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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

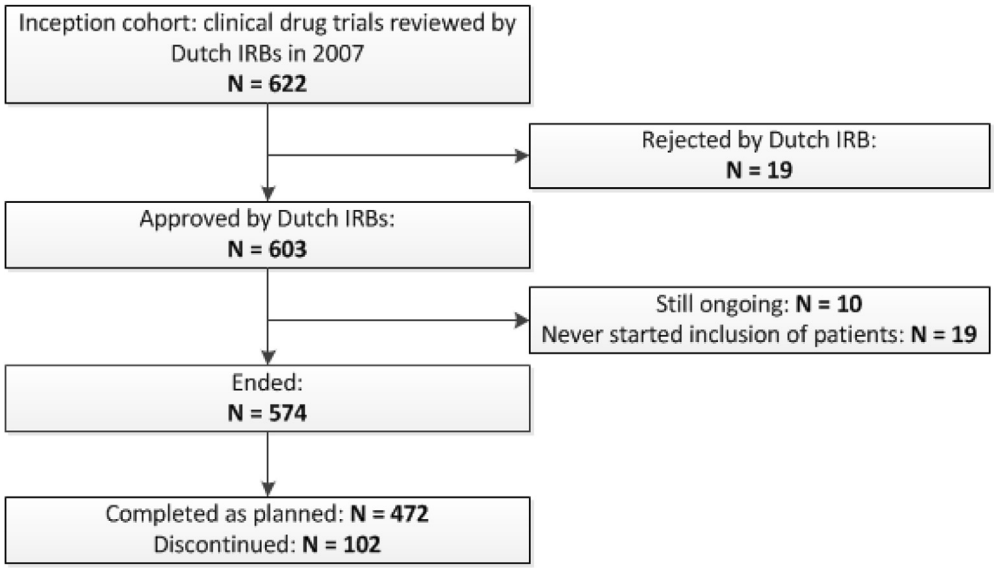

Fig. 1. Selection of the samples for the analysis of the primary outcome, determinant analysis, and protocol evaluation, starting with the inception cohort of all IRB-reviewed trials in 2007. IRB, institutional review board.

attempted to contact colleagues of the PI who were involved in the same trial. After location of the right person, at maximum two reminders were sent. All Dutch accredited IRBs were asked for permission to send the questionnaire to the PIs. All IRBs consented and provided a signed letter of endorsement, which we attached to the questionnaire. The list of 23 Dutch accredited IRBs can be found on the website of the CCMO [15]. The end-of-trial form was missing of 186 of the 574 trials (32%) that were included in the analysis. PIs of 73 of these trials responded to our questionnaire, completing the information on the end-of-trial. Of the remaining 113, of 87 trials we found other documents than the end-of-trial form indicating that the trial had started (e.g., emails from the IRB or amendments) or we found that the trial was published. Of 26 trials, the IRB dossier did not contain information about the completion status and were nonresponding to the questionnaire [13]. After review of these 26 trials by two authors (C.A.v.d.B. and C.T.M.B.), we decided that it would be most reasonable to consider these 26 trials as being completed as planned. In the Netherlands, it is common practice to only report to the IRB in case of irregularities such as discontinuation. Thus, we decided that it would be most reasonable to assume that all discontinuations had been reported to the IRB and/or by the questionnaire and that trials with missing end-of-trial information were completed as planned. Reasons for discontinuation and their classification (in case they were reported in open-text format) were collected in a data extraction document in duplo by one investigator (C.A.v.d.B.), double checked by a research assistant. Differences were solved by consensus.

The investigator-reported reason(s) for discontinuation was the main outcome of the study. We categorized the reasons according to the prespecified categories on the B7-form. Reasons reported in the open text box that could not be reclassified into the prespecified reasons were described separately. Trials could be counted several times if investigators reported more than one reason for discontinuation.

Candidate determinants were trial characteristics planned target sample size, sponsor, phase, centers involved, randomization, and the disease area. These characteristics are filled out by investigators on a standard form for the IRB trial application, which is mandatory and identical throughout the country.

