervous if that would count as a “formal look” – will consult sponsor
- Sponsor agrees that DMC can look at components of primary endpoint by arm, but not the composite itself
- Recommend Continue

Meeting #3

- More pronounced safety imbalances emerging (e.g. pulmonary edema, diarrhea, hyperkalemia, hypotension, dizziness), with excess on “A”
- DMC unmasked themselves – “A” is “Active” as expected
- Deaths balanced at 54 vs. 60
- Components of composite endpoint reviewed, nothing of particular concern
- Recommend Continue

Meeting #4

- More pronounced safety imbalances emerging (e.g. serious events of pulmonary edema, falls, gastroenteritis, chronic renal failure, Vtach/Vfib), with excess on “Active”
- Recommend Continue, next meeting on first formal review of efficacy
- SDAC provided DMC with formal efficacy tables with fake randomization in advance to ensure outputs will be suitable for DMC needs

Meeting #5

- Formal efficacy review at 1/3 total composite endpoints – 288 “Active” vs. 276 “Placebo” – boundary not crossed
- Deaths balanced at 189 vs. 187
- More pronounced safety imbalances emerging (e.g. serious hyperkalemia and renal failure), with excess on “Active”
- Recommend Continue, next meeting sooner than usual
- DMC requests additional outputs such as Kaplan-Meier plots of time to first serious hyperkalemia and time to first serious renal failure

Meeting #5

- "Although there is no formal stopping rule for statistical futility in the DMC Charter, the DMC can still contemplate the issue. However with a full two-thirds of events left to accrue, it still appears there is a chance for a statistically successful trial if these next two-thirds of events occur with the expected level of benefit for study treatment as postulated in the protocol."

Meeting #6

- Continued pronounced safety imbalances (e.g. serious hyperkalemia and renal failure), with excess on “Active”
- Deaths have an excess on “Active” at 246 vs. 227
- Informal review of composite events has excess on “Active” at 420 vs. 397
- Recommend Continue, but also…
- Meet one month later to review ad hoc outputs regarding serious renal events and serious hyperkalemia – recommendation to continue based on that review

Meeting #7

- Formal efficacy review at 2/3 total composite endpoints – 581 “Active” vs. 542 “Placebo” – boundary for efficacy obviously not crossed – strong trend in harmful direction
- Deaths have an excess on “Active” at 307 vs. 289
- Continued pronounced safety imbalances (e.g. serious hyperkalemia and serious renal failure), with excess on “Active”
- Study would normally complete normally in six months
- But, DMC recommend termination for futility…

Meeting #7

- "The DMC recognizes that futility is not specifically mentioned in the DMC Charter. Looking at the primary endpoint results is relevant, though, to ensure that safety risks are not counter-balanced by positive efficacy. The DMC Statistician confirmed there was a very low probability that results in the final ~1/3 of the endpoints would cause results to be able to demonstrate benefit. There was brief discussion about continuing through to the end to get additional safety data which could be useful to the current patient population taking study drug and additional proof, potentially, of harm. …"

Meeting #7

- "… However, the DMC agreed that their mandate was for protection of the patients in the study and the obligation was to recommend termination due to safety concerns, in the context of lack of efficacy. There are still many patients in the study that are being treated and would be at increased risk over the next six months until the normal study completion. The DMC unanimously agreed to recommend early termination of the study. Study participants should discontinue study drug in an orderly fashion, although the study could continue to accrue endpoints to the normal end of the study if desired by the sponsor. "

Meeting #7

- The recommendations of the DMC, including descriptions of the numeric imbalances seen, were written up during the meeting.
- These recommendations were provided initially only to the Executive Committee co-chairs, who were available for in-person discussion.
- These two agreed with the recommendations, and then brought in senior sponsor leadership for a full discussion where the DMC report was discussed in detail.
- Tentative agreement from the sponsor about the recommendation for early termination
- Public announcement of termination of study 6 days later

The Final Exam

Tricky – SDAC/DMC interactions

What should I do if a DMC member asks me “David – should we recommend stopping?”

What should I do if at the end of the meeting, a DMC member asks me “David – did we make the right decision?”

What should I do if the DMC Chair takes 6 weeks to sign the minutes

What should I do if a DMC member is uncommunicative to emails as we try to schedule the next meeting

Tricky – DMC decision making

What should DMC do if safety signal seen that could be relevant for ICF for this and other studies, but study is still ethical to continue. Who/how to communicate without damaging trial integrity?

What should DMC do if study is clearly futile (but safe), but no formal futility rules?

What to do if DMC feels compelled to reveal a by-arm safety signal – but without any ‘so what’ action item proposed?

Tricky -

What to do if DMC has ill-defined recommendations and/or action items – and will be difficult for the SDAC or study team to clearly know how to respond?

What to do if normally have ‘large’ recap sessions – but now the DMC has non-trivial recommendation?

What to do if DMC member wants to micro-manage the study and patient care, or wants a protocol amendment because that’s how they would have designed the study?

What to do if DMC member inadvertently reveals by-arm results during the open session?

Tricky -

How does the statistician on the DMC interact with the clinical members?

How much DMC decision making is statistically based vs. clinically based?

How rigidly should the DMC view efficacy and futility boundaries?

How worried should the DMC be about *a priori* known side effects with large excess in the active arm?

Tricky -

How thorough is the review of materials by the DMC before and during the meeting?

