Clinical Trial Data Release Policy August 2018
Quantitative Data Sciences Core (QDSC)
The Robert H. Lurie Comprehensive Cancer Center (LCC)

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Introduction

Every clinical trial conducted at LCC has an approved study protocol including a statistical section which defines outcomes and endpoints, provides sample size considerations and describes the statistical analysis plan. Often, the study design includes one or more interim analyses for safety or futility. The Data Monitoring Committee (DMC) needs to approve release of data to the study PI before the data can be analyzed and presented.

Clinical trials often span years from initiation to availability of final data for analysis and presentation. It is common for a principal investigator (PI) to request data and permission from the LCC's DMC to analyze and present data at professional meetings prior to study completion. While a PI's interest in updating colleagues on trial progress is understandable, the integrity of clinical trial results can be compromised by informal presentation of premature findings, particularly with regard to outcome data. This document describes the policy that QDSC and DMC consider best practice for data release prior to all data being attained as specified in the protocol.

This document provides the position of the biostatisticians of the Lurie Cancer Center's QDSC on the interim and final release of data from clinical trials conducted at the center. In addition, this document summarizes existing policies for data release at another NCI designated comprehensive cancer centers, cooperative groups and major oncology conferences, with detailed excerpts from relevant documents available from these organizations provided in an Appendix.

On July 29 2018, the directors of Biostatistics Cores at NCI designated cancer centers met in Vancouver BC as part of the national statistical meetings, and was attended by QDSC Director and Associate Professor of Biostatistics Masha Kocherginsky, PhD and Associate Director for QDSC Biostatistics, Professor and Chief of the Division of Biostatistics, Denise Scholtens, PhD. One agenda item was early data release and interim analysis in cancer clinical trials. The QDSC position reflects input from that meeting.

QDSC Position On Data Release

The general position of QDSC and DMC is that endpoint, outcome and related data must not be released prior to completion of follow-up on all participants for final data analysis, as specified in the protocol. In general it is acceptable, however, to report on the trial design, overall recruitment, baseline patient characteristics and some non-outcome data for ongoing trials. For clinical trials with a formal planned interim analysis, only the decision of whether the trial will proceed to the next stage can be reported. If the trial has a designated, independent Data Safety and Monitoring Board (DSMB) charged with making data release decisions, the LCC DMC defers to the independent DSMB on these matters.

Below is a more detailed description of what data can be released, analyzed and presented prior to study end for the most common types of trials.

I. Phase I dose-finding trials, with toxicity as primary endpoint

a. **Toxicity**: because toxicity is the primary endpoint, toxicity data cannot be presented prior to the end of the study. The data can be released to the PI for clinical and trial conduct reasons (e.g. for decisions regarding dose escalation, or to better address toxicity management plans). Data can only be formally presented and discussed after the maximum tolerated dose (MTD) or the recommended Phase II dose has been determined using the design specified in the protocol.
b. **Recruitment**: recruitment counts can be released to the PI, and only the overall study counts (i.e. not by dose level) may be presented at scientific meetings.
c. **Baseline patient characteristics**: summary data for baseline characteristics, including demographic and clinical, may be released to the PI before the study end. Summaries for the study overall, not by dose level, may be presented at meetings. However, no analyses relating patient characteristics to toxicity or dose levels may be presented, since information regarding the primary outcome (toxicity) may be inferred from the dose levels.
d. **Efficacy**: efficacy is often a secondary outcome in most Phase I studies, and is likely to vary by dose level. Therefore, efficacy data cannot be presented at scientific meetings by dose level since it will reveal the status of the primary outcome (toxicity and dose level selection).
e. **PK**: Pharmacokinetic (PK) data at baseline and early changes in PK parameters can be regarded as baseline characteristics as in (c) above.

II. Phase II efficacy trials

The primary goal of a Phase II trial is to demonstrate preliminary evidence of efficacy and to make the decision of whether a larger definitive Phase III trial is warranted. Phase II trial endpoints vary, with the most commonly used endpoints based on tumor response and progression-free survival. Phase II trials can be single-arm or randomized, and typically incorporate some type of an interim data analysis based on efficacy and sometimes safety. Such trials are typically conducted in several stages, and are often referred to as multi-stage or group-sequential trials. Both single arm and randomized trials can have interim analyses as part of the statistical design. The statistical details and decision rules for whether to continue a study after each stage need to be clearly described in the study protocol, and early data release should be consistent with the study design and analysis plan that are specified in the protocol.

