Towards improving quality of the evidence base for medical decision-making

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Chapter 4

Identifying predictors of early trial termination: A meta-epidemiological study utilising elements of the research ethics committee evaluation

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Abstract

Objective: Early trial termination remains frequent. Research ethics committees (RECs) could play a role in reducing the probability of early termination. Their review process provides a window for both identifying trials at high risk of terminating prematurely and imposing preventive measures, such as design modifications. This study aimed to explore whether characteristics of ethics review, alongside trial characteristics, are related to subsequent early trial termination.

Study design and setting: This meta-epidemiological cohort study assessed 198 clinical trials approved by a Dutch REC between 2015 – 2018. Data from archived trial protocols, related study documents and correspondence between the REC and investigators were analysed to identify predictors of early termination during ethics review.

Results: Of the 198 trials, 69 (34.8%) terminated early, most often due to recruitment failure (n = 31, 35.2%). Several characteristics were associated with early termination, such as multicentre design (vs. single centre, RR: 1.89, 95% CI: 1.24–3.14), number of comments raised during ethics review (per comment, RR: 1.02, 95% CI: 1.00–1.05), and specific comments regarding privacy and confidentiality (RR: 1.21, 95% CI: 1.05–1.41) and participant information sheets (RR: 1.05, 95% CI: 1.02–1.08). Investigator sponsorship, longer review durations, and comments raised regarding privacy and confidentiality and subject selection were associated with an increased likelihood of recruitment failure, specifically.

Conclusion: This exploratory study showed that various characteristics of ethics review have the potential to predict early trial termination. Further studies are needed to validate and expand upon these findings.

Plain Language Summary

Clinical trials sometimes end earlier than planned, often due to difficulties recruiting enough participants. When trials stop too soon, their results become less reliable. Research ethics committees (RECs) review trial plans before they begin to make sure they meet legal and ethical standards. RECs may also be able to help prevent early termination by identifying trials at high risk and recommending improvements. This study looked at 198 clinical trials approved by a Dutch REC to see if the characteristics of the ethics review process could predict which trials might stop early.

The study found that about one-third of the trials ended early, most often due to recruitment problems. Trials were more likely to stop early if they involved multiple centres, received more comments from the REC, or received comments specifically about issues related to privacy, confidentiality, or the information given to participants. Recruitment problems were more common in trials that had longer review times, received comments about who was eligible to take part or issues related to privacy and confidentiality, or were run by researchers without commercial sponsorship.

Overall, the findings suggest that by examining the ethics review process more closely, RECs might be able to identify and support trials at higher risk of stopping early. More research is needed to confirm these results and explore how RECs might help improve trial success.

What is new?

Key findings

- One-third of clinical trials approved by a Dutch research ethics committee (2015 – 2018) terminated early, most often due to recruitment failure
- Multicentre design, investigator sponsorship, and several aspects of ethics review were associated with early trial termination or recruitment failure

What this study adds to what was known

- This is the first study to show that ethics review characteristics, such as the number and the content of reviewer comments, have the potential to predict early trial termination

What is the implication and what should change now?

- Ethics review offers a valuable window for identification of trial at risk of early termination, and targeted risk mitigation before trial initiation
- Future research should aim to validate these findings in broader settings

Introduction

Approximately 25-30% of clinical trials are terminated prematurely, with recruitment failure being the most common reason.[1,2] Early terminations raise scientific and ethical concerns. Stopping before the target sample size is reached leaves trials unable to address their primary research question(s) reliably. Clinically relevant effects are more likely to be missed, while statistically significant effects are often (severely) overestimated.[3,4] Consequently, results from prematurely terminated trials are difficult to interpret or even misleading. Ideally, early terminations, specifically due to potentially preventable reasons such as recruitment failure, should be avoided to reduce research waste and ensure that patients' efforts contribute meaningfully to science.