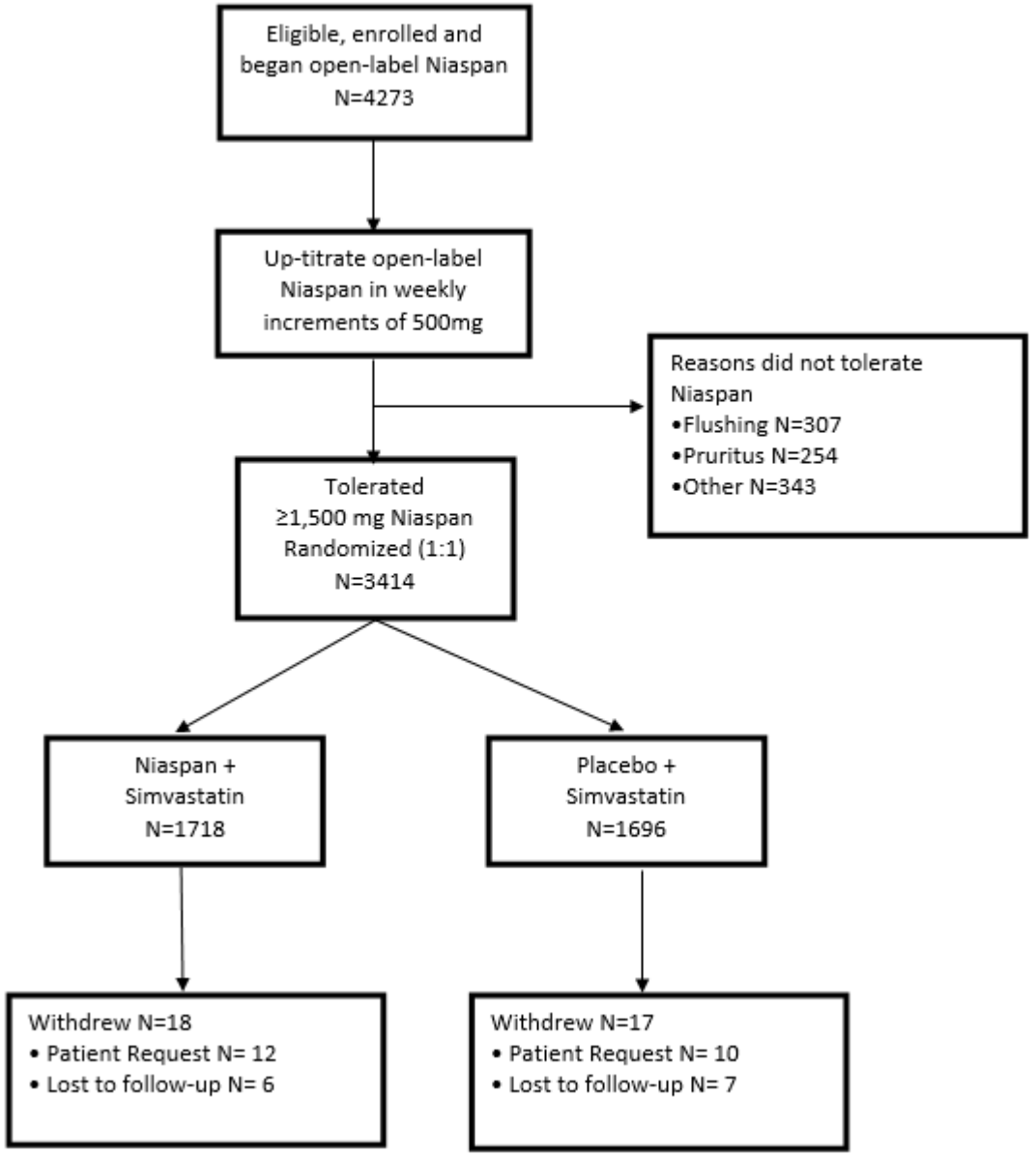
How is consensus achieved? Is there actual voting?

What could cause a DMC member to resign (or be asked to resign)?

