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# Recruitment failure and futility were the most common reasons for discontinuation of clinical drug trials. Results of a nationwide inception cohort study in the Netherlands

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## Abstract

**Objectives:** The objective of the study was to identify the reasons for discontinuation of clinical drug trials and to evaluate whether efficacy-related discontinuations were adequately planned in the trial protocol.

**Study Design and Setting:** All clinical drug trials in the Netherlands, reviewed by institutional review boards in 2007, were followed until December 2015. Data were obtained through the database of the Dutch competent authority (Central Committee on Research Involving Human Subjects [CCMO]) and a questionnaire to the principal investigators. Reasons for trial discontinuation were the primary outcome of the study. Three reasons for discontinuation were analyzed separately: all cause, recruitment failure, and efficacy related (when an interim analysis had demonstrated futility or superiority). Among the efficacy-related discontinuations, we examined whether the data monitoring committee, the stopping rule, and the moment of the interim analysis in the trial progress were specified in the trial protocol.

**Results:** Of the 574 trials, 102 (17.8%) were discontinued. The most common reasons were recruitment failure (33 of 574; 5.7%) and solely efficacy related (30 of 574; 5.2%). Of the efficacy-related discontinuations, 10 of 30 (33.3%) of the trial protocols reported all three aspects in the trial protocol, and 20 of 30 (66.7%) reported at least one aspect in the trial protocol.

**Conclusion:** One out of five clinical drug trials is discontinued before the planned trial end, with recruitment failure and futility as the most common reasons. The target sample size of trials should be feasible, and interim analyses should be adequately described in trial protocols. 

*Keywords:* Clinical Drug Development; Clinical trial; Discontinuation; Interim analysis; Recruitment failure; Futility

## 1. Introduction

Discontinuation of a clinical trial before completion of the planned recruitment and data collection can be the best decision for the trial participants. This is clearly the case if unexpected severe adverse events emerge in one or more trial arms. For example, the Cardiac Arrhythmia Suppression Trial was discontinued after an interim analysis showed a higher mortality rate in the active drug arms compared to the placebo arm [1]. Similarly, a planned interim analysis of the primary outcome of a trial can conclusively demonstrate the futility or superiority of one of the trial arms before the end of follow-up. The ethical principle of equipoise is then violated, and the trial should be discontinued [2,3]. However, concerns exist about whether these interim analyses are in practice adequately planned, conducted, and interpreted [4–6].

Discontinuation for commercial reasons can be at odds with sound methodology, as for example when an interim

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**What is new?**

**Key findings**

- One out of five clinical drug trials is discontinued before completion of the planned recruitment and/or follow-up, and one out of eight is discontinued for questionable reasons, including recruitment failure and unplanned interim analyses.
- Investigator-initiated trials have a higher likelihood of discontinuation due to recruitment failure, whereas discontinuations after an interim analysis demonstrated futility or superiority occurred mainly among industry-sponsored trials.
- Oncology trials are more likely to discontinue all cause and after an interim analysis demonstrated futility or superiority compared to other disease areas.

**What this adds to what was known?**

- Compared to previous empirical studies, discontinuation of clinical trials has not improved.

**What is the implication and what should change now?**

- There is a need for more feasible sample sizes and for more planning and transparency of interim analyses that lead to discontinuation of the trial. Institutional review boards should incorporate these issues in their review and oversight of trials.

analysis was not planned or not performed according to the trial protocol. The likelihood is then increased that a chance finding in the interim analysis leads to a wrong decision to discontinue [7]. The International Conference on Harmonization established guidelines on these issues [8], specifying that clear stopping rules and the moment in the trial progress (at a specified number of included participants or number of events) should be defined and that a data monitoring committee (DMC) should be in place to perform the interim analysis. The European Clinical Trial Regulation (coming into effect as of 2018) also clearly states the importance of describing eventual interim analyses in full detail in the trial protocol [9].

The occurrence and determinants of discontinuation of clinical trials have been empirically investigated in various settings [10,11], but this research may need to be updated as the samples were small and/or their findings may be outdated. Therefore, we investigated the frequency and reasons for discontinuation of clinical drug trials among an inception cohort of clinical drug trials and identified determinants for the most common reasons for discontinuation. Furthermore, we evaluated whether discontinuations after an interim analysis demonstrating either futility or superiority did so according to the trial protocol.

## 2. Methods

The current study is a follow-up analysis of an inception cohort of all clinical drug trials reviewed by one of the accredited institutional review boards (IRB) in the Netherlands in 2007. The design of this study has been published before [12], as well as the results of which trials in the cohort were published in the scientific literature [13]. The data source was ToetsingOnline, the database maintained by the Central Committee on Research Involving Human Subjects (Dutch abbreviation: CCMO) that contains all IRB-reviewed clinical trials in the Netherlands. Other data sources were the complete trial files that were submitted to the CCMO in its role as national competent authority [14], including the original trial protocols submitted to the IRBs, the end-of-trial forms that investigators must submit when the study has ended (the EudraCT B7-form).

All drug trials (both randomized and nonrandomized), reviewed by a Dutch IRB in 2007 ($n = 622$, Fig. 1), were identified and followed until December 2015 (the end of the study period). Trials that were rejected by the IRB ($n = 19$), never started recruitment ($n = 19$), or were still running at the time of data collection ($n = 10$) were excluded from the analysis. Hence, 574 trials were selected for this study.

We used investigator-reported information about the end of trial to the IRB and to the CCMO to classify whether they were discontinued or completed as planned and to classify the reason for discontinuation. The first source was the EudraCT End-of-Trial form (also coded as the B7-form, see Supplement 1/Appendix A at www.jclinepi.com for the two versions that prevailed during the follow-up period). This form, which is used by clinical trial authorities throughout the EU, requires investigators to report whether the trial was completed as planned or discontinued. In case of discontinuation, investigators must provide on this form one or more prespecified reasons for discontinuation (the first version) or write other reasons in an open text box (the second version). If this form was missing or incomplete in the CCMO archive, we searched for other sources in the clinical trial dossier, such as e-mail correspondence between investigators and the IRB, notifying the end of trial. We also used information from a questionnaire sent to all principal investigators (PIs). Questionnaires (Supplement 2/Appendix B at www.jclinepi.com) were e-mailed to the PIs of the trials, asking for reasons for nonpublication for another analysis of the cohort [12], and whether the trial was completed as planned or discontinued, if the other sources were unavailable. If the PI had left the company or the hospital that conducted the trial, we tried to contact the PI at his current affiliation, or otherwise we