First, the frequencies of all reported reasons for discontinuation were described. Three dichotomous discontinuation outcomes were defined for further analysis: all-cause discontinuation, discontinuation due to recruitment failure, and discontinuation because an interim analysis demonstrated futility or superiority (efficacy related). All discontinuations reporting recruitment failure among the reasons were classified as such because we judged reasons reported together with recruitment failure to be related to the recruitment failure. Discontinuations were only classified as efficacy related if no other reasons (e.g., safety issues) were reported. This was done because the goal was to analyze determinants for trials solely discontinued because of an interim analysis that demonstrated futility or superiority. If other reasons, such as safety issues, were reported, the role of the interim analysis for futility or superiority may have been trivial compared to the other reasons for the decision to discontinue the trial. Percentages were described for all trial characteristic categories of these three discontinuation outcomes (all cause, recruitment failure, and efficacy related) and for trials that were completed as planned.

Furthermore, among the efficacy-related discontinuations, we examined the trial protocol if the interim analysis was planned. We examined three aspects that should be

described in the trial protocol according to the ICH guideline [8]: mentioning a DMC, specification of the stopping rule, and specification of the moment (number of included participants and/or number of primary outcome events) of the interim analysis. We calculated the proportion of trials discontinued for efficacy covering at least one of these aspects in their trial protocol.

We used multivariable Poisson regression analysis to evaluate the association of trial characteristics with all-cause, efficacy-related, and inclusion failure-related discontinuation. The crude and adjusted incidence rate ratio (IRR) and 95% confidence interval (CI) were estimated in three models: one with the outcome all-cause discontinuation, one with the outcome efficacy-related discontinuation, and one with the outcome discontinuation due to recruitment failure. All trials were included in the all-cause discontinuation model, and the trial characteristics sample size, sponsor, phase, centers, randomization, and disease area were tested. Only the phases 2 and 3 trials were included in the efficacy-related discontinuation model, as phase 1, phase 4, and other than phases 1–4 trials often do not measure efficacy and are therefore in general not at risk for efficacy-related discontinuation. In the efficacy-related discontinuation model, the characteristics sample size and disease area were tested, based on the descriptive numbers. Phase 1 trials were excluded from the recruitment failure model because these trials have different recruitment strategies (often healthy volunteers), face different recruitment challenges, and should therefore not be included in the multivariable model. In the recruitment failure model, we tested the characteristics sample size and sponsor, to look if we could replicate the findings by a previous study [10]. For the multivariable analysis, we merged the following trial characteristic categories to one category: investigator-initiated trials with and without industry (co-)funding (to investigator-initiated trials); national and international multicenter trials (to multicenter); the trial phases 2, 3, 4, and other than phases 1–4 (to other than phase 1); and the disease areas other than oncology (to other than oncology; as oncology trials include patients who are typically very ill and are therefore interesting to compare against the other disease areas). The multivariable analysis was done in Stata version 14.1.

3. Results

Of the 574 analyzed trials, 472 were completed as planned and 102 (18%) were discontinued by December 2015 (Fig. 1). Table 1 summarizes the characteristics of the included trials, and Table 2 describes the reasons for discontinuation as reported by the investigators. The most frequent reason was recruitment failure (no or slow recruitment): of the 102 discontinued trials, 33 (32%) were discontinued for this reason (or 5.7% of the total number of 574 trials), followed by 31 trials (30%) that were discontinued for futility as demonstrated by an interim analysis (5.4% of the total).

Table 1. Characteristics of the trials included in the analysis

Total clinical trials in cohort: 574	*N*	%
Sample size		
Planned target sample size, median (IQR)	72 (25–320)	
Sponsor		
Pharmaceutical industry	352	61.3
Investigator [industry (co-)funded]	71	12.4
Investigator (no industry funding involved)	151	26.3
Phase		
Phase 1	119	20.7
Phase 2	130	22.6
Phase 3	172	30.0
Phase 4	57	9.9
Other than phases 1–4[a]	96	16.7
Centers		
Single center	249	43.4
Multicenter only in the Netherlands	54	9.4
Multicenter in the Netherlands and the EU	82	14.3
Multicenter in the Netherlands and outside the EU	189	32.9
Randomization		
Randomized trial	418	72.8
Nonrandomized trial	156	27.2
Disease area		
Oncology	113	19.7
Neurological and psychiatric diseases	109	19.0
Cardiovascular diseases	62	10.8
Endocrine diseases	58	10.1
Infectious diseases	42	7.3
Other	190	33.1

Abbreviation: IQR, interquartile range.