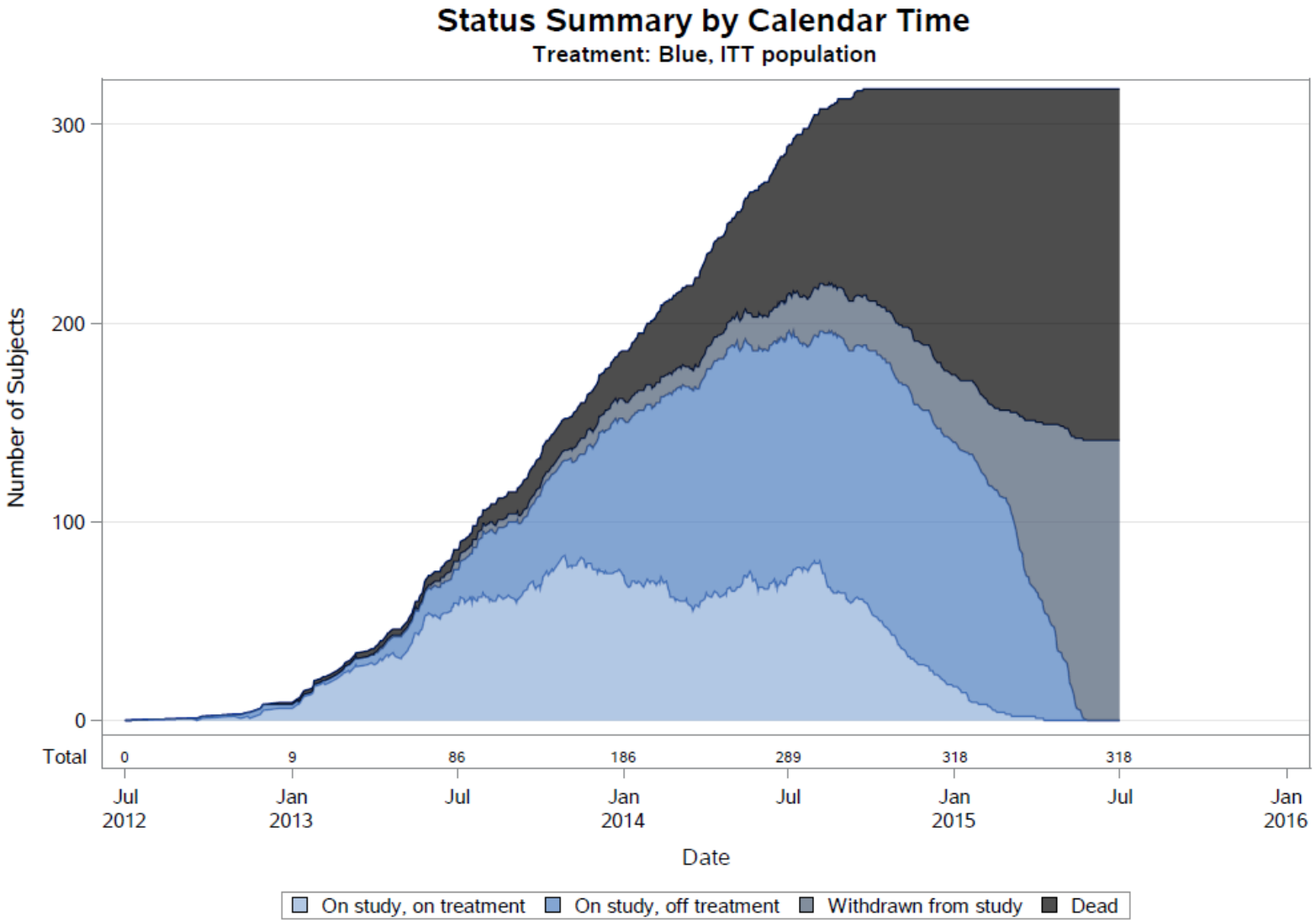
What is the role of the DMC in providing advice on protocol development?

In a ‘program-wide’ DMC review, how much do the other studies influence the recommendation for one study?