Identifying clinical trials at high risk of terminating prematurely before they start, could enable risk mitigation. Measures might include design modifications, securing additional funding, or deciding not to initiate trials that are unlikely to succeed. In this context, research ethics committees (RECs), also known as institutional review boards (IRBs), could play an important role. Their review process presents a valuable window to (1) identify trials with a high-risk for early termination, and (2) to impose preventive measures. Previous research investigated potential reasons of early trial termination and recruitment failure in particular, which included overly optimistic recruitment estimates, insufficient funding and narrow eligibility criteria, among others.[5-7] Investigator sponsorship has also been associated with an increased likelihood of recruitment failure.[1,7,8] However, whether aspects of ethics review itself can predict trial termination remains unexplored. REC reviewers may identify potential risks, such as unrealistic recruitment targets or overly restrictive eligibility criteria.

This study explored whether REC reviewer comments, meta-data of ethics review (such as its duration), and trial protocol characteristics assessed during ethics review, are related to subsequent trial termination. Specifically, we aimed to (1) assess the frequency of early termination among clinical trials approved by an academic REC, (2) assess reasons for early termination, (3) describe the type of comments and stipulations raised by REC reviewers during ethics review, and (4) identify potential predictors of early termination at time of ethics approval, utilising elements of ethics review and trial protocol characteristics.

Methods

We followed an adapted version of the PRISMA guideline for reporting meta-epidemiological studies, using items where applicable.[9]

Study design and sample

We selected a cohort of all clinical trials approved between January 1, 2015, and December 31, 2018, by the Medical Research Ethics Committee Leiden The Hague Delft (METC LDD), located in the Leiden University Medical Centre (LUMC), the Netherlands. During this period, METC LDD operated as 'Commissie Medische Ethiek' (CME) within LUMC and later merged with METC Zuid-West Holland (METC ZWH) in 2019 to form METC LDD. The cohort used allowed for approximately 6-9 years of follow-up since ethics approval, to assess whether a trial had been completed successfully. Trials were eligible for inclusion if they investigated any healthcare intervention aimed at treating or preventing disease. No further eligibility criteria were applied. Assessment of eligibility was performed by one author (MJ).

Background information ethics review in the Netherlands

In the Netherlands, all research subject to the Medical Research Involving Human Subjects Act (WMO) must undergo ethics review by a REC.[10] During the review process, potential issues identified by the REC

are compiled into formal questions and comments, which are sent to investigators in official correspondence. Investigators should address all of these comments in their response. This exchange may continue through multiple rounds until the REC reaches a final decision. Ethics approval is only granted if the REC judges legal and ethical standards are met and all concerns are resolved. Once the study is approved, investigators must provide the REC with regular updates, including a start notification upon the enrolment of the first participant, annual progress reports, a notification of study closure as well as an end-of-study form in which it is indicated whether it concerns an early termination, and a final results report within one year of study closure. In case of early termination, investigators are required to specify the reason(s) for discontinuation.

Data collection

Data were collected by two authors (MJ, LP) in June-November 2024, with a final check on trial completion status being performed on February 14, 2025. Information regarding trial completion status, trial characteristics, and elements of ethics review, was extracted from approved trial protocols, formal correspondence between the REC and investigators, and related study documents. All REC comments were extracted and classified in duplicate (MJ, LP) and subsequently compared. Discrepancies were resolved through discussion. All other data (e.g., trial status, trial characteristics) were extracted in single (MJ or LP) and subsequently checked to ensure accuracy (MJ). Data were collected using Microsoft Access Database (REC comments) and Castor (e.g., trial status, trial characteristics, meta-data elements of the review process).

Early termination

The primary outcome of this study was early termination. Early termination was defined as discontinuation of the trial while the achieved sample size is <90% of the prespecified target sample size of the latest approved protocol, or if otherwise reported as early terminated by the investigators (in line with previous studies on early termination).[1,2] Achieved sample size and reasons reported for early termination were extracted from REC correspondence (e.g., study closure notifications and end-of-study forms), trial records and corresponding publications, if available.