[a] Trials carried out using medicinal products in connection with objectives other than those referred to in the phase definitions 1–4. Such trials are not intended primarily to provide information about the product itself, but a medicinal product is needed to address the objective of the trial.

Thirty discontinuations (5.2%) were solely efficacy related and thus should have been based on a planned interim analysis. Twenty trials (67% of the solely efficacy-related discontinuations) were discontinued while not describing all three essential aspects of an interim analysis (a DMC, the moment of the interim analysis in the trial and the stopping rules) in the protocol. Planning of the stopping rules was the aspect that was most often missing [in 18 (40%) of these protocols].

Table 3 shows the percentages of the trial characteristics for all-cause, solely efficacy-related and recruitment failure discontinuations. The results of the multivariable analysis are shown in Supplement 3, Table S1–S3/Appendix C at www.jclinepi.com. Almost all trials that were discontinued solely efficacy-related were industry sponsored (29 industry sponsored and 1 investigator initiated, Table 3). Because there was only one efficacy-related discontinuation among investigator-initiated trials, the sponsorship variable was not included in the multivariable model for solely

Table 2. Frequencies and percentages of the reported reasons for discontinuation

Reason for discontinuation	Frequency reason was reported[a]	% of the discontinued trials (N = 102)	% of the full sample (N = 574)
After interim analysis that should have been planned			
Interim analysis demonstrated futility	31	30.4	5.4
Interim analysis demonstrated superiority	2	2.0	0.3
Solely efficacy related[b]	30	29.4	5.2
Trial protocol specified DMC[c]	15	14.7	2.6
Trial protocol specified stopping rules[c]	12	11.8	2.1
Trial protocol specified the moment of the interim analysis in the trial progress[c]	18	17.6	3.1
Trial protocol specified all three aspects[c]	10	33.3	1.7
Trial protocol specified at least one of the three aspects[c]	20	19.6	3.5
After interim analysis that could not have been planned			
Interim analysis due to safety signals	14	13.7	2.4
Interim analysis because results from other trials became available	2	2.0	0.3
Other reasons			
Recruitment failure	33	32.4	5.7
Financial issues	10	9.8	1.7
Product manufacturing or regulatory issues	4	3.9	0.7
Only Dutch sites closed, international trial continued	2	2.0	0.3
Unfeasible pharmacokinetics	1	1.0	0.2
Suspension of trial after GCP inspection	1	1.0	0.2
Organizational issues	1	1.0	0.2
Reason missing	5	4.9	0.8

Abbreviations: DMC, data monitoring committee; GCP, good clinical practice.

[a] Ninety-three trials reported 1 reason, 4 trials reported 2 different reasons, and 5 trials only reported discontinuation but not the reason.

[b] Only examined among the protocols of the 30 trials that were discontinued solely efficacy related.

[c] Solely efficacy related was after interim analysis demonstrated either futility or superiority. Three trials were excluded because reporting also other reasons than interim analysis demonstrating futility or superiority. Two of these three trials reported discontinuation after an interim analysis due to safety signals, and one trial reported recruitment failure as other reasons for discontinuation.

efficacy-related discontinuation (Table S2/Appendix C at www.jclinepi.com). Investigator-initiated trials were associated with discontinuation due to recruitment failure: 23 (10.4%) of the 222 investigator initiated vs. 10 (2.8%) of the 352 industry-sponsored trials were discontinued due to recruitment failure (adjusted IRR 2.0; 95% CI: 0.9, 4.6, Table S3/Appendix C at www.jclinepi.com). The association was not statistically significant in the multivariable analysis due to the low numbers.

