

Acceptance Program
Guidelines

Clinical Trial Protocols

Council on Scientific Affairs **Clinical Trial Protocols**

Scope:

The Council on Scientific Affairs has developed these guidelines for clinical trial protocols to assist manufacturers and investigators in designing clinical protocols to evaluate products to be considered for the Acceptance Program. It is encouraged that such protocols be submitted to the Council for their review before clinical trials begin.

I. SUBMISSION DIRECTIONS

The contents of a clinical trial protocol should generally include the following items. However, specific information related to the type of product to be evaluated may be provided on separate protocol page(s), or addressed in a separate document.

1. General Information

- A Protocol title and date.
- B Name and address of the sponsor.
- C Study organization including clinical centers involved and study committees. A data safety protocol should be prepared for each clinical study to ensure that patient rights and risks are evaluated using current research and ethical standards. The protocol should detail how the investigators plan to monitor side effects and how patients will be protected from harm. Preferably, the protocol should include a review by an independent committee or research team not associated with the sponsor or clinical investigators.
- D Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
- E Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- F Name and address of clinical laboratories and other medical or technical departments involved in the trial, if applicable.

II. BACKGROUND INFORMATION

1. Name and description of the product(s) to be evaluated.
2. A summary of findings from relevant nonclinical studies that potentially have clinical significance, and from other clinical trials that are relevant to the trial. This should include a short systematic review (evidence tables) of relevant clinical trials.
3. Summary of the known and potential risks and benefits, if any, to human subjects.
4. Description of and justification for the use of the product and the study duration.
5. A statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirement(s).
6. Description of the population to be targeted for recruitment.
7. Hypothesis to be tested (when applicable). (equivalency or superiority trial)
8. References to literature and data that are relevant to the trial and that provide background for the trial.

III. TRIAL OBJECTIVES AND PURPOSE

A detailed description of the objectives and the purpose of the trial.

IV. CLINICAL TRIAL DESIGN

The scientific integrity of the clinical trial and the credibility of the data from the clinical trial depend substantially on the design. A description of the clinical trial design should include:

1. A specific statement of the primary outcome variables and the secondary outcome variables, if any, to be measured during the trial. Methods used to enhance the quality of measurements (e.g. assessor training) should be described.
2. The quality assurance (QA) protocol should be described. The QA protocol should describe how the investigators plan to ensure that the data collected are accurate and unbiased. For example, if clinical outcomes are measured, the protocol should explain how the examiners are trained, calibrated, and monitored during the study. If a questionnaire is used, the protocol should describe how the interviewers are trained and evaluated to ensure that the administration of the questionnaire is consistent. The QA protocol should describe the procedure used to enter and check the data before analysis.
3. A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
4. A description of the measures, in addition to randomization, taken to minimize/avoid bias, including (when applicable and appropriate):
 - A Blinding at assignment.
 - B Blinding during the trial (e.g. outcomes assessment and patient assignment).
 - C Blinding at the data analysis stage.
5. A description of the trial treatment(s) and the usage of the product(s). Also include a description of the instructions, packaging, and labeling of the product(s), if available.
6. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
7. A description of the discontinuation criteria for individual subjects, parts of the clinical trial and entire clinical trial.

V. SELECTION AND WITHDRAWAL OF SUBJECTS

1. Randomization procedures. Assignment of patients to treatment and control groups is expected to be random. If randomization is not feasible or practical, an appropriate rationale is required, preferably in advance.
2. Screening procedures including subject inclusion criteria and subject exclusion criteria.
3. Procedure for obtaining informed consent. The protocol should explain when and how informed consent is obtained.

4. Subject withdrawal criteria (i.e., terminating product use) and procedures specifying:
 - A When and how to withdraw subjects from product use.
 - B The type and timing of the data to be collected for withdrawn subjects.
 - C Whether and how subjects are to be replaced.
 - D The follow-up for subjects withdrawn from product use. Use the Consolidated Standards for Reporting Trials (CONSORT) Format [3].

VI. SUBJECT TREATMENT

1. The treatment plan, including the name(s) of all the product(s), product usage schedule(s), and the treatment period(s), including the follow-up period(s) for subjects for each clinical trial treatment group/arm of the trial.
2. Medication(s) permitted (including rescue medication) and not permitted before and/or during the clinical trial.
3. Procedures for monitoring subject compliance.

VII. EFFICACY ASSESSMENTS

1. Specification of the efficacy parameters.
2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.

VIII. SAFETY ASSESSMENTS

1. Specification of all clinically relevant safety parameters.
2. The methods and timing for assessing, recording, and analyzing safety parameters.
3. Procedures for obtaining reports of and for recording and reporting adverse events.
4. The type and duration of the follow-up of subjects after adverse events.

IX. STATISTICS *(FOR ADDITIONAL GUIDANCE SEE [5])*

1. A description of the statistical methods to be employed, including timing of any planned interim analysis (es). Depending on the type of trial different statistical methods e.g. paired t-test, chi-square analysis, odds ratio will be required. The role of a positive control (if used) on the statistical methods should be elucidated.
2. The number of subjects planned to be enrolled. In multicenter trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including calculations of the power of the trial and clinical justification should be given. For most clinical trials, minimum power of 80% is expected (For superiority trials use Type I error of 0.05 and Type II error of 0.10; for equivalency trials follow the ADA guidelines (see[6])).

3. The level of significance to be used (for most studies the minimum should be a 5% level of significance).
4. Criteria for the termination of the trial.
5. Procedure for accounting for missing, unused, and spurious data.
6. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
7. The selection of subjects to be included in the analyses (e.g., all randomized subjects, all eligible subjects, all evaluable subjects).

X. TRIAL MONITORING

The sponsor should ensure that it is specified in the protocol that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s).

XI. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

All quality control and assurance procedures should be described including training and certification procedures and the site monitoring and data monitoring procedures.

XII. DATA HANDLING AND RECORD KEEPING

The sponsor should ensure in the protocol that all records must be complete and how data will be assessed for accuracy and corrected, if necessary. In addition the length of time all study documents will be maintained should be specified.

XIII. CONFIDENTIALITY POLICY

Policies for monitoring confidentiality of patient information and records should be described.

XIV. PUBLICATION POLICY

Publication policy, if not addressed in a separate agreement.

XV. SUPPLEMENTS

XVI. REFERENCES

1. Good Clinical Practice Consolidated Guideline. Ottawa, Ontario, Canada: Health Canada, 1997.
2. ADA Council on Scientific Affairs. Acceptance Program Guidelines: Chemotherapeutic Agents to Slow or Arrest Periodontitis. Chicago: American Dental Association, 1998.
3. Revised CONSORT Statement for Reporting Randomized Trials. *Ann. Int. Med.* 2001; 134:663.
4. Guidelines for Developing a Manual of Procedures. Bethesda, Md: National Institute of Dental and Craniofacial Research, 2002.
5. E9 Statistical Principles for Clinical Trials. Rockville, Md: U.S. Department of Health and Human Services, Food and Drug Administration, 1998.
6. ADA Council on Scientific Affairs. Acceptance Program Guidelines: Determination of Efficacy in Product Evaluation. Chicago: American Dental Association, 1999.



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