

EXHIBIT 1

Guidance for Industry

E9 Statistical Principles for Clinical Trials

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 1998
ICH**

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F. Data Capture and Processing (3.6)

The collection of data and transfer of data from the investigator to the sponsor can take place through a variety of media, including paper case record forms, remote site monitoring systems, medical computer systems, and electronic transfer. Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. *Missing values* should be distinguishable from the *value zero* or *characteristic absent*.

The process of data capture, through to database finalization, should be carried out in accordance with good clinical practice (GCP) (see ICH E6, section 5). Specifically, timely and reliable processes for recording data and rectifying errors and omissions are necessary to ensure delivery of a quality database and the achievement of the trial objectives through the implementation of the planned analysis.

IV. TRIAL CONDUCT CONSIDERATIONS

A. Trial Monitoring and Interim Analysis (4.1)

Careful conduct of a clinical trial according to the protocol has a major impact on the credibility of the results (see ICH E6). Careful monitoring can ensure that difficulties are noticed early and their occurrence or recurrence minimized.

There are two distinct types of monitoring that generally characterize confirmatory clinical trials sponsored by the pharmaceutical industry. One type of monitoring concerns the oversight of the quality of the trial, while the other type involves breaking the blind to make treatment comparisons (i.e., interim analysis). Both types of trial monitoring, in addition to entailing different staff responsibilities, involve access to different types of trial data and information, and thus different principles apply for the control of potential statistical and operational bias.

For the purpose of overseeing the quality of the trial, the checks involved in trial monitoring may include whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trials, and so on (see sections IV.B to IV.D). This type of monitoring does not require access to information on comparative treatment effects nor unblinding of data and, therefore, has no impact on Type I error. The monitoring of a trial for this purpose is the responsibility of the sponsor (see ICH E6) and can be carried out by the sponsor or an independent group selected by the sponsor. The period for this type of monitoring usually starts with the selection of the trial sites and ends with the collection and cleaning of the last subject's data.

The other type of trial monitoring (interim analysis) involves the accruing of comparative treatment results. Interim analysis requires unblinded (i.e., key breaking) access to treatment group assignment (actual treatment assignment or identification of group assignment) and comparative treatment group summary information. Therefore, the protocol (or appropriate amendments prior to a first analysis) should contain statistical plans for the interim analysis to prevent certain types of bias. This is discussed in sections IV.E and IV.F.

B. Changes in Inclusion and Exclusion Criteria (4.2)

Inclusion and exclusion criteria should remain constant, as specified in the protocol, throughout the period of subject recruitment. Changes may occasionally be appropriate, for example, in long-term trials, where growing medical knowledge either from outside the trial or from interim analyses may suggest a change of entry criteria. Changes may also result from the discovery by monitoring staff that regular violations of the entry criteria are occurring or that seriously low recruitment rates are due to over-restrictive criteria. Changes should be made without breaking the blind and should always be described by a protocol amendment. This amendment should cover any statistical consequences, such as sample size adjustments arising from different event rates, or modifications to the planned analysis, such as stratifying the analysis according to modified inclusion/exclusion criteria.

C. Accrual Rates (4.3)

In trials with a long time-scale for the accrual of subjects, the rate of accrual should be monitored. If it falls appreciably below the projected level, the reasons should be identified and remedial actions taken to protect the power of the trial and alleviate concerns about selective entry and other aspects of quality. In a multicenter trial, these considerations apply to the individual centers.

D. Sample Size Adjustment (4.4)

In long-term trials there will usually be an opportunity to check the assumptions which underlie the original design and sample size calculations. This may be particularly important if the trial specifications have been made on preliminary and/or uncertain information. An interim check conducted on the blinded data may reveal that overall response variances, event rates or survival experience are not as anticipated. A revised sample size may then be calculated using suitably modified assumptions, and should be justified and documented in a protocol amendment and in the clinical study report. The steps taken to preserve blindness and the consequences, if any, for the Type I error and the width of confidence intervals should be explained. The potential need for re-estimation of the sample size should be envisaged in the protocol whenever possible (see section III.E).

E. Interim Analysis and Early Stopping (4.5)

An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. Because the number, methods, and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol. Special circumstances may dictate the need for an interim analysis that was not defined at the start of a trial. In these cases, a protocol amendment describing the interim analysis should be completed prior to unblinded access to treatment comparison data. When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, this is usually accomplished by the use of a group sequential design that employs statistical monitoring schemes as guidelines (see section III.D). The goal of such an interim analysis is to stop the trial early if the superiority of the treatment under study is clearly established, if the demonstration of a relevant treatment difference has become unlikely, or if unacceptable adverse effects are apparent. Generally, boundaries for monitoring efficacy require more evidence to terminate a trial early (i.e., they are more conservative) than boundaries for monitoring safety. When the trial design and monitoring objective involve multiple endpoints, then this aspect of multiplicity may also need to be taken into account.