Potential predictors

Trial characteristics

Trial characteristics were extracted from the initially approved trial protocols and General Assessment and Registration (ABR) forms, as the aim was to identify predictors of trial termination at the time of first ethics approval (and thus not during later amendments). Trial characteristics included sponsorship, subsidising parties, single or multicentre design, overarching purpose, medical field, study design, number of arms, trial phase, intervention type, comparators, allocation, blinding, number of primary outcomes, planned study duration, individual participant duration, target sample size, projected recruitment rates, number of eligibility criteria, inclusion of vulnerable participant groups, participant reimbursement, investigator reimbursement, and planned interim analyses. For multicentre trials started elsewhere for which the global planned study duration was not available from the trial protocol or ABR form, planned study durations were calculated using estimated start- and stop data listed on the first version of the trial record.

Ethics review

Comments and stipulations raised during ethics review were extracted from formal correspondence between the REC and investigators and classified according to **Table 1**. This classification was adapted from Van Lent et al., who analysed REC comments for industry-sponsored and investigator-initiated drug trials in the Netherlands,[11] during a pilot phase of the current study. We used predefined extraction rules to increase consistency (**Supplementary Material S1**). If a single sentence identified multiple conceptual issues, the sentence was extracted multiple times and each issue was categorised separately, except for comments related to participant information sheets (category 6) and editorial comments (category 14), which were extracted only once when listing multiple minor errors. Sentences addressing a single issue but requiring changes to multiple sections or documents were extracted once and categorised by the issue. Further details of the extraction and classification process are provided in **Supplementary Material S1**. In addition to classifying REC comments, several meta-data elements of ethics review were collected, including the number of review rounds, total number of comments, word count of each comment, and the duration of the review process (from submission to approval).

Statistical analysis

Binary variables were summarised as frequencies and proportions, while continuous variables were reported as medians with interquartile ranges. For the main analysis, trials that never started, were still ongoing or had an unclear status were excluded. Univariable log-binomial regression models were used to identify potential predictors of early trial termination, with the potential predictor variables listed earlier as independent variables. Similar models were fitted with termination due to recruitment failure as the dependent variable (vs. completed or terminated trials that did not experience recruitment failure). In case log-binomial regression models did not converge, Poisson regression models with robust standard errors were used instead to estimate risk ratios and 95% confidence intervals on early trial termination and recruitment failure. For categories of variables with no observed events, exact logistic regression was used to estimate odds ratios and 95% confidence intervals.

Preplanned sensitivity analyses were conducted with the following modifications to the regression models: (1) trials with an ongoing or unclear status were included and classified as successfully completed (best-case scenario); (2) trials with an ongoing or unclear status were included and classified as early terminated (or terminated due to recruitment failure for recruitment failure regression models; worst-case scenario); (3) early termination due to preventable reasons was modelled as a dependent variable, for which recruitment failure, organisational/strategic reasons, limited resources, other and unclear reasons were counted as preventable; (4) the discrepancy between planned and achieved sample size was modelled as a continuous dependent variable (percent difference, ((target sample size – achieved sample size) / target sample size) x 100%, and included trials that completed or were stopped early due to preventable reasons) using linear regression; (5) two subsets were analysed to assess early termination frequency and potential predictors during the COVID-19 pandemic and the preceding period: one subset included trials with a planned end date on or after March 1, 2020 (start of COVID-19 regulations in the Netherlands), and the other included trials with a planned end date before March 1, 2020.

All analyses were performed using R (version 4.2.1).

Preregistration

The protocol for this study was pre-registered at the Open Science Framework (OSF) and is available from: https://osf.io/ucn3j.

Ethics approval

This study did not involve human participants and therefore did not require ethics approval for participant involvement under Dutch law. However, as the research involved extracting data from confidential documents of our local REC, approval was obtained from the METC LDD.

Results

Trial characteristics and completion status

In the period of 2015 – 2018, 511 studies subject to the WMO were reviewed by METC LDD. Of these, we identified 198 approved clinical trials investigating a healthcare intervention aimed at treating or preventing disease and were included in our study (see **Figure S1** for selection details). Most trials were investigator-initiated (n = 143, 72.2%), multicentre (n = 125, 63.1%), involved two arms (n = 125, 63.1%), had a parallel design (n = 140, 70.7%), and investigated a medicinal product (n = 108, 54.5%) (**Table 2**). The median target sample size was 100 (IQR: 53.5 - 240).

