

Section 27: Department of Biostatistical Science

The DF/HCC Biostatistics Core is a shared facility. One part of the core's mission is to provide biostatistical expertise for the planning, conduct, analysis, and reporting of clinical trials. Statisticians are available for consultation for all investigator-initiated trials conducted by the cancer center, and for the review of protocols developed elsewhere. Staffing is allocated by disease program and/or modality and is provided by statisticians located at DFCI, MGH, and BIDMC. A list of statisticians assigned to various disease/modality committees is available www.dfhcc.harvard.edu/core-facilities/biostatistics/contact.

Here is a summary of how statisticians support investigators in the conduct of clinical trials:

27.1 Biostatistics Support for the Protocol Development Process

Ideally, the PI will meet with a statistician early in the development process to discuss possible primary endpoints, expected results in the population eligible for the trial, and preliminary sample size. Once the Disease or Discipline-based Program approves a concept for a trial, the PI meets with the statistician and other key staff to discuss the concept and review preliminary ideas, needs, sample size, and timelines for development. The statistician prepares a full statistical considerations section on this first draft. This includes identification of the primary endpoint, statistical justification of all sample sizes, and accrual duration. Plans for sequential testing and interim monitoring should be specified if appropriate.

The following is a checklist of things to consider in designing your trial or in considering participation in other trials. The statistician is an important resource in helping to address these issues.

- Is the phase of the trial consistent with its objectives?
- If the trial is a combination of phases, is the combination clearly justified?
- Does the design reflect both phases?
- Rules for reporting SAEs should be consistent with the lower numbered phase.
- Are response definitions based on RECIST criteria? If not, have you provided a rationale for the criteria being used?
- Are toxicities being assessed using appropriate criteria? Most trials should use the current version of the NCI Common Terminology Criteria. One common exception is the use of the RTOG criteria in radiation trials. If other terms or systems are being used, this choice should be justified.
- Is the statistical considerations section consistent with other parts of the protocol? Especially consider objectives, design, patient population, and endpoint definitions. The endpoint(s) used in the sample size justification should be based on the primary objective(s).
- Are the trial's assumptions evidence-based? Assumptions regarding the null and alternative hypotheses should be consistent with the background and rationale, and hypothesized effects should be reasonable and attainable within the proposed trial. The "null" assumptions should be based on literature cited in the introduction or in the statistics section.
- Is the sample size appropriate? The statistician is your primary resource for information about

appropriate sample size.

In trials with sample size based on a statistical test, type I and type II errors should be reasonable; levels beyond the usual range typically used in clinical trials should be clarified. If a one-sided test is used, the one-sided hypothesis should be justified adequately if the direction of the outcome cannot be determined a priority.

Phase I trials may have sample size based on the probability of dose escalation, the probability of seeing at least one toxicity of a given type, a confidence interval for the probability of a given type of toxicity, or the properties of a decision rule based on the percentage of subjects able to receive adequate treatment. If a Phase I trial has sequential increases in dose, then both the size of the cohorts started on a single dose and the number of additional subjects added at the MTD must be justified statistically. The probability coverage of a confidence interval (e.g., 95%) should be reasonable. The probability of increasing dose should be reasonable both for true rare probabilities of toxicity (large probability of dose increase) and for true common probabilities of toxicity (small probability of dose increase).

Phase II trials may have sample sizes based on a confidence interval or a decision rule for the primary endpoint. Again, the coverage probability of the confidence interval and the probabilities associated with the decision rule should be reasonable.

- Are early stopping rules incorporated into the design appropriately? Some reasons for a sequential design include: chance of serious toxicity, chance of a treatment having fewer efficacies than current standard therapies, a much larger than usual sample size, or anticipated slow accrual.
- If there is high probability of missing data for the primary endpoint, does the statistical considerations section address how they are being handled? This is especially important in questionnaire and psychosocial trials, in which subjects may leave some questions blank and in which a subject may not provide data at each of the protocol-specified times. If missing data may be correlated with worsening disease status, statistical methods must take this into account.
- If you are using questionnaires, have you provided data on the validity of the questionnaire and its reproducibility? Have you provided a reference for the scoring techniques? If the questionnaire is not part of the primary endpoint, the trial should describe how the questionnaire would be used.
- Is the statistical analysis plan clear about which subjects will be included in the analysis? The denominator for analyses should be specified (e.g. eligible participants, intent-to-treat [all participants as randomized], or required minimum therapy). Trials that exclude ineligible participants (or un-evaluable participants) from the analysis should specify the total number of participants to be enrolled.
- Is the trial clear about how stratification factors will be used? Single treatment trials should not have stratification factors but may accrue separately to two or more distinct cohorts. If the protocol proposes to stratify in order to analyze treatment within subgroups, sample sizes for the subgroups should be specified that are adequate for this. If stratification is being done for balancing purposes only, it is helpful to state this.
- Should secondary endpoints have sample size justification? Sample size justification may be appropriate for secondary endpoints, especially those that may result in additional pain, inconvenience, or cost to the subject (e.g., follow-up biopsies, scans, or tests that are not usually done for this disease).

