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Three steps to writing adaptive study protocols in the early phase clinical development of new medicines

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Abstract

This article attempts to define terminology and to describe a process for writing adaptive, early phase study protocols which are transparent, self-intuitive and uniform. It provides a step by step guide, giving templates from projects which received regulatory authorisation and were successfully performed in the UK. During adaptive studies evolving data is used to modify the trial design and conduct within the protocol-defined remit. Adaptations within that remit are documented using non-substantial protocol amendments which do not require regulatory or ethical review. This concept is efficient in gathering relevant data in exploratory early phase studies, ethical and time- and cost-effective.

Keywords: Adaptive study design, Adaptive protocol, Protocol writing, Early phase clinical research

Findings

Background

The use of adaptive study design in early exploratory clinical drug development, if thoroughly planned, is beneficial as it allows continuous learning from data that is being gathered. Thus, the study conduct can be adjusted accordingly within pre-specified boundaries, maximising the yield of useful information. Adaptations of the study conduct are protocol defined design features and not based on ad-hoc decisions [1]. An adaptive study protocol needs to be sufficiently detailed, clear and systematic whilst allowing for flexibility and evolution. Regulatory acceptability and efficient study conduct depend on a study protocol that is fit for purpose. It is desirable to define a uniform and intuitive terminology for adaptive protocols and to optimize a sufficiently comprehensive format, allowing the full assessment of risks and benefits of a proposed protocol, which can be easily followed in a global environment. The benefit of a standardised layout is that it facilitates ethical and regulatory review and makes subsequent adaptive protocol changes easy to document and follow.

In simple terms, there are three major elements to adaptive protocols in early phase drug development:

1. The description of the changes that can be made to study design and conduct, i.e. its *adaptive features*
2. The definition of the *boundaries* to these changes beyond which Regulatory and Ethics Committee approval needs to be obtained prior to implementation
3. The description of *control mechanisms* setting out how decisions will be made and how changes to the study will be managed and by whom

This article attempts to define terminology and to describe a clear process of writing an adaptive study protocol for the exploratory development of new medicines. It provides a step by step guide to protocol writing, including templates from projects we have authorised and performed in the UK. We have recently published an example which demonstrates the benefits of this concept [2]. Exploratory early phase trials are hypothesis forming, not hypothesis testing. Statistical analysis of these exploratory trials is descriptive in nature. Our paper does not aim to deal with statistical aspects of adaptive study design for confirmatory, hypothesis testing clinical trials. This manuscript describes a process and not research in human subjects, material or data, therefore it did not require REC approval.

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