Of the included trials, 96 (48.5%) were completed successfully and 69 (34.8%) were terminated early, with 60 (30.3%) having an achieved sample size of <90% of their target sample size. Additionally, 17 (8.6%) trials were still ongoing, 11 (5.6%) trials never started, and 5 (2.5%) trials had an unclear completion status. Early terminated trials most often mentioned recruitment failure (n = 31, 35.2%) as reason for discontinuing prematurely (**Table 3**). For trials that were successfully completed, trial durations were exceeded by a median of 10.5 months (IQR: 1.1 – 20.9) in comparison to their planned durations.

Ethics review

The median time from submission to approval was 4.6 months (IQR: 3.3 – 6.6) (**Table 4**). Most trial protocols (n = 116, 58.6%) were reviewed twice until approval (once after initial submission, and once after investigators' response to an official question letter sent by REC reviewers). The median number of comments raised by REC reviewers per protocol, during the entirety of the review process, was 5 (IQR: 3 – 9). Protocols most often received comments regarding the participant information sheet and consent form (n = 150, 75.8%), followed by methodology and statistical considerations (n = 86, 43.4%).

Potential predictors of early termination and recruitment failure

Risk ratios (RR) and 95% confidence intervals (CI) of early termination and recruitment failure are outlined in **Table 5** and **Table 6** for each of the potential predictor variables.

Early Termination

Multicentre trials were more likely to terminate early than single-centre trials (RR: 1.89, 95% CI: 1.24 – 3.14). Early termination was also associated with the number of comments during ethics review (per comment, RR: 1.02, 95% CI: 1.00 – 1.05), total comment length (per 100 words, RR: 1.06, 95% CI: 1.00 – 1.13), and specific comments on privacy and confidentiality (per comment, RR: 1.21, 95% CI: 1.05 – 1.41) and participant information sheets (per comment, RR: 1.05, 95% CI: 1.02 – 1.08). Other factors such as larger target sample size, additional eligibility criteria, and longer participant duration were associated, but had very small effect sizes.

Table 1. Classification of REC comments (adapted from Van Lent et al.[10])

Category	Definition	Examples of comments raised during ethics review
1 **Proportionality**	• Risks and burdens to subjects are reasonable in relation to anticipated benefits • Trial leads to important medical knowledge and/or considerable health benefits • Participation does not involve unacceptable/disproportionate risks or burdens to subjects, use of placebo in trial is ethically justified	• "The committee is of the opinion that this study involves a very high burden for patients. Considering that the effectiveness of the drug used in these patients has not been demonstrated, the committee questions whether this burden is justified by the expected study effects. The committee asks for your perspective and requests an explanation of why you believe this burden is warranted." • "The proposed study design appears to involve suspending an indicated treatment, [...] for 15 weeks (i.e., a potential disadvantage for participants is that they may be denied a more suitable treatment). Please provide your explanation."
2 **Minimisation of risks and burdens**	• Risks and burdens to subjects are minimised • Research question cannot be answered without inclusion of human subjects • Research question cannot be answered by more simple or less risky/burdensome research	• "The committee has discussed the fact that participants in the placebo group are not allowed to use any pain relief. Specifically, for lower back pain, the committee could imagine that participants might be allowed to continue using standard medication such as Diclofenac or Ibuprofen. Please provide your response." • "The committee would like to see the burden on participants minimised as much as possible. [..] The protocol mentions that three visits may take place elsewhere, but this is not further specified. The committee requests a more detailed explanation of this point, including how it reduces the burden on participants."
3 **Privacy and confidentiality**	• Adequate provisions are made to protect privacy of subjects and maintain confidentiality of data and body tissues • Trial data and body tissues are adequately coded, stored and protected, with restricted access for third parties • (Long-term) storage of body tissue for purposes outside of the original study is done in a biobank	• "The committee has noted that urine samples are sent to [...]. The committee asks how these samples are coded and emphasizes that the key to the code must remain at [...]. This should be explicitly specified in the study protocol." • "Both [...] state a retention period of 10 years; however, this is incorrect—the legal retention period is 15 years. The committee requests that you correct this." • "The committee asks you to refer to "coded data" rather than "anonymous data," as the data can still be traced back to individuals via the code."
4 **Patient safety**	• Adequate provisions are made to ensure safety of subjects during the trial • Collected data are adequately monitored and (if necessary) a Data and Safety Monitoring Board (DSMB) is installed • Individual and group level stopping criteria are adequate	• "The committee wonders whether patients will be able to travel home independently after the study. How is this aspect ensured in the research?" • "The committee strongly recommends establishing a DSMB to monitor the study. This is a randomized and blinded study with unknown potential risks. Please provide your response." • "Escalating doses are being administered. However, the protocol does not mention any precautions to prevent accumulation between two doses. The committee requests that you include stopping rules in the protocol to ensure participant safety."