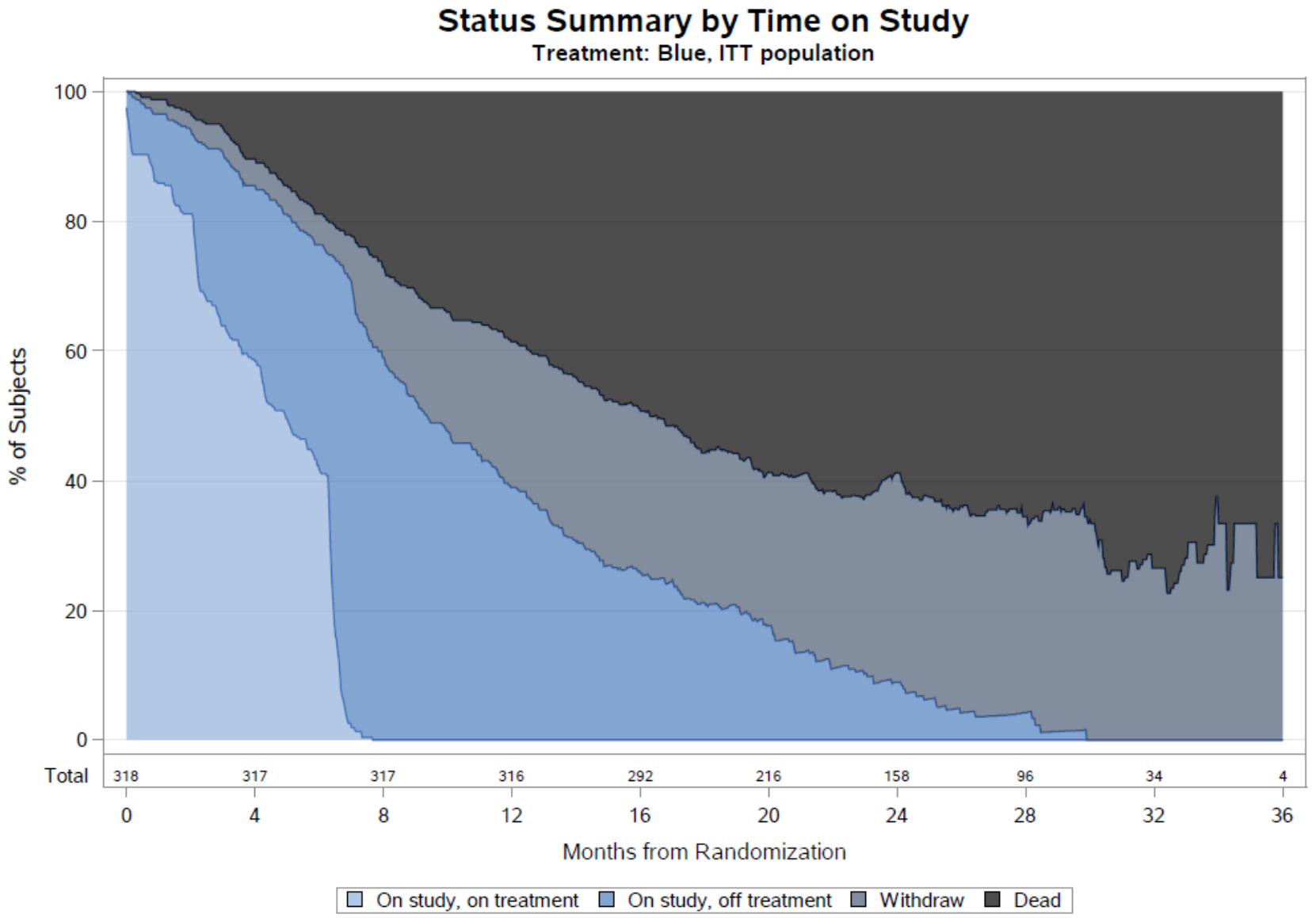
Graphics – CONSORT



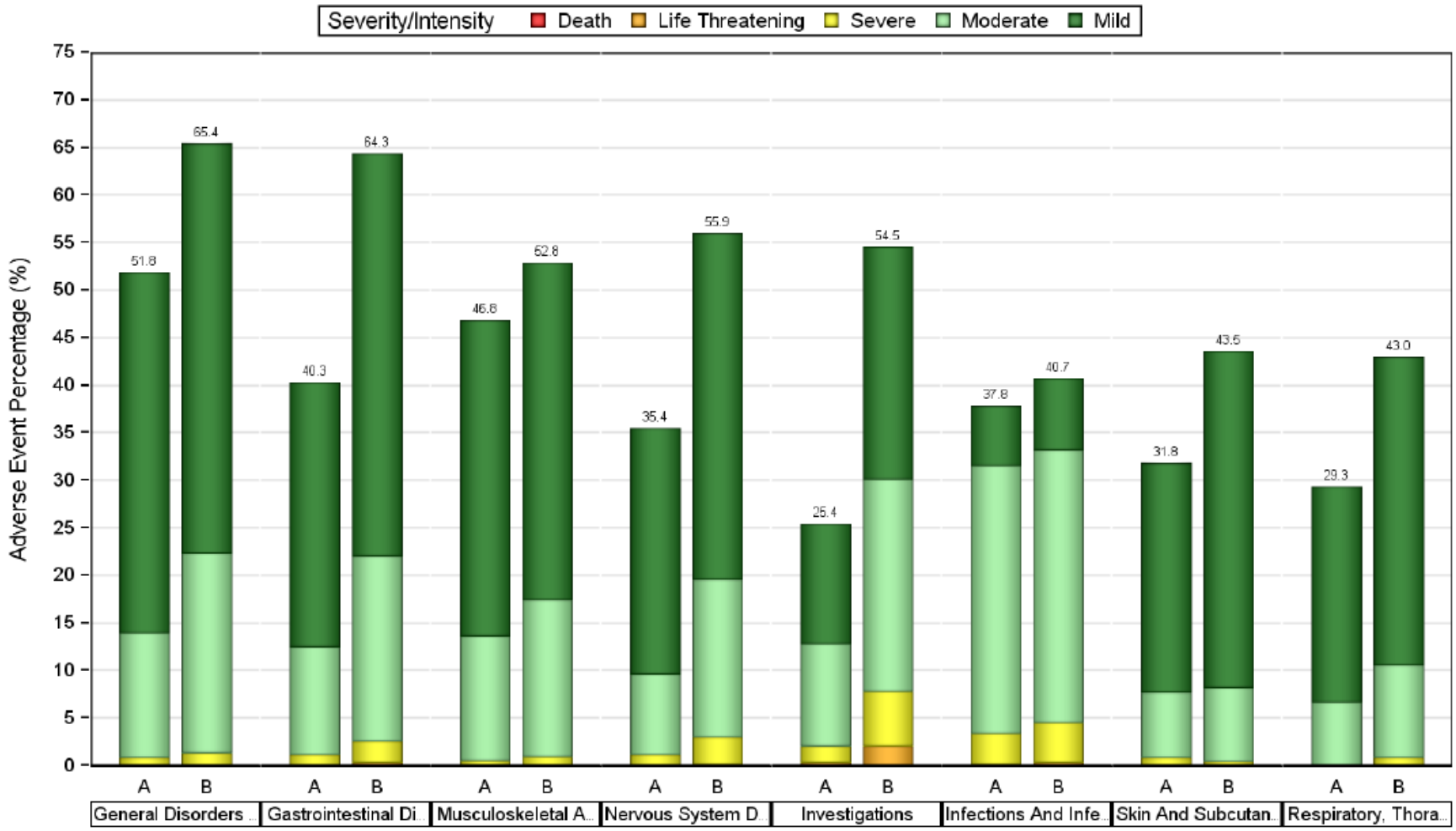
Graphics – Disposition Over Time



