Within-trial decisions: Unblinding and termination

Introduction

‘Within-trial decisions’ are decisions that need to be made once a clinical trial has already begun, for instance if an unexpected problem comes to light. These decisions may result in procedures to mitigate the problem or even the early termination of the trial.

This article looks at two specific kinds of within-trial decisions: Unblinding (code-breaking) and premature termination.

Unblinding (Code-breaking)

What is unblinding?

Many clinical trials are blinded – they are conducted in such a way that investigators and/or participants are unaware of which treatment an individual participant is receiving.

Unblinding occurs when that ‘blind’ is removed, and investigators and/or participants are informed which treatment the participant is receiving.

Why would a participant be unblinded?

In cases of medical emergencies or serious medical conditions that occur while a participant is taking part in a study, the participant may not be able to be treated adequately unless the doctors know which treatment they have been receiving. In such situations, unblinding may be necessary.

How does the unblinding work?

Pharmaceutical companies and contract research organisations have strict unblinding procedures, and study sponsors must provide documentation of the unblinding procedure for a clinical trial as part of the regulatory requirements. These usually take the form of a standard operating procedure (SOP) and an accompanying guidance document. The unblinding process differs from organisation to organisation, in some organisations they may use a call-centre or automated system to manage the process on behalf of the study sponsor. There is often a provision in the procedure for an on-call doctor who can discuss the request for unblinding before it takes place, in order to protect participants from serious adverse effects that might result from rapid removal of the treatment or drug-drug- interactions.

How does the unblinding process affect participants?

Trial participants receive ‘patient cards’, which carry information about the clinical trial, the principal investigator and the institutions’ contact details, and the number to call for emergency unblinding. They are instructed to show the card to any healthcare professional they may see who is not involved in the clinical trial they are participating in.

Unless there is an unblinded phase in the trial design, unblinded participants will be required to discontinue the trial due to the possibility of introducing bias. If too many participants are unblinded in a trial, then the statistical integrity of that trial may be jeopardised.

Premature termination

What is premature termination?

Premature termination is when a clinical trial is stopped earlier than planned, before the pre-designated endpoints of the trial are reached.

What are interim analyses and what role do they play in stopping trials early?

Interim analyses examine current data from an ongoing trial. Interim analyses are usually performed to identify the safety profile between the treatment arms or to assess whether there is an imbalance in efficacy between treatments.

There must be detailed instructions within the trial protocol about how to approach interim analyses and the decision-making processes used when evaluating the data. Interim analyses **cannot** be planned simply to have a quick check of the data during the trial – they must be clearly defined beforehand, including the time point at which the analysis will occur and why.

There are rare occasions where an interim analysis can be added to an ongoing protocol, but the reason for this would need to be clearly defined and would require regulatory approval and ethical assessment.

Why might trials be stopped early?

Researchers may consider ending a trial early for many reasons, including difficulties recruiting sufficient numbers of participants. In most cases, the decision to end a trial early is made after new scientific evidence emerges, often during planned interim analyses. This new trial data may lead to a reassessment of the benefit-risk ratio for the

participant such as:

- A serious adverse reaction (ADR) where the risk to the participant is considered too great to continue treatment.
- Clear identification of the superiority or lack of effect of one of the treatments.

How does the process of stopping a clinical trial early work?

In trials that allow the trial to be stopped following an interim analysis, clearly defined stopping rules must be included in the protocol and in the informed consent form. This should include provisions for continued treatment access, if beneficial and needed, after the trial stops, as described in the Declaration of Helsinki.

An independent committee should make the decision about whether the data returned from an interim analysis meets the stopping criteria, in order to decrease bias. In most cases, stopping a clinical trial requires the approval of senior medical management.

If recruitment of participants has proven challenging, and it is unlikely that the scientific question will ever be answered, it is considered unethical to continue the trial. In these situations, the regulatory authorities that approved the study must agree to the termination.

Attachments

- Within-Trial Decisions Unblinding and Termination
  Size: 375,386 bytes, Format: .pptx
  A presentation describing Within Trial Decisions, Unblinding (Code Breaking), Termination.

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