Why trials may stop early

Why may a trial stop early?

The number of participants in a trial needed to get a reliable result is calculated in advance and recorded in the trial protocol. Usually, the trial will continue until all participants have been followed until the last measurement. There are several reasons why a trial may stop early, which may have to do with the intervention (drug) that is investigated or with factors external to the trial.
Before you decide to participate in a trial, it is important to be aware that this may happen, and to know what the consequences for the trial participants are.

Who decides about early stopping of a trial?

The Sponsor, usually a pharmaceutical company or a hospital, decides to organize a trial and can stop the trial at any moment. Before a trial can start, an Institutional Review Board (IRB) or a Medical Research Ethics Committee (MREC), needs to give permission.
In many (drug) trials an independent Data Safety Monitoring Board (iDSMB) is installed to review the accumulating data for safety. If there are signals that it is not safe for trial participants to continue the trial, the DSMB will warn the Sponsor. Sometimes the DSMB will also warn the Sponsor if the effect of the intervention appears to be much larger or much smaller than expected. Stopping (too) early limits the possibility to learn more about the drug. The general rules of the DSMB are described in a DSMB charter, The DSMB does not make decisions itself, but advises the Sponsor about continuing or stopping the trial.

Stopping for efficacy

Very rarely a new drug is much more efficacious than expected. This may become clear before all participants have finished the trial. If there is sufficient information to assume that the drug is also safe, the decision may be made that it is not ethical to continue the trial, and all patients should get access to the drug as soon as possible.

Stopping for safety

Although the safety of an investigational drug is the most important aspect that is studied from the first clinical studies in humans onwards, (serious) adverse events may happen during a trial showing that it may not be safe to receive the drug, or a particular dosage. This can be a reason to stop the trial immediately for all participants.

Stopping for other reasons

A reason for early stopping of a trial that is often mentioned by Sponsors is failure to recruit sufficient trial participants in a reasonable time.
Other reasons may have to do with the Sponsor's business economics, which may for instance be influenced by shareholders' decisions, market value and acquisition of a company, sometimes having very little to do with a particular trial.

Stopping for futility

Before the start of a trial, the Sponsor sometimes decides about a level of futility. The Sponsor reports the stopping guidance for futility in the trial protocol and in the DSMB charter.
If it becomes very likely that the drug effect is smaller than some pre-defined limit, the Sponsor stops the development of the drug for that particular indication.

Possible benefits for patients

in the trial

Stopping early for:

- *efficacy*: **the drug may become available soon**
- *safety*: **no unnecessary unsafe drug use**
- *futility*: **no unnecessary ineffective drug use**
- *other reasons*: **none**

not in the trial

Stopping early for:

- *efficacy*: **the drug may become available soon**
- *safety*: **being spared the use of an unsafe drug**
- *futility*: **being spared the use of an ineffective drug**
- *other reasons*: **none**

Possible downsides for patients

in the trial

Stopping early for:

- *efficacy*: sometimes the drug is not available or not reimbursed right away
- *safety*: some of the participants will have experienced safety problems
- *futility*: some of the participants will have been exposed to the ineffective drug
- *other reasons*: the possibility that an effective drug is not developed further; participants have invested time and effort without clear result

not in the trial

Stopping early for:

- *efficacy*: sometimes the drug is not available or not reimbursed right away
- *safety*: none
- *futility*: none
- *other reasons*: the possibility that an effective drug is not developed further

General advice before participating in a trial

Read the Patient Information Folder very carefully. Ask questions to the investigators about the DSMB, and what are the stopping rules. If the trial investigates a new drug which is not yet available, ask about the rules for Compassionate Use. Compassionate Use means that a pharmaceutical company makes a drug available for free to trial participants who experienced a positive effect after the trial has finished until it becomes available via the usual routes (market authorization and reimbursement decision).
Ask if the Sponsor will publish the results, no matter whether positive or negative.

More information

For more information on Interim Analyses and Futility see the EUPATI Glossary
www.eupati.eu/glossary/

Viele K (2016) Interpretation of clinical trials that stopped early. JAMA 315(15): 1646 -1647

Contact details

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