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# The Independent Statistician Model

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## Non-Disclaimer:

The views and opinions expressed in this presentation are those of the individual speaker.

But they're probably also the views and opinion of Axio Research because I helped write the SOPs and WIs and I lead the training - and after 20 years and nearly 500 DMC meetings the people there (usually) listen to me!

## My Truth as SDAC Statistician:

I serve the sponsor and the DMC – but I also serve the current and future patients. I want the ‘right’ recommendation to be made.

As an independent statistician at an SDAC I will do what I can to enable that to happen through collaboration with the DMC – without exceeding my authority. I recognize that I am **not** a voting member of the DMC.

## Some Ugly Truths:

**DMC:** Not every DMC member is as experienced or engaged as the DMC members that will appear before you today.

**Sponsor:** Not every study team understands and respects the DMC process – or wants an 'involved' DMC.

**SDAC:** Not every SDAC is experienced – and we hear the complaints about other SDACs from our DMC members.

## Some Ugly Truths - DMC:

I know that some DMC members download the report an hour before the meeting – or not at all.

I know that some DMC members cancel a week in advance or are no-shows despite many reminders.

I know that some DMC members want only teleconferences – and short ones at that.

## Some Ugly Truths - DMC:

I know that some DMC members will want to leave the Closed Session after 15 minutes to go into surgery or catch a plane.

I know that some DMC members come into the meeting and say “Everything looks good. Does everyone agree we can recommend continuing?”

I know that some DMC members will not be able to remember protocol details or previous discussions – especially for our ‘program-wide’ DMCs.

## Some Ugly Truths - Sponsor:

I know that some study teams see that the study is the 15th in a clinical program with well-understood and accepted toxicity profile and don't expect any issues and are not interested in convening an 'active' DMC.

I know that some study teams declare this a 'safety only' DMC and steadfastly refuse to show even basic summaries of efficacy data.

I know that some study teams obfuscate/minimize issues pertaining to study conduct.

I know that some study teams withhold data by only sending the 'clean' data.

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## Some Ugly Truths - SDAC:

I know that some SDACs send 1000s of pages, and as 100 individual files.

I know that some SDACs do not take charge of the meeting logistics and facilitating discussion.

I know that some SDACs do not have experience with clinical trials, DMCs or a working knowledge of the specific study and DMC Charter.

I know that some SDACs mistakenly send the ‘fake randomization’ report to the DMC or send the ‘real randomization’ report to the sponsor.

## Primary job – get a recommendation

- Get all members to the meeting, or at least quorum
- Check for new potential conflict of interest
- Review previous minutes and action items and questions posed in Open Session
- Get through review of (key sections of) Closed Report
- Enumerate detailed action items – including next meeting
- Make top-line recommendation

## The review of the Closed Report:

The Chair leads the DMC through the TLFs, or

The Chair defers to the SDAC independent statistician to lead the DMC through the TLFs, or

The Chair solicits items of focus from the DMC, shares his or her own, and these are visited in turn.

## 80% of the time the DMC asks Axio statistician to lead

Take at least 15 seconds on each table – read title, then: “Any comments or questions from the DMC?”

We display on the projector or shared screen a .PDF with highlighting added. Highlighting is based on previous and current imbalances – many times directly comparing previous results compared to current. Typically 30-40 rows in the ~150 page Closed Report will be highlighted.

We try not to editorialize: “We note a numeric imbalance here. Any comments from the DMC on this numeric imbalance?” (Or use words like “possible signal” or “trend” or “excess”.)

## Executive Summary? No.

Too enabling. Concern is that the DMC members will simply read the 5-page summary and not do their due diligence.

I do not want to be responsible for identifying what is (and what is not) included.

A 0 vs. 4 imbalance could be the most critical line in the report and would unlikely be called out prospectively in an Executive Summary.

## Statistics

Usually not much inferential stats. Typically only show p-values during formal evaluations – typically from survival models (lots of time to death and/or PFS analyses).

'Well-understood' stopping boundaries are still the norm. (Not much uptake on innovative adaptive designs yet.)

Sometimes need to remind clinical members on the hazards of multiple comparison – hopefully DMC Statistician can echo that caution. A marked imbalance in one AE on a 20-page summary is difficult to interpret without additional context.

## Master of Ceremonies

SDAC statistician has to take the lead if the DMC Chair defers.

Make sure a clear recommendation is formed, and that action items are clear for who, what, when.

Taking minutes, looking up *ad hoc* queries, leading group through the Closed Report, handling meeting logistics (shared screen / telephone lines) is definitely a challenge! Typically exhausted at the end – especially for introverts.

In advance, SDAC working on scheduling, sending calendar invites, drafting agenda, in consultation with study team and DMC.

## TLFs

Axio's typical TLFs are standard (but pretty to look at) –

- enrollment
- demographics/disease characteristics
- study disposition
- treatment exposure
- adverse events (including AEs of special interest),
- laboratory data
- maybe vital signs, ECG, etc.
- deaths
- (hopefully) some efficacy results (perhaps with p-value, perhaps not)

## TLFs

Definitely fine-tuned based on DMC comments at organizational meeting and throughout the study.

Moderate number of tables, Moderate number of figures (e.g. labs over time), Minimal listings (e.g. SAEs, deaths) – hopefully just ~150 pages.

Contingency budget in contract that can be drawn upon without pre-approval for (potentially confidential) DMC requests for new/changed TLFs.

