



Controlling your research programme through expert adaptive design and Bayesian methods

Pete Cooper of Quanticate outlines the high importance of appropriate and intelligent study design before commencing a clinical trial programme.

When planning a clinical study there are considerable financial benefits to seeking out the latest available scientific knowledge and most appropriate statistical approaches to study design. Over the years many Adaptive Design and Bayesian methodologies have become widely used, but choosing the right ones at the right time is crucial to placing control over research programmes at all stages of development. Well planned study designs ensure the best project go/no go decisions and lead to the earliest possible technical and regulatory success.

Bayesian methods are accepted in early phase studies and provide the opportunity for direct incorporation of knowledge and an alternative approach to study design, sample size calculation and decision making. A Bayesian approach can provide a more suitable framework for scientists and statisticians to reach consensus on objectives and the appropriate level of evidence required. With freedom from the usual constraints of frequentist standards for sample size, smaller PoC (Proof of Concept) studies can result.

The most appropriate design option may not be to simply run the study from start to finish, regardless of the accumulating information. Studies should be reviewed as to their suitability for interim review and early stopping. The stopping boundaries for success and futility in Group Sequential Trials can be designed to best match the particular study in question. Incorporation of stopping rules for futility using

Conditional Power can enable early trial termination and consequently allow for the best focus of limited resources.

Sample Size Re-estimation can be beneficial and provides reassurance if there is uncertainty about variability of data or response rates. Seeking out a statistician who has experience of a high number of study types incorporating the design features of Conditional Power and/or Sample Size Re-Estimation will result in the all important tailoring in approach.

Fully adaptive design in the form of p-value combinations is also an option, however its role is limited as the regulatory guidance (e.g. FDA Adaptive Design Clinical Trials Drugs and Biologics) is clear on the potential limitations. These can include such fundamental issues as difficulties in interpretation of results and estimation of treatment effects.

Detailed simulations at the study design stage offer the opportunity to open up the scientific and clinical discussions and to fully incorporate the available knowledge. The performance of different designs and the sensitivity to study design assumptions can be readily explored. In a recent project, simulations covered the full range of design considerations including design configuration, endpoints and power. In this particular case the proposed study design was completely changed following simulations that demonstrated the original design (a randomised withdrawal following treatment) would not meet the project needs as well as a standard randomised parallel group design.

The design of studies should take into account the expected returns on investment. Statistical decision theory can be used to explore the costs and benefits of alternative studies and ensure the most appropriate design is chosen to maximise return.

The best research involves using the very latest knowledge to ensure clarity of decision making at each review and planning stage. A broad range of statistical methods can help ensure this is achieved. It is therefore well worth seeking expert consultancy right at the start of a clinical programme.

About the Author: Pete Cooper is Manager of Statistical Consultancy with Quanticate Ltd, a CRO with a special focus on biometrics (www.quanticate.com). He has over 25 years of experience in the design of study programmes to meet scientific, regulatory and commercial needs. Pete is passionate about optimal study design and ensuring the best evidence is available at all stages of decision making.