5	**Recruitment process**	• Recruitment methods and payments to subjects are acceptable • Investigator has access to population that allows recruitment of required number of subjects • Subjects are given adequate opportunity and time to ask questions and decide about participation	• "The committee has noted that participants are offered €10 upon completing the final questionnaire. The committee does not approve of this approach. All participants in the study, including those who do not complete the final questionnaire, must receive the payment." • "the committee has noticed that [..] submitted another protocol for the same patient group. It follows a similar design but with a different drug. The committee questions whether there are enough of these patients in the department to run both protocols simultaneously.[...]" • "The committee requests a detailed explanation of how informed consent will be obtained in this study. Since the angioplasty procedure is conducted under emergency conditions, there will be no opportunity to adequately inform participants in advance."
6	**Information sheet and consent form**	• Subject information sheet and consent form contain all required elements • The length, structure and language use of the information sheet and consent form will allow subjects to understand them correctly • No coercive language is used	• "The committee finds that the presence of a placebo arm in the study is mentioned only in passing in the participant information sheet. The committee requests that this be given more prominence." • "The committee finds it striking that the participant information sheet [...] does not mention or explain the burden of the study. The committee considers this an omission and requests that this important aspect be further elaborated." • "The committee believes that the participant information sheet is not always clear. For example, terms such as "osteoporotic" and "osteopenia" are used. The committee requests that complex terms be replaced with more commonly understood alternatives."
7	**Subject selection**	• Subject selection is appropriate to answer the research question • Inclusion and exclusion criteria are adequate and complete, equity in subject selection	• "The committee points out that no distinction is made between anxiety symptoms and an anxiety disorder. The group is now so diverse that the research question may not be answered. Please provide your response." • "The exclusion criteria include the use of benzodiazepines [...] but without specifying the time frame. The committee requests that this be phrased as follows: "use of benzodiazepines in the past 2 weeks." If it has been longer, tolerance will no longer be an issue, and excluding participants based on a longer time frame may unnecessarily limit recruitment. Please update the relevant documents." • "The committee would like to know why individuals over the age of 75 cannot participate in the study. The committee cannot imagine that the study poses additional risks for this age group. Please provide your response."
8	**Protection vulnerable subjects**	• No vulnerable subjects are included, unless they may benefit themselves from participation or trial cannot be conducted without them • When vulnerable subjects are included, there are additional safeguards to protect their rights and well-being	• "The committee would like to point out that a study like this may only be conducted with minors if it is not possible to perform it with adults. Since the committee understands that the study has already been conducted with adults, and this protocol is investigating whether the same results can be achieved with minors, the committee would like to receive the relevant publications of [...]." • "You also expect to include incapacitated participants. In light of this, you should incorporate the Code of Resistance in your protocol and describe how the Code will be applied in practice. We request that you supplement your protocol on this point."