## Prep work

Send through secure Internet portal – one bookmarked .PDF with hyperlinked ToC (but paper for Prof. Fleming!) with page numbers – easily searchable and DMC members can add their own electronic notes to their version.

I will know the status of the data – clinical cut-off date, snapshot date - and can quickly describe key definitions e.g. treatment-emergent AE and Grade 3 hypoglycemia.

I will know a bit about some particularly odd patients, but will need to open up datasets if DMC has questions about specific patients.

## Prep work

Axio SDAC statisticians are not an expert in the disease area – we are well-versed on DMCs and well-versed in standard clinical trial methodology and will willingly share that experience. But we don't immediately know what level of toxicity is expected or the biologic 'method of action' of the new treatment.

We know the study synopsis, but are not experts on the protocol. We will look up details of the protocol on the fly if need be. We do know the DMC charter and formal stopping rules well.

## ‘Black box’ DMCs

For cost savings and concern about consistency, study team may create programming – SDAC simply merges in real randomization.

Less desirable outcome – outputs generally look less pleasing to the eye than Axio norms or are excessively lengthy, Axio cannot explain underlying filters/definitions, cannot easily create *ad hoc* outputs for DMC.

Nonetheless, we facilitate these when called upon and do our best to serve the DMC and the study participants.

## Training -

For our fresh PhD and MS from Biostats programs -

Read FDA and CTTI guidance. Read ‘the little red book’.

First 6 months they work with programmers as datasets and TLFs are specified, programmed, and tested, and participate in study team calls, and quietly listen in on DMC calls and draft minutes (~15-20 meetings).

Then we have them lead ~2 DMC meetings internally – with fellow Axions asking good and/or stupid questions and causing general logistical mischief.

## Training -

Next 6 months lead “easier” DMC meetings with senior Axion (generally) quietly listening in on the side (~10-15 meetings).

Weekly meetings of all statisticians – share anecdotes of good/bad/strange DMC experiences.

After a year (or more), and after thorough feedback on performance, SDAC statisticians are permitted to lead “easier” DMC meetings solo or “harder” meetings with assistance.

## Training -

Yes – this takes a lot of time! But we cannot in good conscience put an untrained SDAC statistician in front of a DMC or study team.

Suggest sponsors work with CROs that have DMC work as a primary focus, not as just an extra service that's thrown in along with data management or FSR work.

Axio as an SDAC is pragmatic – we propose CTTI standards, but will serve in the best of our capacity to protect the interest of the study even if study team or DMC deviates.

## Non-Statistics Intangibles -

Deferential – when needed (it's the DMC's meeting after all)

Assertive – when needed (get discussion back on track)

Confident – or at least the appearance of confidence

Good English writing skills (precise minutes and emails)

Good English speaking skills (precise diction, no "ums…")

Good English listening skills (understand global accents)

Read body language at in-person meetings and – more important and difficult – read emotion over the phone (detect DMC member frustration)

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## Non-Statistics Intangibles -

Poker-face (when discussing DMC activities with study team)

Tech savvy – understands our ‘shared screen’ and teleconference services to manage the meeting smoothly and give tech support to struggling attendees

Collaborative with DMC – repeat/rephrase their question back to them to make sure it’s really understood, and perhaps suggest a counter-proposal that addresses the concern but may be more practical to enact

Quick thinking – if asked a question can decide whether able to answer immediately or need to defer on answering.

Diplomacy – especially for the study team / DMC interaction

## SOPs and WIs:

SOPs on:

- Specification and programming of datasets and TLFs (multiple reviewers and independent programming)
- DMC Minutes
- DMC Charter
- DMC production checklist for each meeting
- Printing and Distribution of DMC materials, etc.

WIs on:

- DMC passwords
- Scheduling meetings
- Using WebEx and ShareFile and Egnyte
- Printing and Distribution of DMC materials, etc.

A specific focus of SOPs and WIs is confirming accurate randomization has been used and maintaining blind.

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## Tricky -

DMC asks me “David – should we recommend stopping?”

Study is clearly futile (but safe), but no formal futility rules.

DMC member wants to micro-manage the study and patient care.

DMC member inadvertently reveals by-arm results during the open session.

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

## Tricky -

Study is limping along – low enrollment, few events being observed. What should the DMC recommend?

Study has large number of withdrawal of consent or lost-to-follow-up. What should the DMC recommend – purview of DMC to recommend major change?

Important safety signal 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?

Having ‘big’ recap sessions – but now the DMC has non-trivial recommendation.

## Tricky -

DMC member wants a protocol amendment because that's how they would have designed the study.

DMC wants just a 5-minute closed session.

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

## SDAC – Stuck in the Middle

Used to say SDAC was servant of **two** masters – DMC and sponsor. What if they have disagreement and we're caught in the middle? What if DMC wants updates and sponsor won't pay for SDAC work?

Truly the servant of **three** masters – DMC, sponsor, and current/future patients. Look out for patients even if DMC and sponsor see the DMC process as simply a box to be checked off, or work differently than current best practices.

## Final truths -

Reality is messy – lots of guidance mentioned today will be unknown or ignored by DMC and study teams.

The study team may not have experience with DMCs, or motivation to adequately support a DMC.

Most DMCs won't have vastly experienced DMC membership – and maybe it matters, maybe it doesn't.

Nonetheless, the SDAC should be experienced and vocal enough to at least facilitate the DMC – even an inexperienced or unengaged one – to make a reasoned and thoughtful decision that protects patients and preserves study integrity.