Summary of discussion on "Statistical Oversight ", DSBS afternoon meeting, 22 October 2025, Zealand Pharma

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Introduction

This document provides a summary of "Statistical Oversight" a DSBS afternoon meeting held on 22 October 2025 at Zealand Pharma.

59 statisticians from 11 companies (service providers counted as one company) registered for the meeting. 36 attended the meeting.

Before the meeting the organizing committee selected 7 themes and provided a commented overview with suggested discussion points for each theme.

The on-site attendees were assigned to one of 4 groups for the discussion. Offsite attendance was done through an online meeting.

Each group selected 3 themes for discussion.

Each group had a facilitator and note-taker identified premeeting by the organizing committee.

The present summary of the discussion is based on the notes taken at the meeting and compiled by the authors listed in Table 1. The responsibility for the summary is the Organizing Committee only. The summary is for informational purposes only and may contain omissions or misrepresentations. The Organizing Committee will appreciate receiving corrections. Please send corrections to Thor Schütt Svane Nielsen (ThN@zealandpharma.com).

Table 1 Persons arranging and facilitating in the meeting

Name	DSBS affiliation	Function (*)
Birgitte Rønn	Member	FA
Mads Wessel Pedersen	Board substitute Member	OM, FA, NT
Marc Andersen	Member	OC, NT, AU
Mikala Fiig Jarner	Board Member	FA
Ólöf Thórisdóttir	Board Member	FA
Per Sørensen	Member	FA

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Sofie Korn	Board substitute Member	OC, NT, AU
Søren Rasmussen	Board substitute Member	OC, NT, AU
Thor Nielsen	Board Member	OC, NT, AU

*: OC: Organizing committee; OM: on-line meeting responsible; FA: facilitators, NT: note-takers, AU: author

Table 2 Document history

Version	Date	Rationale
0.0	28 October 2025	Initial version
0.1-Draft	10 November 2025	Draft version finalised for review of DSBS board
1.0-Final	13 November 2025	Final version

Theme #1 Qualification process

The following criteria could be used for short-listing providers.

- **Strategic fit**: therapeutic area experience, similar trial designs.
- **Capacity**: evidence they can start quickly and dedicate senior staff; avoid being deprioritized by "biggest companies get the most experienced persons."
- **Operational maturity**: SOPs, QMS, inspection history etc.
- **Technology:** validated, integrated (EDC-eTMF-CTMS-Safety-Stats).

RFP and bid defense

Request for Proposal: asking CROs or functional service providers to propose how they would deliver your study, who they would assign, how long it will take, and how much it will cost.

How it fits in the process

- Before the RFP: Many sponsors issue an RFI (Request for Information) to scan the market and narrow to a shortlist.
- RFP stage: You share enough study detail for vendors to build a concrete plan and budget. They respond with a detailed proposal and then defend it in a bid-defense meeting.
- Selection: You score proposals, hold clarifications, and pick a winner; negotiations finalize scope, team, milestones, KPIs, and price.
- Require a named team with CVs and committed allocation percentages; include a clause that substitutions require sponsor approval.
- Ask for a resourcing plan that can be rebalanced at milestones.Compare full-service vs in-house/FSP models with a hybrid option

Scoring matrix example (each item can weight differently)

- Experience similar trials, regulators, geographies.
- Team quality : seniority, turnover, backup, fluency across sponsor/CRO leadership.
- Quality/compliance : audit history, inspection outcomes, SOP robustness.
- Data/Stats/SAP readiness : SDTM/ADaM pipeline, traceability, submission readiness.
- Commercials price transparency, change order discipline, milestone triggers.

Challenges

No named senior staff; various subcontractors; vague standards; unrealistic timelines; default-to-legacy approach.

Theme #2 Statistical oversight during trial conduct

What is a sufficient level? Is it the same for all trials/projects?

- One size doesn't fit all. The level of oversight should be discussed, specified and documented. It should be decided on trial level and should be a trial level discussion.

- Tailor to risk drivers: trial phase, design complexity, and prioritization of the trial. Prioritize what matters most. A Phase 3 trial may not need heavy oversight if routine; in open-label Phase 1 trial, a statistician may not need to join data cleaning.

- Vendor context matters: less oversight with trusted/preferred vendors and established relationships; more when it's a first collaboration.

- Outsourcing a submission: if the sponsor owns the submission, use submission requirements to set oversight expectations.

- Expertise balance: assess sponsor know-how vs. CRO/service-provider experience in the specific indication; don't assume the vendor statistician has the same depth. Oversight level may change when the service provider has experience with the therapy/indication.

- Quality & risk focus: decide which in-house checks remain when outsourced so sponsor priorities aren't diluted.

- Scientific rigor in new areas: increase oversight when entering new indications; operational bias can't be fully removed.

