

Common Misconceptions About Interim Analysis and Flexible Clinical Trial Designs

Technical Feasibility

a. Claim

Taking multiple looks at interim data and stopping trials early compromises the type-1 error and/or power of the study and should be avoided.

a. Response

Naive stopping boundaries which are identical to those of fixed sample trials will indeed inflate the type-1 error and invalidate the study. However, statistical methods for adjusting these boundaries to take interim looks, and preserve the type-1 error, are well recognized and widely available.

b. Claim

When you take an interim look for efficacy, you pay a large penalty in terms of inflated sample size and smaller p-value.

b. Response

This is not always true and can be controlled by the sponsor. The FDA does require that you pay some penalty in exchange for taking interim looks, and if there is a strong desire to stop early for benefit, the sample size can inflate as much as 20%. If there is little desire to stop early for benefit, the penalty can be very small. The stopping boundaries, and, correspondingly, the penalty, are determined by the choice of α -spending function. For instance, a study employing a spending function that generates O'Brien Fleming stopping boundaries inflates the sample size only 2-3%, and reduces the p-value from .05 to .042. The same study, designed using the gamma family of spending functions, with $\gamma = -8$, requires no inflation in sample size, and a reduction in p-value from .05 to .049. In this latter study, it is virtually impossible to stop the study early for benefit; therefore the penalty paid is very small.

Applicability

a. Claim

Interim efficacy analyses play no role in a study where one does not wish to stop early for benefit.



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a. Response

There are many reasons to perform interim analysis other than early stopping for benefit. Interim response data can be used for portfolio planning, starting follow-up studies sooner, identifying underpowered studies and adjusting sample size, identifying and terminating futile studies, and dropping ineffective doses or study arms. There is a wealth of information available at interim time points that investigators can and should employ.

Regulatory Response

a. Claim

The FDA does not approve of adaptive or group sequential studies, unless there is an ethical imperative to stop the study early for benefit.

a. Response

This is not the case. Some of the leading papers on flexible methods have been written and published by FDA biostatisticians. FDA biostatisticians have delivered talks on adaptive and group sequential designs at DIA and ASA forums, and at the annual FDA and Industry Workshop. The FDA is keenly interested in running clinical trials more effectively and efficiently than has been done historically, and employing novel statistical methods to do so. However, the FDA is especially vigilant that these novel methods are properly employed. Their main concern is that these methods be prospectively specified, clearly spelled out in the protocol, and respected.

b. Claim

European and Japanese regulatory agencies have a different position on flexible clinical trials than the FDA.

b. Response

The ICH-E9 guidance, a joint guidance developed in 1998 by the FDA, European and Japanese regulatory agencies, specifically allows for group sequential studies as well as sample size re-estimation. These methods have been approved by all regulatory agencies, and jointly agreed upon guidelines have been clearly spelled out.

Logistical Feasibility

a. Claim

Planning interim analysis restricts flexibility, because investigators must adhere to the number and spacing of the interim looks. This can cause logistical difficulties.



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a. Response

As long as the spending function is specified in the protocol and respected in the interim analysis, the investigator is free to change the spacing between interim looks and even take unplanned looks, or no looks.

b. Claim

Interim analysis increases the administrative burden and adds to the cost of the trial.

b. Response

It is true that, today, the data manager will be the last person to suggest adding interim analysis to the trial. However, interim analysis can provide important insights and improve the quality of the data. With proper upfront planning and technology support, interim analysis can actually reduce the overall data management effort compared to one final analysis.

c. Claim

All studies incorporating interim analysis require a formal external data monitoring committee. Otherwise, interim efficacy results may be leaked prematurely to the investigators, thus biasing the future course of the study.

c. Response

Large, multi-year pivotal trials, especially where safety is concerned, should have a data monitoring committee (DMC) in place. However, the presence of planned interim analysis in and of itself does not mean a study must have a formal external DMC. Sponsors can ensure the confidentiality of interim efficacy results by appointing an external or internal unblinded statistician who is firewalled from the study investigators, or, if safety is not an issue, by adopting automated systems that don't require human intervention.

About Cytel Software Corporation

Cytel Software Corporation is a biostatistics services and software development house with a 15 year track record of serving the biopharmaceutical industry. Cytel is world-recognized for its break-through work in exact, non-parametric statistics and in group sequential and adaptive clinical trial design. Today, nearly every bio-pharmaceutical company, academic research organization, and government research organization, including the FDA, uses our software East® for the design, simulation and interim analysis of flexible clinical trials, or StatXact® for exact non-parametric inference of continuous and categorical data.

Contact us to learn more about how Cytel can help you design more efficient, effective clinical trials.



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