For example, a commonly used single arm Simon's two-stage design enrolls an initial cohort of patients (Stage I) whose outcomes are formally analyzed for futility, i.e. a pre-planned assessment is made whether the probability of trial success is too low to continue the study to full enrollment. If at this analysis time point the likelihood of study success is low based on the first stage, the study is stopped for futility after Stage I; otherwise additional patients are enrolled (Stage II) in order to obtain the full sample size. Randomized trials proceed in a similar fashion, with different statistical methods used to determine the decision rule at each interim analysis (e.g. using the O'Brien-Fleming bounds).

Such multi-stage trials use formal statistical procedures during study design which ensure that Type I and Type II errors are controlled at known levels at the end of the study, if the study is not stopped early. At the first stage analysis, or at any early unplanned analysis, the Type I (false positive) and II (false negative) error rates are higher than specified in the protocol and the uncertainty of the estimates themselves is high because of the reduced samples size, both of which can lead to the low confidence of the interim results, and to the interim results being inconsistent with the final analysis of the full sample. In addition, if the magnitude of the effect size is large at the time of the early analysis, it may erroneously bias the investigator and the scientific community if the early results are presented at scientific meetings.

For these reasons, early presentation of clinical trial results is discouraged or specifically prohibited at such major meetings as ASCO and others (see Appendix). The LCC DMC and QDSC agree with this position.

a. **Study Endpoints**: this includes primary and secondary efficacy outcomes, including tumor response, progression free survival, and overall survival. Endpoint data cannot be released to the study PI for analysis, or presented at scientific meetings, prior to the end of the study.
b. **Multi-stage studies:** For multi-stage studies, following the interim analysis the PI may present the decision of whether the study will continue to the next stage based on the interim analysis. No additional summary data for the endpoints (e.g. response rate, or median time to progression) or analysis relating study outcomes to other characteristics may be presented.
c. **Early stopping for efficacy:** It is possible that successful outcome is observed before the full sample size is attained (e.g. the total number of responses exceeds the protocol-designated number required to declare success). If sufficient positive outcomes are attained before the total sample size has been observed, the study may not be stopped, and the full sample size must be observed in order to preserve the a priori precision of the outcomes measures. If early stopping for efficacy is desired, it has to be formally included in the statistical design and specified in the study protocol to maintain the pre-specified Type I and II error rates and reasonable precision of the estimates. Note: early stopping for efficacy is not commonly done in Phase II trials.
d. **Recruitment**: recruitment counts can be released to the PI and presented at meetings. This includes the overall patient recruitment summary for single arm studies, or recruitment summary by treatment arm or overall for multi-arm trials. The extent of follow-up may only be presented for the study overall and not by treatment arm as this may reveal outcome differences between arms.
e. **Baseline patient characteristics**: summary data for baseline characteristics, including demographic and clinical, may be released to the PI before the study end. Summaries for the study population overall, as well as associations among baseline characteristics (e.g. difference in baseline biomarker expression by disease stage) may be presented at meetings. However, no analyses relating patient characteristics to endpoints may be presented.
f. **Biomarker data**: baseline biomarker data at baseline and early biomarker changes can be regarded in the same way as baseline characteristics as described in Section I-(c) for Phase I studies above.

III. Phase III efficacy data

Phase III studies are large definitive studies. Treatment blinding adds to the statistical rigor that needs to be described in the protocol, and any interim analysis of Phase III studies needs to be described clearly in the protocol. Phase III studies likely will have independent and often external data monitoring committees. Therefore, it is unlikely that the LCC DMC will be making decisions about data release for Phase III studies. In the case that a study-specific DMC is not assembled, guidelines for Phase II trials should be used.

IV. Studies with adaptive designs.

Adaptive designs (e.g. adaptive Bayesian trials) often allow continuous data monitoring. Such designs must be clearly described in the study protocol. In such cases, DMC may release the data in a manner that is consistent with a particular adaptive design and the study protocol.