- Maintaining scientific integrity: oversight should not compromise the scientific integrity of the trial by introducing bias in decisions. If performing unblinded or potentially unblinded data review, the risk to scientific integrity should be considered.

- Sponsor is encouraged to develop an oversight plan detailing the level of oversight and defines SME responsibility. The plan will help to ensure cross-functional input to the oversight level and tasks and thereby help to ensure no double work and no task being lost.

Risk-proportionate approach; where and how do you/your company implement this?

Risk assessment for each new trial is done by the trial team and identification of the risks on trial and project level. Then the team assesses how to conduct oversight to appropriately cover the risks. It is recommended to have a documented version-controlled specification of roles for risk assessment.

Recurrent meetings to update risks and mitigation strategy are recommended.

There is currently a transition from Risk Assessment Categorization Tool (RACT) to Risk-Based Quality Management (RBQM). The RACT/RBQM processes may be a tedious task, but statistical input is important to defining risks in a measurable way.

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How is the process around quality tolerance limits (QTLs, ICH E6 R2) definitions in your company (ICH E6 R3 term is "acceptable ranges")?

QTL may include primary endpoint data, recurrent SAEs etc. Thresholds are set after discussion in the trial team.

Sponsor defined standards may be inspired by Transcelerate standards quality tolerance limits.

The setup for monitoring of QTLs should be specified. If the monitoring lies with full-service providers, it should be specified when/if they contact Sponsor if nearing the threshold. Another setup is that Service Provider presents monthly.

How to prioritize what to review?

Data checks should be identified based on risk. If Sponsor have checks done when in-house, but not necessarily when the trial is outsourced, this could be considered in the sourcing process.

Prioritization may be specified in a Statistical monitoring plan for describing the ongoing controls of data.

As a statistician, consider what data is used for the primary objective and conduct oversight on this.

Statistical modelling can be used to inform decision on doing extended Source Data Verification (SDV), i.e. optimize monitoring based on collected data.

For lab measurements a useful tool for ongoing review is based on graphical presentation of data. Example: in the case measurement equipment is not the same across sites graphical comparison of data by site may offer insights for decisions.

Example of important data features to review is whether the patient population is according to expectations. Inclusion criteria and timelines may lead to unrepresentative selection of data.

When comparing sites, consider the inherent differences in the data generating process. For example, the effect of low number of sites or low number of participants per site. Statistical methods to identify issues such as outliers or systematic differences can be helpful to guide the interpretation.

The application of different data review approaches should be considered. This includes individual data review, by-site summary, total summary and statistical methods for assessing data.

Review of data

- Ad hoc queries raised during monthly cross-functional team meetings (sponsor + service provider)
- Review of data – downloads of data during conduct. May also consist of dry run of SDTM, ADAM and TLFs

- Pricing for data transfer varies among Service Providers and depends on several factors, such as frequency and number of datasets
- In addition to data transfers direct access to data can be used
- Use of meta data oversight

Communication from Sponsor to Service provider

How are the known risks with the product conveyed to the Service Provider, so it can be included in the ongoing data review. This may translate into request for reports.

If inhouse experience of risks for a trial, this could be suggested to the Service Provider.

Key design features in e.g. CTP – if inconsistencies are discovered – should be commented on. Perhaps even corrected directly in the document.

What and how do you document oversight?

For essential documents, it is important to have documented that you have reviewed them.

Oversight documented in an Oversight Plan – level of detail ranging from only "date and reviewed" to describing the changes and comments.

What level of documentation is needed? Do we need to document the actual comments etc. during a review or is it enough to document that the review has occurred.

Th approach to storing, for example, comments to draft SAP differs between companies. The approach ranges from storing all versions in the eTMF or only the final version in the eTMF and the previous draft versions elsewhere.

Review process and timelines.

It is important to have a good starting point, good protocol, good SAP, then everything is easier.

Early review of SAP is recommended, for example to ensure flow between STDM and ADAM.

Review of tables shells and outputs (TFL) are important items.

In case a Sponsor has different templates for study documents and deliverables, it is recommended that the Sponsor statistician obtains clear guidance on which templates to use. This is also relevant for versions of coding dictionary and other choices, which are often included in the protocol and SAP.

When receiving a delivery, consider having one person to screen and send back immediately to save other Subject Matter Experts (SME's) time and for it NOT to count as a review round was done at one company. At another company the vendor works directly in the eTMF vault, and no screening is needed. This works when the quality is good.

Similarly, another approach for the review process is having the "Owner function" screen the delivery (statistical programmer for SDTM and ADAM, biostatistician for TFLs, and so on) – if not good enough quality, then return the delivery promptly as not ready for review. This saves time for other sponsor functions.

It is not a good idea to send a document and only require review of certain sections. If you review a document, you review the entire document.