Another determinant for both efficacy-related discontinuation and discontinuation due to recruitment failure is the number and location of centers involved. Multicenter trials also conducted outside the EU had a significantly higher likelihood of efficacy-related discontinuation compared to single-center and multicenter trials within the Netherlands or the EU (13% vs. 0.4–4%, Table 3), whereas single-center trials and multicenter trials only in the Netherlands had a higher likelihood of discontinuation due to recruitment failure compared to multicenter trials outside the Netherlands (7–13% vs. 2–3%, Table 3). These findings could be explained by the fact that most of the international multicenter trials were industry-sponsored phase 3 trials and that most of the nonphase 1 single-center trials were investigator initiated. Because of this multicollinearity with sponsorship and trial phase, we did not include the center variable in the multivariable models.

Overall, 32 (28.3%) of the 113 oncology trials were discontinued vs. 70 (15.2%) of the 461 trials in other disease areas (Table 3). Table S1/Appendix C at www.jclinepi.com shows that this association is statistically significant after adjusting for the other trial characteristics (adjusted IRR 1.7; 95% CI: 1.1, 2.7). We also found that oncology trials were at statistically significant higher risk of efficacy-related discontinuation (adjusted IRR 2.5; 95% CI: 1.2, 5.1, Table S2/Appendix C at www.jclinepi.com).

4. Discussion

In our study, we showed that a substantial proportion (18%) of all clinical drug trials was discontinued before the planned end of recruitment and/or end of data collection. The proportion of discontinuation is within the range identified by previous studies of 11–45% [10,11,16–21]. Differences may be explained by different selection criteria, as previous studies also included nondrug trials, only randomized trials [10], or selection of exclusively oncology trials [11]. Further reasons for the varying results may be the dependence on registries, publications, or questionnaires instead of IRB-files [16,17,19] or chance. Furthermore, our results show that the problem of poor recruitment remains of concern for in particular (but not only limited to) investigator-initiated trials. Recruitment estimations can be overoptimistic and should therefore be justified in the protocol. When in the trial protocol strict inclusion and exclusion criteria are given, investigators should provide data indicating that recruiting the needed number of participants from

Table 3. Proportion of clinical drug trials discontinued (all cause, solely efficacy related, and recruitment failure), stratified by trial characteristics

All trials (n = 574)	Completed as planned N = 472 (82.2%); N (%)	Discontinued (all cause) N = 102 (17.8%); N (%)	Discontinued for efficacy[a] N = 30 (5.2%); N (%)	Discontinued for recruitment N = 33 (5.7%); N (%)
Sample size				
Planned target sample size, median (IQR)	68 (24–314)	120 (40–392)	309 (78–635)	78 (23–180)
Sponsor				
Pharmaceutical industry (N = 352)	288 (81.8)	64 (18.2)	29 (8.2)	10 (2.8)
Investigator (industry [co-]funded) (n = 71)	56 (78.9)	15 (21.1)	0 (0)	8 (11.3)
Investigator (no industry funding involved) (N = 151)	128 (84.8)	23 (15.2)	1 (0.7)	15 (9.9)
Phase				
Phase 1 (N = 119)	108 (90.8)	11 (9.2)	1 (0.8)	2 (1.7)
Phase 2 (N = 130)	98 (75.4)	32 (24.6)	16 (12.3)	9 (6.9)
Phase 3 (N = 172)	133 (77.3)	39 (22.7)	13 (7.6)	12 (7.0)
Phase 4 (N = 57)	45 (78.9)	12 (21.1)	0 (0)	7 (12.3)
Other than phases 1–4[b] (N = 96)	88 (91.7)	8 (8.3)	0 (0)	3 (3.1)
Centers				
Single center (N = 249)	219 (88.0)	30 (12.0)	1 (0.4)	18 (7.2)
Multicenter only in the Netherlands (N = 54)	43 (79.6)	11 (20.4)	1 (1.9)	7 (13.0)
Multicenter in the Netherlands and the EU (N = 82)	68 (82.9)	14 (17.1)	3 (3.7)	2 (2.4)
Multicenter in the Netherlands and outside the EU (N = 189)	142 (75.1)	47 (24.9)	25 (13.2)	6 (3.2)
Randomization				
Randomized trial (N = 418)	344 (82.3)	74 (17.7)	23 (5.5)	22 (5.3)
Nonrandomized trial (N = 156)	128 (82.1)	28 (17.9)	7 (4.5)	11 (7.1)
Disease area				
Oncology (N = 113)	81 (71.7)	32 (28.3)	15 (13.3)	7 (6.2)
Neurological and psychiatric diseases (N = 109)	93 (85.3)	16 (14.7)	3 (2.8)	5 (4.6)
Cardiovascular diseases (N = 62)	52 (83.9)	10 (16.1)	3 (4.8)	3 (4.8)
Endocrine diseases (N = 58)	47 (81.0)	11 (19.0)	3 (5.2)	1 (1.7)
Infectious diseases (N = 42)	38 (90.5)	4 (9.5)	0 (0)	1 (2.4)
Other (N = 190)	161 (84.7)	29 (15.3)	6 (3.2)	16 (8.4)