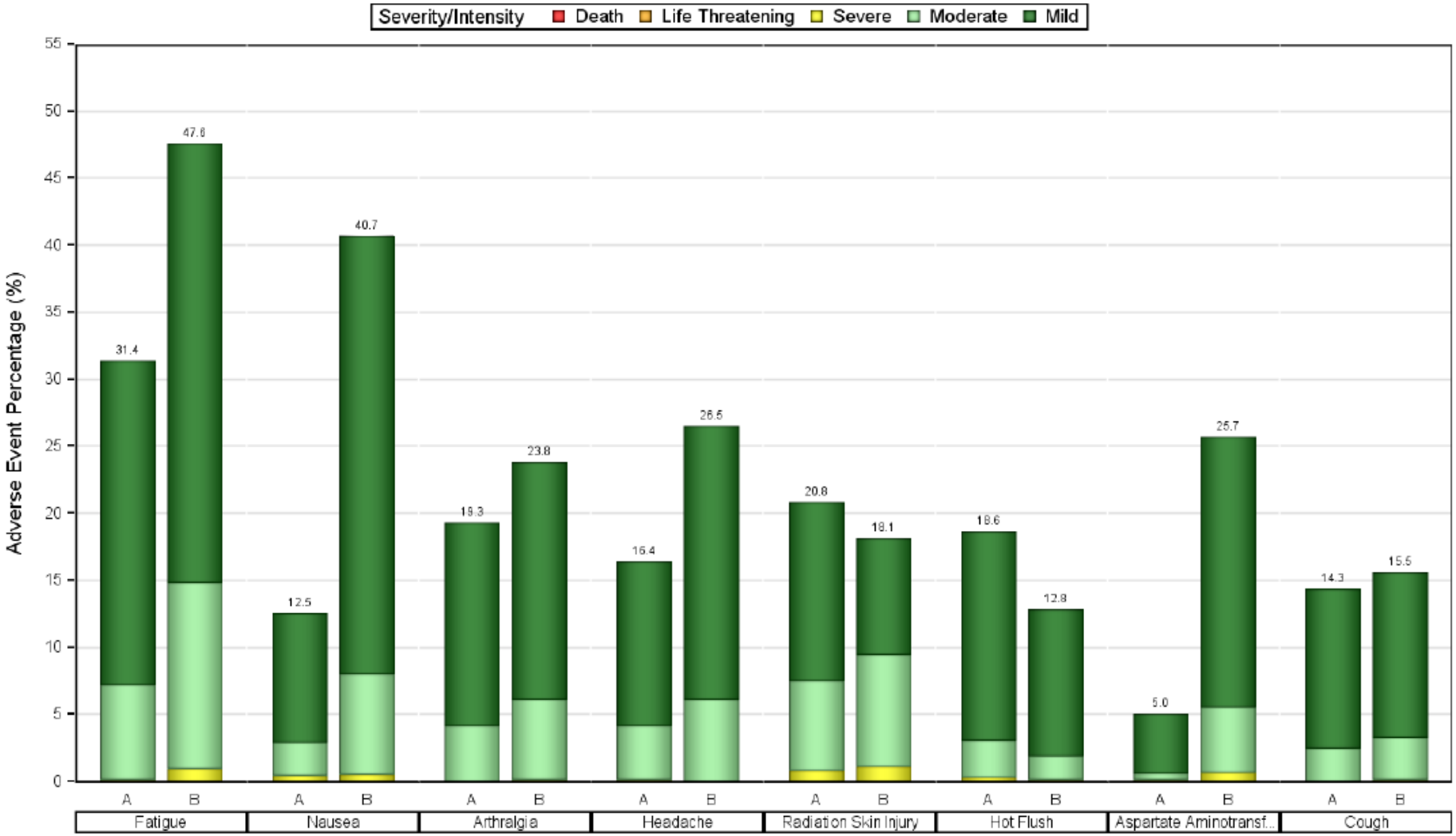
Graphics – Disposition Over Time



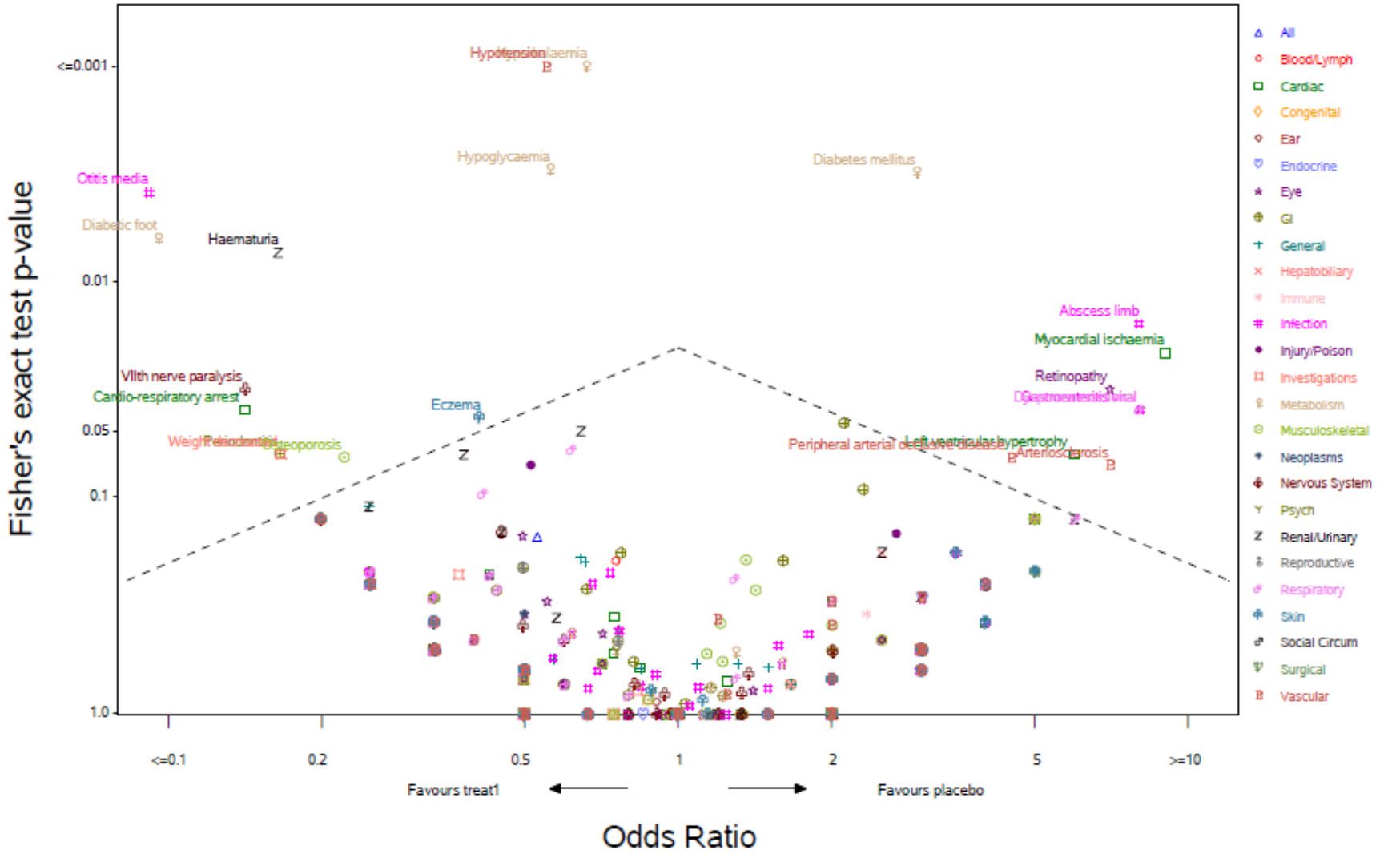
Graphics – AE SOC Plot



