

# Clinical Trial Design and Informed Consent Language to Avoid Missing Data Bias

[version 12-28-2011]

## **National Research Council of the National Academy of Sciences 2010 panel charged to:**

Develop recommendations to handle an increasing problem of missing data in clinical trials. Concerns were raised about the potential to take advantage of missing data problems to bias trial results.

National Research Council Panel on Handling Missing Data in Clinical Trials. The Prevention and Treatment of Missing Data in Clinical Trials, 2010. <http://www.nap.edu/catalog/12955.html>

**Statement of the problem:** Missing data reduces the benefit provided by randomization, and may lead to biased conclusions. It can arise from a variety of reasons, including the inability or unwillingness of participants to meet appointments for evaluation. In addition, inadvertent loss of data occurs when participants, who discontinue treatment, are no longer followed. Although many statistical methods have been developed over the past 25 years to adjust for missing data bias, the panel (many of whom developed those methods) concluded that no method has been proven to work well. Their strongest recommendation was to *avoid missing data if at all possible*.

**Missing Data Due to Discontinuation of Study Treatment:** It is common for some participants in a clinical trial to discontinue study treatment because of adverse events or lack of efficacy. The panel advised trialists to develop plans to continue to follow these participants and to gather detailed information about the participant's decision to discontinue. The panel advised investigators to obtain information about drop-outs "to the extent possible, and to anticipate and plan for missing data in trial protocols." "Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol specified intervention in the course of the study..., and this information should be recorded and used in the analysis." They considered this one out of the five recommendations is most important. The other four were about statistical analysis and study design.

**"Informed consent documents should emphasize the importance of collecting outcome data from individuals who choose to discontinue treatment during the study, and they should encourage participants to provide this information whether or not they complete the anticipated course of study treatment." [NSF Panel report, page 43]**

## **Center for Biostatistics Advice to Clinical Trial Investigators on Avoiding Missing Data**

Data completeness is critical for the integrity of trials, and substantial missing data will cast doubt on the validity of results. Plans for inclusion criteria and follow-up to best avoid missing data are crucial to help preserve the quality of the study and limit the extent of missing data.

We have noticed that the language in most consent forms equates discontinuation of treatment and discontinuation of data collection. We recommend that informed consent be used to educate the participants about the critical value of continued follow-up after treatment discontinuation, and to advise them that they will

be given choices about this at the time of their discontinuation decision. **The following is an example of language that we recommend should be added to the consent document for research studies, as applicable:**

***“You are free to discontinue the study treatment or refuse further contact at any time. If you discontinue treatment or refuse further contact before the study is finished, there will be no penalty to you. You will not lose any benefits to which you may be otherwise entitled. However, we wish to emphasize that the value of this study is based on the quality and completeness of the data. To ensure completeness, if you decide to discontinue treatment, we will then ask whether you are willing to allow us to continue to obtain data about you during the study period.”***

The research team should then present the following options to the subject at the time of discontinuation of treatment:

***1. You wish to discontinue treatment, but are willing to be contacted for follow-up visits or questionnaires and allow us to obtain data from your medical records through the study period.***

*Or*

***2. You wish to discontinue treatment and are no longer willing to be contacted for follow-up visits or questionnaires. You continue to agree to allow us to obtain data from your medical records through the study period.***

*Or*

***3. You wish to discontinue treatment, are no longer willing to be contacted for follow-up visits or questionnaires and you do not agree to allow us to continue to obtain data from your medical records after the discontinuation date.***

### **Guidance for protocol development and IRB submissions**

Language to this effect should be included in the protocol as well as in the consent document and IRB Application for Initial Submissions. The recommended text from above can be inserted into the consent document. Moreover, the process by which participants who voluntarily choose to prematurely withdrawn can at the time of withdrawal be presented with the three options listed above. The participant’s choice will then to be documented in the appropriate source document (e.g., case report form, study chart).

For more information or to speak with a biostatistician about this issue, [submit a resource request to the CCTS](#).