Abbreviation: IQR, interquartile range.

[a] Solely efficacy related was after interim analysis demonstrated either futility or superiority. Three trials reporting futility were not defined as solely efficacy related because they reported also other reasons than interim analysis demonstrating futility or superiority. Two of these three trials reported discontinuation after an interim analysis due to safety signals, and one trial reported recruitment failure as other reasons for discontinuation.

[b] Trials carried out using medicinal products in connection with objectives other than those referred to in the phase definitions 1–4. Such trials are not intended primarily to provide information about the product itself, but a medicinal product is needed to address the objective of the trial.

this population is feasible within the planned time. Literature and pilot research could for example identify whether sufficient candidate participants fulfilling the trial population criteria are willing to participate [22,23].

The percentage of discontinuations for futility and superiority reasons is consistent with the findings of Kasenda et al. [10]. Discontinuation of a clinical trial after a well-designed interim analysis is not a failure. A research question can be answered by conducting the interim analysis at the right time, applying adequate stopping rules for statistical significance, and under supervision of an independent and skilled DMC. These aspects of the interim analysis should be described in the trial protocol. If the interim analysis is not described appropriately in the protocol, scientific objectivity is at risk to be preceded by personal or commercial motivations, for example through p-hacking [24]. Of the efficacy-related discontinuations in our study, two-thirds described at least a responsible DMC, the moment of the interim analysis in the trial, or the used stopping rule. However, only one-third described these three essential aspects of an adequate procedure for an interim analysis [8] in the trial protocol. The proportion of trials with at least some planning in the protocol in our study is considerably higher compared to the one-third found by Stegert et al. [25]. However, efficacy-related discontinuations are still often based on inadequately described procedures. The suggestion to improve trial protocols with regard to interim analyses is in particular, as our results show, for the industry-sponsored trials. Oncology trials were both at a statistically significant higher risk for all-cause discontinuation and for efficacy-related discontinuation. Possible explanations are the pressing need for effective therapies against various cancers [26] and the competitive drug market in oncology [27]. These reasons may be incentives to finish trials and act on their preliminary results. Our results show that these discontinuations are often not justified. The small number

of discontinuations for superiority reasons in our study is contrary to the concerns expressed in the literature that this is a rising and questionable phenomenon [4,7,28,29]. It may be that these publications have led to a cautious attitude toward discontinuations due to interim analyses demonstrating superiority, diminishing its occurrence.