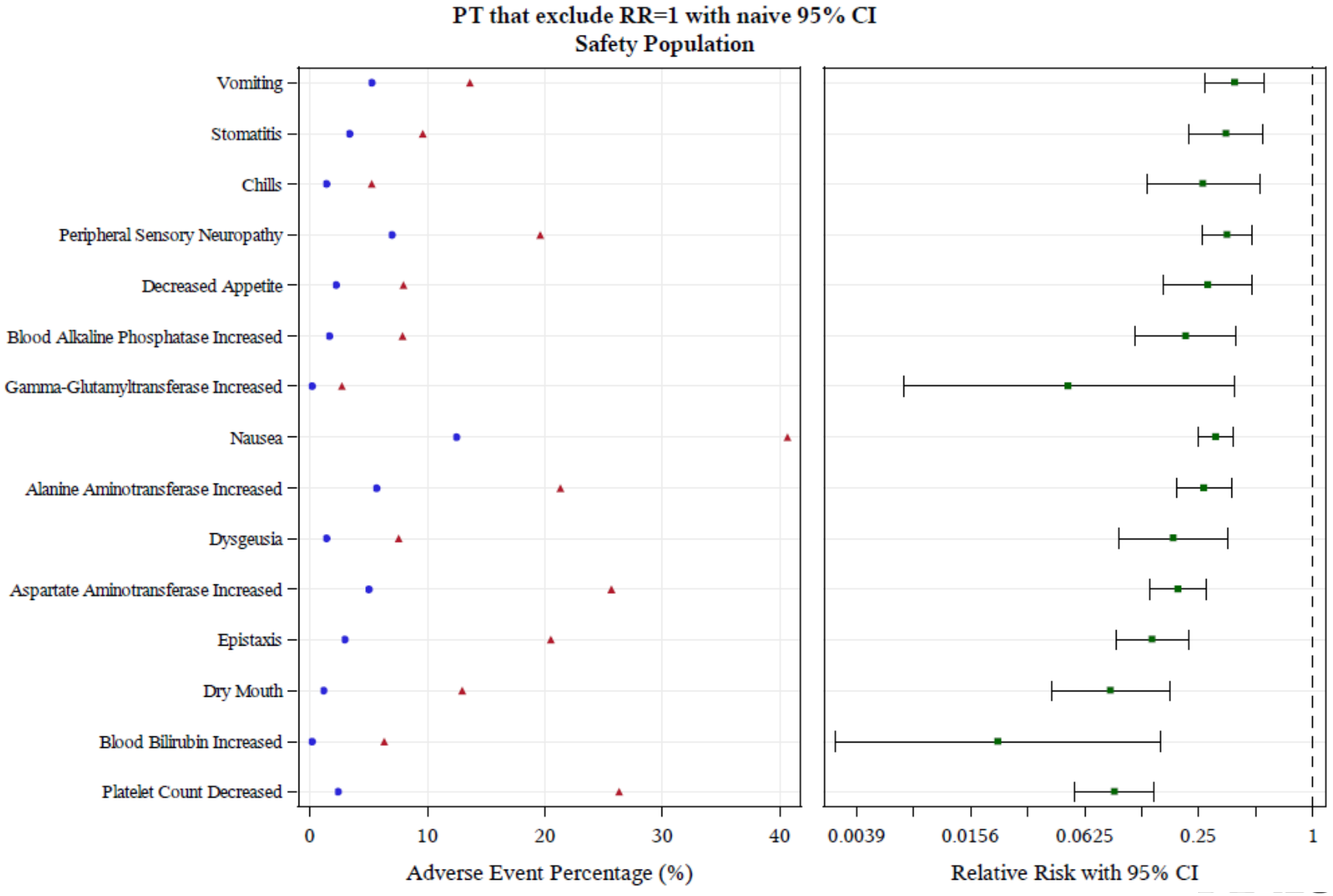
Graphics – AE PT Plot



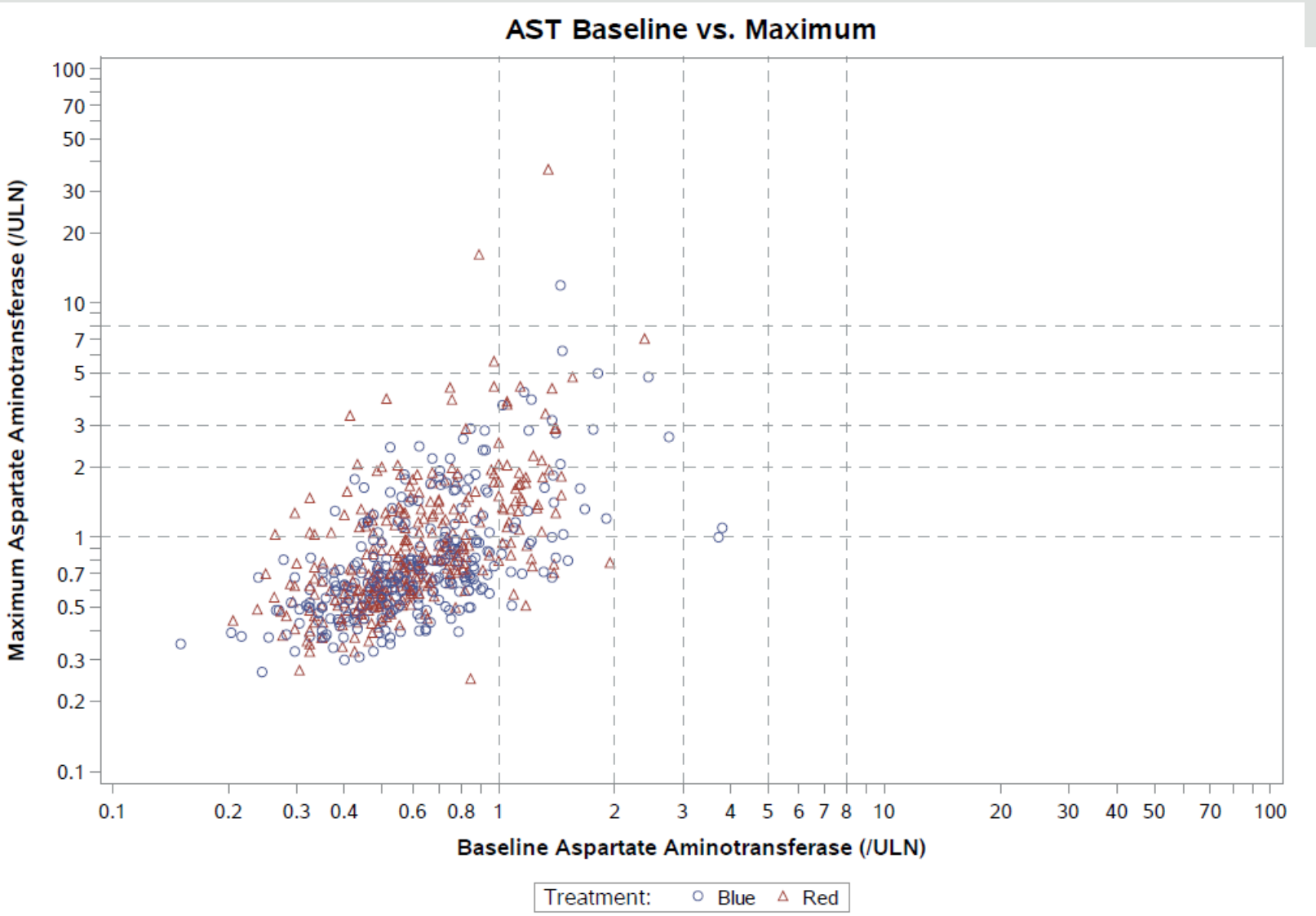
Graphics – AE Modified Volcano Plot