Appendix

SUMMARY OF EXISTING POLICIES REGARDING DATA RELEASE OUTSIDE OF NORTHWESTERN

1. Cancer centers may have mixed policies on unplanned releasing of data on an *ad hoc* basis to PIs for the purpose of informal data evaluation (e.g. assess progress, plan publications).
2. The primary goal of cancer center or cooperative group data monitoring committees is to protect patient safety. An additional goal is to preserve the scientific integrity of the study.
3. Cooperative groups on occasion allow the early release of data, especially for data such as toxicities or enrollment issues that are not related to the primary outcome. Such release of data is rare. Cooperative group policies do not indicate the role of the *a priori* protocol description for interim or final sample size or analyses. What appears to be a more lenient cooperative group policy for data release is in conflict with conference data reporting policies.
4. In general, reporting 'trial in progress' at conferences does not allow any data. ASH allows the reporting of interim analyses provided (a) they were specified *a priori* in the protocol and (b) the interim data are mature as required in the protocol.
5. These early release of data issues was discussed at the meeting of cancer center biostatistics core directors at the Joint Statistical Meetings (JSM) conference in August, 2018. This is a recognized issue at many centers, although the majority do not have a formal written policy. The consensus of the discussion was that early presentation of results is discouraged for the reasons described earlier in this document, and that only the study design, recruitment and potentially baseline characteristics can be presented at scientific meetings, and not the outcome data. For larger randomized trials, an independent study-specific DMC (or DSMB) is often convened and makes study-specific decisions on early data release.

DETAILS OF EXISTING POLICIES REGARDING EARLY DATA RELEASE

Cooperative Group Policies

Alliance - The first abstract/manuscript is expected to be based on the mature primary endpoint of the study. Submission of abstracts before data on the primary endpoint are completed is not generally endorsed, but may be considered on individual cases. Some examples are description of unexpected toxicities, enrollment procedures or data, and companion studies that are not dependent on the primary endpoint. This decision to submit an abstract before primary endpoint data are mature is made as a collaborative effort between the study chair, study primary statistician, committee chair, Group chair, and Publications Committee.

ECOG-ACRIN - Requests are reviewed for early release or use of study outcome data. The DSMC considers each request based on the importance and usefulness of the requested information and the potential risk to the integrity of the study. Access to interim outcome results is granted only rarely while patients remain on protocol treatment or while other interventions are continuing. After most patients have completed protocol therapy, the risk to the study is usually small, and access is allowed more routinely. In discharging these responsibilities, the DSMC's primary consideration will be to protect the safety of the patients enrolled on the studies. An additional consideration will be to preserve the scientific integrity of the studies to address their objectives in a manner consistent with the study designs, with other guidance from the study team and Group leadership and with sound scientific principles.

NRG - The DMC will also consider, on a case-by-case basis, special requests for release of information prior to the time point when accrual and treatment of all patients has been completed. Examples of such circumstances would be requests for toxicity findings from the Chair of a DMC of another trial external to the NRG, or situations where it is important for the health community to be informed of the possible presence or non-presence of a possible toxicity.

FDA - Confidentiality of Interim Data and Analyses As described in 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices). Sponsors of well-controlled studies should take appropriate measures to minimize bias. Knowledge of unblinded interim comparisons from a clinical trial is generally not necessary for those conducting or sponsoring the trial; further, such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses. Unblinded interim data and the results of comparative interim analyses, therefore, should generally not be accessible by anyone other than DMC members or the statistician(s) performing these analyses and presenting them to the DMC (see id.).

Individual Cancer Centers

Washington University - At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial principal investigator only for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials.

Conference Policies

ASCO (American Society of Clinical Oncology) - Trials In Progress Abstract Submissions: All phases of clinical research (phases I to III, supportive care, nonpharmacologic interventions) may be considered for inclusion as a Trials in Progress submission. Trials submitted to this session are ongoing and have not reached pre-specified endpoints for analysis. As such, inclusion of results would be improper and is strictly forbidden. The following information is not acceptable in a Trials in Progress abstract and/or poster: Any preliminary data including toxicity, response rate, pharmacokinetic, or correlative analyses. Abstracts including results or preliminary data will be rejected without further review.

ASH (American Society of Hematology) - Trials in progress do not contain data, and as such are ineligible for submission. Interim analysis of a prospective randomized clinical trial will be considered only if it is performed as planned in the original protocol and is statistically valid. If your abstract involves interim analysis, use the Interim Analysis of a Clinical Trial section of the abstract form to explain the details of your study. The reviewers will have this information available during their evaluation.

ASTRO (American Society for Radiation Oncology) - In general, ASTRO does not accept abstracts reporting an interim analysis that is intended to evaluate experimental treatment regimen(s) with respect to efficacy or safety at any time prior to formal completion of a trial. Abstracts reporting trial process updates, such as accrual, baseline characteristics, and non-protocol specific safety information, will be considered for Poster for informational purposes only.

ESMO (European Society for Medical Oncology) - Abstracts including results or preliminary data will be rejected.