It was mentioned that sharing experience on how to validate outputs and approach for parallel programming could be helpful.

When performing review as statistician, be cognizant about when commenting outside your area – whether you are too burdensome.

For the statistician it is nice with a scientific understanding of what investigational compound you are looking at.

Regarding getting the programs it was discussed when it was relevant. Obviously, a version of the programs is part of the final delivery; is Sponsor review of programs during conduct feasible?

In the same direction is it worthwhile for Sponsor to get access to the raw data during conduct phase?

Allocate sufficient resources to prepare for Database Lock (DBL) and unblinding (if applicable). pre-DBL preparations such as review of listings dry-run and mock DBL meeting may be helpful.

Responsibility split as described in current ICH E6 R3 has changed since R2, in the sense that R3 adds descriptions of sponsors, investigators, and service providers' roles.

First time a new type of trial is done a task is done in-house (dose escalation report for example) to get experience and to ensure that everything runs as expected. Then at a later stage the task can be outsourced.

For Sponsors also executing trials in-house an interesting question may be the number of review rounds reviewers: for an outsourced trial should the number of review rounds and reviewers be the same as in an in-house trial? If yes, then what is the point of outsourcing?

Theme #3 Statistical programming and data analysis

What is meant by "QC'ed" or "validated" outputs? It is important to define at the initial meetings to have a common understanding.

When quality is assessed as "not good enough", then there should be a requirement to include a senior reviewer at the service providers before delivery to the sponsor.

Proposal to do project SAP incl. example shells if you are to embark on e.g. a larger phase 3 program with multiple trials of similar reporting requirements.

Example SAS procedures documented in SAP – including specific options – is recommended.

Triple programming, double programming, review

Some companies always perform triple programming for a primary endpoint and the primary safety endpoint. Not necessarily agreement to what was put in the pre-read examples. It is a cost/resource investment issue. Maybe press release could drive this decision.

Sponsor's reputation is at stake as the most important results are typically communicated externally.

Review of ADaM is required, but not necessarily double programming. No need to recreate full data sets. Timing of triple programming is when deliverables of TFLs + ADaM are available, providing an opportunity to check.

In the old days, the statistician was expected to program the endpoint from the raw data to the ADaM to the final analysis table. This is most likely not needed anymore due to the ADaM standards.

Statisticians are responsible for checking the primary endpoint. For ADaM, the efficacy ADaMs. Especially complex endpoints where it is difficult for e.g. monitors to find stuff – statistician probably needs be involved.

Data checks

The data checks are a Statistical Programming and Data management task. Sometimes these functions are not available, so it is the statistician's responsibility. Statisticians should be part of defining what edit checks should be done, for example to check across forms and identify important checks for the primary endpoint.

SDTM and ADaM checks – ranging from checking close to nothing to checking data related to primary/secondary analyses and endpoints. Ask yourself; can my statistical model run on the current data? If not, why?

Statisticians should look at data all the time during conduct. Also, because, if results are not as expected – you need to be prepared with your story. Difficult to do.

In the beginning is it important to have a lot of oversight. Look for endpoints, ensure they are derived correctly – right unit. It can be difficult. It is the responsibility of the Sponsor to act if a quality risk is identified. Often when we find things that are not correct, it is too late.

One proposal was to get a report of most critical items with traffic light indicators – send to a small group of key stakeholders – review daily but only use 15 minutes or so.

When are CDISC deliverables made available for Sponsors review – during or after TFL production?

Deliverables Ph1 – most lean set up: 1st after 50% of patients we get data deliverable, 2nd deliverable for dry run, 3rd before DBL and 4th after DBL and 5th is the final delivery.

On larger projects, it is recommended to have at least monthly SDTMs and ADaMs every 3rd month. Some companies get data every month and non-validated data bi-weekly.

It is not a statistician's task to review pinnacle reports, it is a Statistical Programming task.

Sometimes CDISC deliverables prior to TFLs, sometimes combined

Statistical programs

What do you get at the end of the trial? Is there a common understanding of what a submission ready program is? There can be a need to re-do the programs to ensure submission readiness.

In some instances, the analysis programs are received after database lock or at the time of final TFLs. In other instances, the programs are delivered after finalization of the trial (or CSR finalization). Then it is expected to get submission ready programs, and the SAP contains example code for the most important analysis.

The is also a difference in whether analysis programs are delivered with TFLs during trial conduct. It can be a challenge to receive analysis programs (proprietary thinking).

Some SP have proprietary macros, which the SP are reluctant to provide. This should be handled as part of the contract discussion. An alternative to providing the proprietary macros could be a contractual agreement one also provide the stand-alone version of programs.