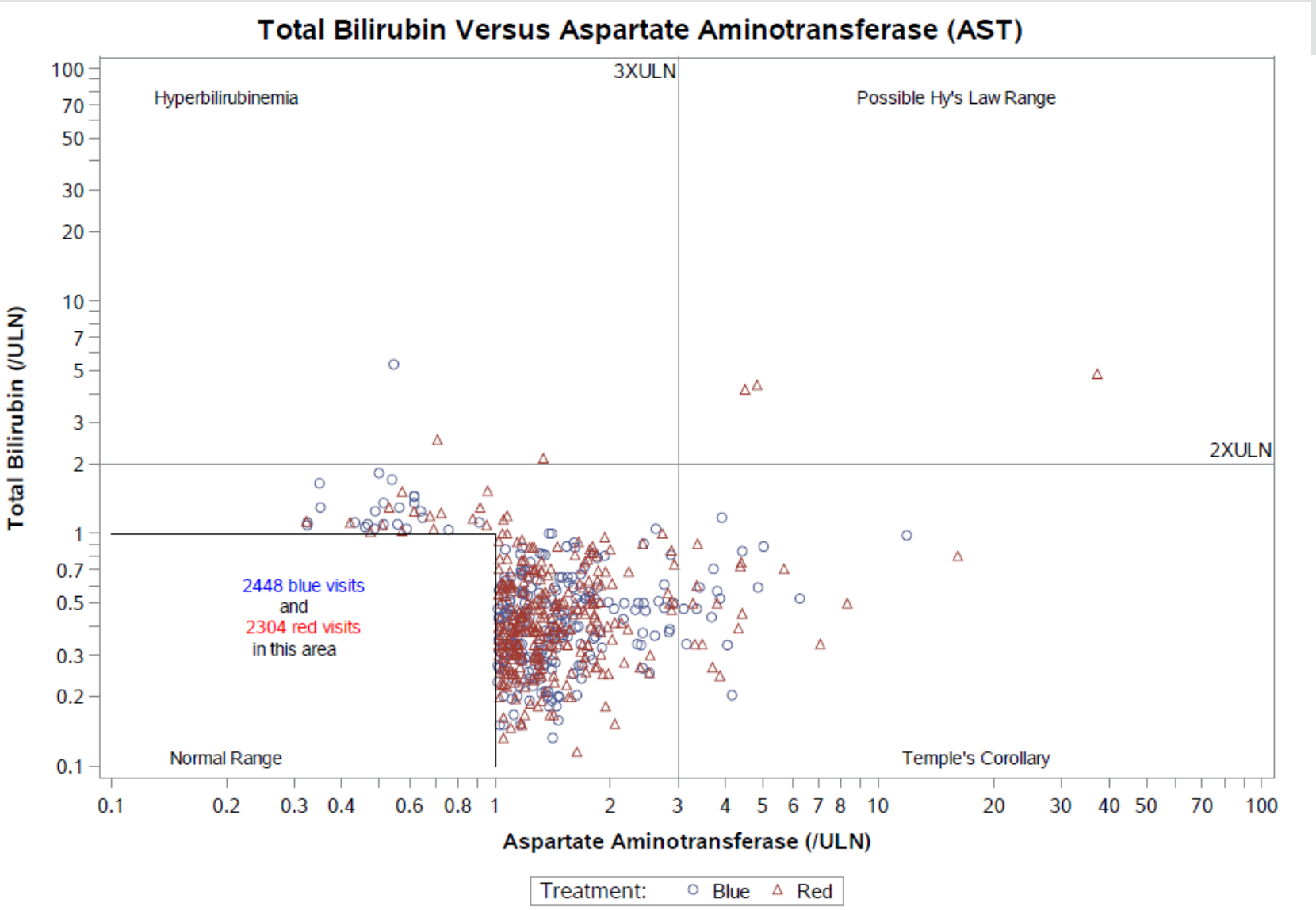
Graphics – AE Plot



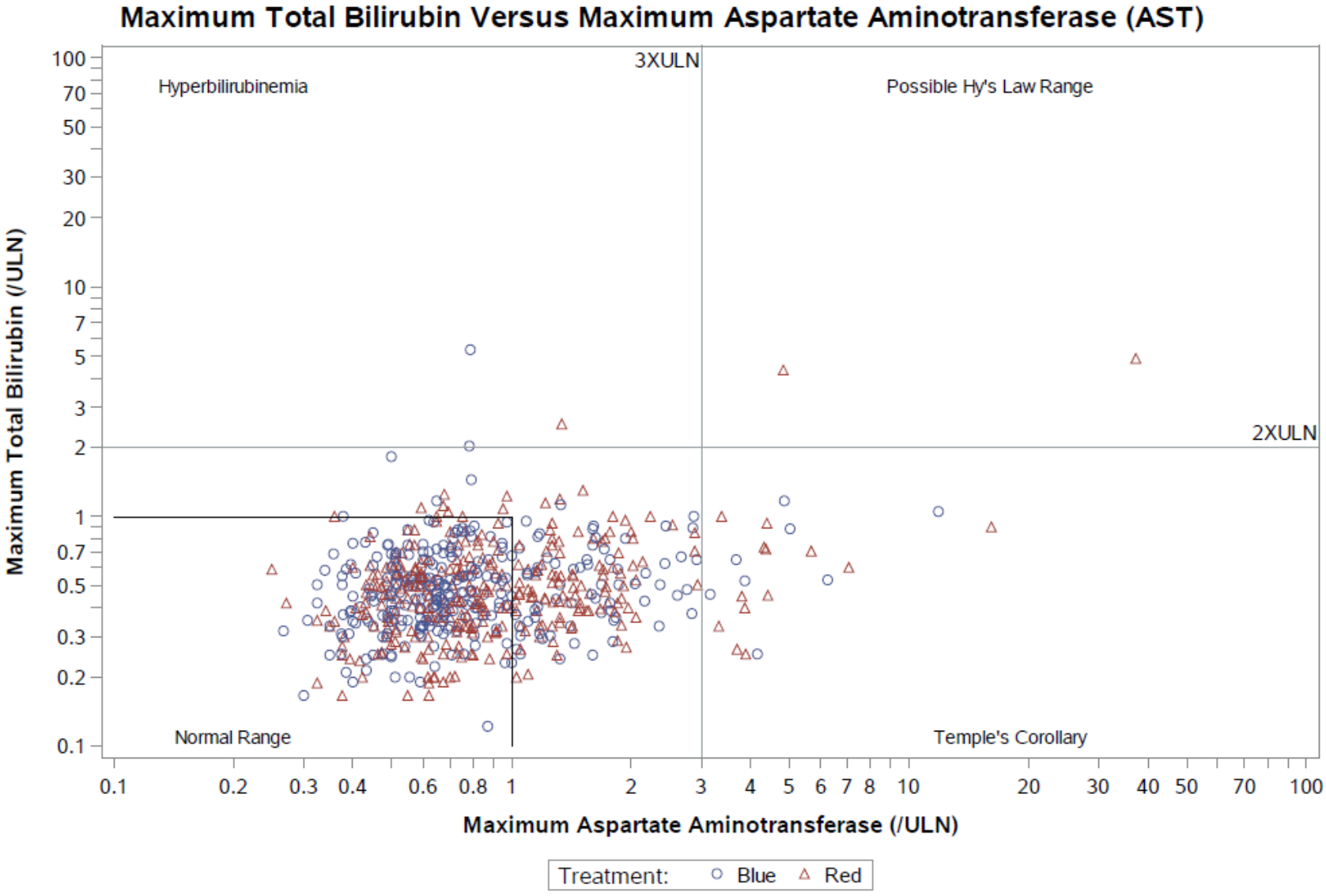
Graphics – eDISH



Graphics - eDISH



Graphics - eDISH



• Maximum values are those maximum values that occur post_baseline(no time constraints and not necessarily concurrent events)

Graphics - Profile