

Updated Methods for Reporting Clinical Trials

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The reporting of early clinical trials is in evolution. As new drugs that target molecules that are selectively altered in cancer cells become available, much more will be expected from early trials than was expected in the past. Our concept of phase I trials that only determine maximum tolerated dose and recommended phase II dose of a drug will be replaced by different endpoints. These will include definition of a dose of drug that is sufficient to reach the target and produces the desired downstream effect, which may or may not produce significant side effects. Furthermore, early trials will also be designed to test the validity of "theranostic" tests, i.e., markers of patient susceptibility to a specific target therapy. Finally, one can anticipate that early clinical trials will also evaluate surrogate markers of response, i.e., early changes seen on dynamic images or transcriptional or translational profiles of posttreatment tumor samples, blood, and urine.

Accordingly, the Editors asked Dr. Stephen L. George, a noted biostatistician at Duke University Medical Center, to revisit the traditional methods of reporting clinical trials and update them for our readers, contributors, and reviewers. This "checklist" is presented here with the kind permission of Dr. George and will be incorporated into *Clinical Cancer Research's* Information for Authors and become part of the review process.

A Checklist for Reporting the Results of Clinical Research Studies in Cancer¹

Papers reviewing the adequacy of reporting research results in the medical literature have been published regularly for several decades, with the distressingly common finding that reporting of basic elements of design, conduct, or analysis is often inadequate (1–3). Some of the problems discovered are major ones, calling into question important conclusions of the paper. In recent years, efforts of editors of clinical journals have improved the situation. For example, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (4), aimed at improving the reporting of randomized clinical trials, have been adopted by over 150 journals. However, reports of randomized trials represent only a small fraction of the clinical research literature, including those published in *Clinical Cancer Research*. Early phase nonrandomized clinical trials and studies of prognostic (5), predictive (6), surrogate (7) or other biomarkers (8, 9) in cancer prevention, diagnosis (10), prognosis, and therapy are much more common.

The following checklist gives some guidance to contributors and reviewers of manuscripts submitted to *Clinical Cancer Research* by providing a brief summary of items that should be addressed in the reporting of clinical research studies. Some

clinical trial-specific items are included for completeness (11–16), but for the special case of a randomized clinical trial, the CONSORT guidelines should be followed (<http://www.consort-statement.org/revisedstatement.htm>).

Checklist

I. Design

1. Objectives: state the objectives and major hypotheses.
2. Outcome measures (endpoints): define the outcome measures or endpoints under study.
3. Design specification: describe and justify the particular design chosen to address the objectives (e.g., observational, retrospective, case-control, clinical trial, etc.).
4. Sample size (planned): give the planned number of study participants and the reasons for this planned number (e.g., power, size of detectable difference, etc.) for the chosen design.
5. Target population: define the target population and how study participants were selected for (or excluded from) the study.
6. For studies of prognostic, predictive, surrogate, or other biomarkers: provide justification and details on the statistical models and approaches used.
7. For clinical trials (in addition to the relevant points above):
 - a. Registration: give details of the registration process
 - b. Quality control: describe data quality control procedures, including any independent review mechanisms.
 - c. Interim analyses (planned): describe the plans for interim analyses

II. Analysis

1. General: provide enough detail on the analyses carried out to enable a reader to reproduce the analyses if the data were available.
2. Statistical methods: identify and define all statistical methods. Give references to standard statistical sources (with page numbers). Identify and reference all computer programs or statistical packages used in the analysis.
3. Precision: present measures of precision and uncertainty for all statistical estimates (e.g., standard errors, confidence intervals, or other measures). Plots of estimated parameters should give error bars if possible, with a clear explanation of what is being plotted (e.g., 95% confidence interval).
4. Statistical significance tests: for tests involving key outcome measures, identify the statistical test used, the value of the test statistic, and the degrees of freedom of the test statistic. Use observed P values (e.g., not $P < 0.05$ or NS). Avoid spurious precision in P values (a maximum of three significant figures is generally sufficient).
5. Regression models: validate any regression models used in the analysis.

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6. Multiplicity adjustments: explain any adjustments made for multiple testing, subgroup analyses, or similar procedures.
7. Missing data: explain how missing or incomplete data were handled in the analysis.
8. For studies of prognostic, predictive, surrogate, or other biomarkers: devote special attention to the assessment of internal and external validation of the markers.
9. For clinical trials (in addition to the relevant points above):
 - a. Dates: give the important study dates (e.g., date the study opened, date the last patient was admitted, and approximate date of analysis).
 - b. Sample size (actual): justify any difference between the planned and actual sample size, if any.
 - c. Interim analyses (actual): provide a brief summary of the results of any interim analyses, including both planned and unplanned analyses. State why the study was stopped and why it is being reported now.
 - d. Compliance to treatments: give an assessment of compliance to the treatment regimens, including both patient compliance (e.g., for self-medications) and physician compliance (e.g., for surgery, radiotherapy, chemotherapy). Give a summary comparison of planned versus actual treatment. Give the proportion of patients who completed treatment.
- e. Patient accounting: account for all registered patients in the analysis. If there were any exclusions from the primary analyses, give the numbers and the reasons for the exclusions.
- f. Patient characteristics: give a table showing the distribution of patient characteristics and important prognostic factors by treatment groups.
- g. Follow-up: account for the number (and timing) of patients who were lost to follow-up or who dropped out. Give the reasons for these losses. Present the losses separately by treatment group. State how these patients were treated in the analysis. Give the reasons for "censoring." Give the duration of follow-up (median, percentage at various time points, etc.).
- h. Toxicity: give tables of toxicity, side effects, and complications.
- i. Negative studies: address statistical power and/or precision for so-called "negative" studies, those that fail to reject the null hypothesis of equality. Be especially cautious in claiming equivalence unless the study was designed to address this issue.

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