There is a wish from a SP to have audit trail on programs (because then there is the documentation of what was delivered and later changed by the Sponsor). The audit trail also be beneficial for documentation of the oversight. It would be relevant to know to which extend regulatory authorities view this as important.

Budget

Careful review of budget with respect to number and format of TFLs can be beneficial to avoid out-of-scope situations later in the process. Alignment between protocol, SAP and TFLs shells should be ensured.

For sponsor using central personnel across studies with expertise on outsourcing can ensure overview of costs associated with trials and change orders. Also using experience from outsourcing experts can provide a more efficiently assessment of budget impacts and support for change orders.

Theme #4 Documentation of oversight

Oversight should be documented in TMF during trial conduct. This often does not happen. Achieving this requires the statistician to be conscious of when the review of a deliverable needs to be documented, especially while the trial is ongoing.

It is unclear to what degree the oversight should be documented – is documentation of dry run, comments etc. needed?

TMF closure activities ensure that oversight plans are filled out during trial completion

Sponsor should have documented knowledge of service providers processes. Understanding the processes is useful but resource intensive. Apply a risk-based approach to determine which documents and processes to review.

Theme #5 Quality

The main question is: How to ensure quality?

The discussion mainly represented the Sponsor perspective were:

- Starting position is trust.

- Quality: like house building – do not want to have a half build house to half price.
- Trust and verify
- Escalation: as soon as possible. Suggest predefined escalation strategy. Delay may be important to factor in – for example if a site includes to many patients.
- When is the trust lost?
- What to do when the trust is lost? Change service provider or reprogramming?
- Mitigation strategy – could quality related economic aspect be part of the contract?
- KPI may drive actions in an undesired way; better KPI may have undesirable side effects. How can this understanding be included in the planning?
- Sponsor consideration when selecting Service Provider: should Sponsor try to get the A-team? Is that possible?

Relationship between Sponsor and Service Provider:

- Sponsor may have Oversight Committee (governance level), who requests and reviews reports provided by Service Provider.
- Communication type and frequence between sponsor and SP biostatistician depends on study characteristics, such as study phase.
- Asymmetrical: at Sponsor one statistician performs oversight of several trials; at Service Provider there is a statistician per trial.
- The interaction between requirements should be considered. For example, requiring fast recruitment may be detrimental to quality. This may be more an internal sponsor discussion, like considering caps on enrollment, for example site level, country level.
- When Sponsor performs selected checks on data (SDTM, ADAM, TLFs) should the checks be shared with Service Providers or only the issues? Some Sponsors may choose not to disclose the checks.

Standard compliance

When Sponsor in-license products which approach should be used to ensure data (SDTM and ADAM) are compliant?

What are the requirements for the SDTM and ADAM programs? It appears that the requirements differ between companies.

Study level data must be submission ready.

Usually, ADAM datasets are used for submission, which lead to higher requirements for compliance.

Programs and data tasks

- Problematic issues may be identified by biostatisticians.
- Graphical overview may be useful for review.
- "All" outliers in data may be relevant to investigate.
- It is not always a requirement that programs are executable.
- Sponsor may have in-house programs for analysis of (primary) endpoints for performing verification of Service Providers analysis.

Theme #6 Collaboration between sponsor and service provider

Kick-off and Communication

- Kick-off meetings are crucial to ensure a good collaboration, ideally face-to-face.
- Establish clear communication channels (via email or Teams, single point of contact).
- Be mindful of cultural differences in communication (tone, time-zones).
- Define up front how to flag issues and escalate problems (quality issues, incompetent personnel assigned etc.)
- Have a clear mapping of deliveries, timelines, review rounds etc.
- Arrange for more frequent milestone meetings early in the trial startup/set up phase, to ensure a good start for the project.

Collaboration

- Treat the service provider as a colleague; aim for common goals and teamwork. The relationship should be a partnership: "One goal – one team."
- Weekly meetings between Sponsor and Service Provider are beneficial during trial conduct.
- Provide feedback after each delivery, not just at the end of the trial.
- Collaboration challenges arise when teams change frequently (this can be difficult to avoid in practice).
- Difficulties in rejecting poor-quality document reviews should be acknowledged.
- Recognize there is inherent friction in Sponsor–Service Provider relationships: awareness helps manage it.
- Ensure your counterpart at the service provider is informed about relevant changes in the project (don't assume they are aligning within functions, they might have a silo-setup).
- A shared understanding of the statistical analyses is essential: Conduct joint SAP reviews, use shells and code examples to clarify interpretations and test implementations. Define the level of model control needed.

Oversight and documentation

- Oversight often requires more time than expected - view this as a learning process that improves over time.
- Keep responsibilities at the agreed level; avoid scope creep.
- Conduct evaluations of studies to improve and share knowledge for future projects.

Theme #7 Technology and methodological advance

Not selected by any group.