Six percent of the trials were discontinued due to recruitment failure, which is somewhat lower compared to the 10% found by Kasenda et al. [10]. This figure was slightly lower in our study among randomized compared to nonrandomized trials (22 of 418, 5.3% vs. 11 of 156, 7.1%, respectively), also when excluding the phase 1 trials (31 of 364, 7.8%). Another study previously found higher incidence of recruitment failure among randomized trials compared to nonrandomized trials. The difference with our study may be explained by that they excluded crossover trials or that they included relatively more phase 1 trials [30]. We replicated the finding that the risk of investigator-initiated trials to discontinue due to recruitment failure is more than twofold compared to industry-sponsored trials [10,31], although the small sample size prevented a statistically significant effect in our multivariable model. Furthermore, we descriptively showed that phase 4 trials have a higher likelihood of discontinuation due to recruitment failure compared to other phases. Although the sample size was too low to test this association in multivariable analysis, it suggests that the motivation to recruit and/or to participate in a trial is limited after a drug also has become available in regular clinical practice. It also highlights the challenge of solving safety issues about newly approved drugs in the postmarketing phase [32].

A recent study showed that information about trial discontinuation is often not updated in trial registries [33]. In addition, the discontinued trials in our cohort remained significantly more often unpublished: 36% of the trials that were completed as planned remained unpublished vs. 67% of the discontinued trials (manuscript submitted). Discontinued trials may be sometimes considered as failures and therefore as being not interesting or relevant to publish or disclose the details about. Nevertheless, transparency and traceability of such trials are important to prevent future failures for the same reasons.

The finding that only 14 trials were discontinued for safety reasons suggests that the likelihood of safety problems in drug trials is not very high (2.4%, Table 1) and similar compared to other studies [10,25]. However, we did not have access to the individual trial safety data to further investigate this, and thus, the issue of safety is outside the scope of our study. Recent events show that the safety of trial participants remains of primary importance for investigators, sponsors, and IRBs [34].

Discontinuations due to recruitment failure, financial reasons (90% of these were industry sponsored), suspension after an inspection identified Good Clinical Practice issues, product manufacturing or regulatory issues, organizational issues, and after an interim analysis not or incompletely described in the protocol can be considered as being probably unjustified but at least questionable for various reasons [2,4,5,21,22,26,28,29,35–39]. Together, these reasons sum up to 69 trials (12% of the cohort, Table 1). Probably, a number of these discontinuations were due to nonanticipatable misfortunes. Others may have been avoided if the conduct was preceded by a better trial protocol, planning, justification of sample size, and/or organization [22,25,35].

Based on our findings, we propose three recommendations for improvement of the conduct of clinical trials. These are relevant for all stakeholders. In particular, as the gatekeeper of clinical research, IRBs can play an important role in their implementation. The first recommendation is to include realistic sample size justifications and a critical assessment of the burden posed on trial participants. Future research should focus on how to measure the feasibility of recruitment numbers and timelines, enabling to reduce the rate of these trial failures. The second recommendation is that the interim analysis plan in trial protocols should be improved [2,7]. Preventing discontinuations after unplanned interim analyses found futility or superiority can lead to less research waste, as trials completed as planned deliver information that is more useful and less influenced by chance [38]. The final recommendation is that IRBs should only approve trials with clear contracts stating that it is the responsibility of the sponsor to complete the trial and not allowing questionable reasons for discontinuation.

A strength of our study is that we included on a nationwide level all trials approved within the inclusion period, from 23 different IRBs. Therefore, the findings are both complete and can be considered as generalizable across the broad activity of clinical drug trials in the Netherlands. Our study adds geographic representativeness to the existing literature, as we were able to largely confirm the findings of trials reviewed by IRBs in Germany, Canada, and Switzerland [10,25]. We had full access to the documents of the national competent authority and collaborated extensively with the local IRBs and investigators. Despite having access to a full cohort of drug trials, numbers in certain categories of potential determinants were small, with impacted our ability to obtain precise estimates in our multivariable models.

To conclude, one out of five clinical drug trials is discontinued before the planned trial end. Most of these discontinuations are related to recruitment failure or interim analyses demonstrating futility. One out of eight clinical drug trials is discontinued for a questionable reason. IRBs should request more realistic recruitment targets. They should also request industry-sponsored multicenter trial applications to provide an adequate plan for an interim analysis in the trial protocol, including DMC oversight, the moment of the interim analysis in the trial progress, and the stopping rule that will be used.

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Supplementary data

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