27.2 Biostatistics Support for Forms Development

Most DF/HCC trials require unique case report forms (CRFs) to collect data. The data analyst in the QACT gives draft CRFs to the statistician and the PI for review. It is a good idea for the PI, the statistician, data manager, study coordinators, etc. to meet to discuss the forms and see if they are feasible and collect data necessary for all endpoints. Forms development should start as soon as possible.

27.3 Biostatistics Support for Data Collection and Storage

Mechanisms for data collection and storage vary from informal methods (e.g., non-computerized data, tables on word processors, data collected by a laboratory's computer and transmitted via disk or email) to more formal methods, including the QACT. Responsibility for maintaining the database could reside with the investigator, clinical data manager, nurse, secretary, and/or data analyst (QACT). The statistician works closely with whomever is maintaining the data for data monitoring and quality assurance.

27.4 Biostatistics Support During Protocol Activation

If the trial involves randomized treatment assignments, the statistician must prepare randomization sheets so that treatments can be assigned through the QACT or research pharmacy. The PI should communicate with the statistician to ensure that randomization sheets are available at the time the protocol is activated.

27.5 Role of Biostatistics in Monitoring Active Trials

Statisticians participate with disease and discipline-based programs in monitoring accrual to active trials. If the statistical section of a trial has a monitoring plan based on toxicity rates or failures, the statistician is responsible for checking these outcomes and generating reports when necessary. If an interim-monitoring plan is part of the trial's design, the statistician will conduct interim analyses and present results to the appropriate data monitoring committee as required.

27.6 Biostatistics Involvement in Protocol Addenda

Needs for protocol addenda may include changes to treatment, statistical design, consent form, eligibility, measurements of effect, and protocol schema. The statistician is responsible for any changes to the statistical section. These changes should be given to the statistician for review and then submitted to the OHRS by the PI for review and approval by the appropriate scientific review committee and the IRB.

27.7 Analyses/Reports on DF/HCC Trials

Data Monitoring Reports/Interim Reports

Generally, the statistician will prepare reports and/or present the report to a monitoring committee, if the trial has one. Currently, monitoring committees are required for all DF/HCC-initiated Phase III trials and Phase I/II trials that are multi-site, are blinded, or employ particularly high-risk interventions or vulnerable populations. Trials that are done within the DF/HCC umbrella (e.g., DFCI, MGH, BIDMC, official affiliates, etc.) are not considered multi-site. Examples of high-risk interventions or vulnerable populations include vaccine trials or gene transfer.

These reports generally consist of accrual, toxicity, and or outcome information. Once a trial has completed accrual, interim reports may continue to be written until the trial has matured enough for a final report. The data and safety monitoring board (DSMB) or committee (DSMC), if the trial has one, conducts a periodic review of the trial, in accordance with the trial's sequential design.

Final Analysis

The trial is ready for analysis when the conditions set forth in the statistical considerations section of the protocol for achieving the desired precision have been met and the data have been reviewed and finalized. These will vary by trial type and disease site.

The statistician is available to help with analyses of the results of PI-initiated trials if there are statistical analyses involved. If the report is straightforward and no statistical analyses are required (as with most Phase I trials), the statistician may not need to be involved. Investigators can contact the statistician to discuss the analysis plan.

Abstracts and Manuscripts

Statisticians take an active part in preparation of abstracts and manuscripts involving their trials. Note that with rare exceptions, data cannot be made public while a trial is still accruing participants, and in some cases, still following or treating participants. For Phase III trials, DSMB approval must be obtained prior to submitting an abstract if the DSMB has not already released the data.

Statisticians should be given adequate time to complete the statistics needed for an abstract or manuscript. Also, the QACT should be contacted in advance, when appropriate, so that the data can be cleaned for analysis. For abstract submissions requiring data analysis, investigators should contact the disease site statistician at least one month prior to the abstract deadline. For abstract submissions involving statistical review only, at least two weeks should be allowed. For manuscripts, a mutually agreeable schedule should be worked out and agreed on by the investigator and the statistician before beginning the project.