The protocol should describe the schedule of interim analyses or, at least, the considerations that will govern its generation, for example, if flexible alpha spending function approaches are to be employed. Further details may be given in a protocol amendment before the time of the first interim analysis. The stopping guidelines and their properties should be clearly described in the protocol or amendments. The potential effects of early stopping on the analysis of other important variables should also be considered. This material should be written or approved by the data monitoring committee (see section IV.F), when the trial has one. Deviations from the planned procedure always bear the potential of invalidating the trial results. If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of Type I error is controlled.

The execution of an interim analysis should be a completely confidential process because unblinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should be informed only about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures.

Most clinical trials intended to support the efficacy and safety of an investigational product should proceed to full completion of planned sample size accrual; trials should be stopped early only for ethical reasons or if the power is no longer acceptable. However, it is recognized that drug development plans involve the need for sponsor access to comparative treatment data for a variety of reasons, such as planning other trials. It is also

recognized that only a subset of trials will involve the study of serious life-threatening outcomes or mortality which may need sequential monitoring of accruing comparative treatment effects for ethical reasons. In either of these situations, plans for interim statistical analysis should be in place in the protocol or in protocol amendments prior to the unblinded access to comparative treatment data in order to deal with the potential statistical and operational bias that may be introduced.

For many clinical trials of investigational products, especially those that have major public health significance, the responsibility for monitoring comparisons of efficacy and/or safety outcomes should be assigned to an external independent group, often called an independent data monitoring committee (IDMC), a data and safety monitoring board, or a data monitoring committee, whose responsibilities should be clearly described.

When a sponsor assumes the role of monitoring efficacy or safety comparisons and therefore has access to unblinded comparative information, particular care should be taken to protect the integrity of the trial and to manage and limit appropriately the sharing of information. The sponsor should ensure and document that the internal monitoring committee has complied with written standard operating procedures and that minutes of decisionmaking meetings, including records of interim results, are maintained.

Any interim analysis that is not planned appropriately (with or without the consequences of stopping the trial early) may flaw the results of a trial and possibly weaken confidence in the conclusions drawn. Therefore, such analyses should be avoided. If unplanned interim analysis is conducted, the clinical study report should explain why it was necessary and the degree to which blindness had to be broken, and provide an assessment of the potential magnitude of bias introduced and the impact on the interpretation of the results.

F. Role of Independent Data Monitoring Committee (IDMC) (4.6)

(see sections 1.25 and 5.5.2 of ICH E6)

An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC is a separate entity from an institutional review board (IRB) or an independent ethics committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines, including statistics.

When there are sponsor representatives on the IDMC, their role should be clearly defined in the operating procedures of the committee (e.g., covering whether or not they can vote on key issues). Since these sponsor staff would have access to unblinded information, the

procedures should also address the control of dissemination of interim trial results within the sponsor organization.

V. DATA ANALYSIS CONSIDERATIONS

A. Prespecification of the Analysis (5.1)

When designing a clinical trial, the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol. This section should include all the principal features of the proposed confirmatory analysis of the primary variable(s) and the way in which anticipated analysis problems will be handled. In the case of exploratory trials, this section could describe more general principles and directions.

The statistical analysis plan (see Glossary) may be written as a separate document to be completed after finalizing the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included (see section VII.A). The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data (see section VII.A for definition) and should be finalized before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalized as well as when the blind was subsequently broken.

If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment. Otherwise, it should suffice to update the statistical analysis plan with the considerations suggested from the blind review. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

In the statistical section of the clinical study report, the statistical methodology should be clearly described including when in the clinical trial process methodology decisions were made (see ICH E3).

B. Analysis Sets (5.2)

The set of subjects whose data are to be included in the main analyses should be defined in the statistical section of the protocol. In addition, documentation for all subjects for whom trial procedures (e.g., run-in period) were initiated may be useful. The content of this subject documentation depends on detailed features of the particular trial, but at least demographic and baseline data on disease status should be collected whenever possible.

If all subjects randomized into a clinical trial satisfied all entry criteria, followed all trial procedures perfectly with no losses to follow-up, and provided complete data records, then the set of subjects to be included in the analysis would be self-evident. The design