9 Methodology and statistical analysis	• Trial design/methodology is appropriate and properly motivated in protocol • Selected primary & secondary endpoints and dosage regimen are appropriate • Sample size calculations and planned statistical analyses are adequate	• "[...] you state that dropouts in the EMDR group will be replaced by new participants placed into the EMDR group. This method of replacement undermines the randomization process. The correct approach is to continue with randomization [...]" • "It is unclear what the primary effect parameter is. Please add this to the protocol." • "The committee asks that you provide further justification for the chosen dosages." • "The committee observes that you based the sample size calculation on the secondary outcome measure. This is highly unusual. The committee requests that you provide a calculation based on the primary outcome measure."
10 Product information	• Product information on the medicinal product(s) and/or device(s) used in the study is adequate • Investigator's Brochure (IB) and Investigational Medicinal Product Dossier (IMPD)/ Summary of Product Characteristics (SPC) are acceptable	• "The committee has noted that a preservative is used in [...]. It is not known whether this preservative is suitable for inhalation. This information is not found in the documentation (other inhalation preparations do not contain or contain a different preservative). The committee requests clarification on this matter." • "The committee asks you to provide more information about the app. Based on the information provided, the committee is unable to assess whether this app should be considered a 'medical device.' If the app is solely used for data storage, the software does not need to be reviewed by the committee. However, if the app is used for therapy or treatment purposes, the committee would like to receive additional information, such as the CE marking. The committee kindly requests that you submit a detailed description of the app so we can proceed with the assessment."
11 Supporting documentation	• Other documents submitted as part of the research proposal are complete and acceptable • Data in General Assessment and Registration (ABR) form are complete and correct and the Clinical Trial Agreement is in accord with Dutch regulations • Required insurances for medical research with human subjects are arranged	• "The committee believes that the [...] questionnaire could be made more visually accessible by using a scale instead of a list format. The committee requests that you provide a revised, more accessible version of the questionnaire." • "The committee has noted that this is a multicentre trial, but the ABR form only mentions [...]. The committee requests that you list the other participating centres along with the number of patients to be included in the form." • "The committee understands that the standard treatment for these patients consists of calcium and vitamin D. Since treatment with zoledronic acid infusion is not considered standard care, the committee does not grant an exemption from the participant insurance requirement. Please update the protocol and the participant information form accordingly."
12 Facilities and research staff	• Research staff members are experienced and qualified to conduct trial procedures • Investigator has adequate facilities to conduct the trial	• "The committee requests you to confirm that the participating physicians have experience with both standard treatments." • "The monitoring is carried out by the internal monitoring pool of [...]. This is not feasible due to the involvement of other participating centres. Please adjust this." • "The committee inquires who will perform the whole genome or exome sequencing. The committee points out that, as far as is known to [...], such tests are not yet possible using saliva samples, either for clinical diagnostics or research purposes."

13	**Financial aspects**	• All costs incurring during the trial are adequately covered • Compensation fees paid to investigators or institutions are proportional to the size, nature, and purpose of the trial • Conditions (e.g. financial interests) leading to conflicts of interest are prevented	• "The committee has understood that all participants will receive a proton pump inhibitor, including those in the placebo group. These medications must now be paid for by the patient and can no longer be reimbursed by health insurers. The committee would like to know how this medication will be financed within the context of the study." • "The committee requests you to specify the cost breakdown of the €24,000 per patient, detailing the exact expenses per cost category in euros." • "The committee has noted that the company [...] has drafted a research contract with [...], indicating a compensation of approximately €120,000. The committee requests you to substantiate the amount of compensation stated in the contract."
14	**Editorial, inconsistencies and formalities**	• Correction of spelling mistakes and grammar • Inconsistencies between study documents or sections of the protocol • Use of incorrect / old templates • Lack of signatures on study documents	• "The committee has noted that the [...] questionnaire contains various unusual language errors. Please review it carefully and correct any mistakes as necessary." • "The sample size in the ABR form and protocol are discrepant. The committee requests you to bring both in alignment." • "Please revise section 9 'Amendments' in accordance with section 13 of the CCMO template for research protocols [...]." • "The signature page of the protocol is not signed. Please provide a signed version."
15	**Other / non-categorizable**	• All comments that could not be categorized elsewhere • E.g., outdated versions of Declaration of Helsinki	• "The committee does not agree with the sponsor's position that it can only refer to the 1996 version of the Declaration of Helsinki because this version is cited in the Clinical Trial Directive (2001/20/EC). The Committee believes that the most recent version of the Declaration of Helsinki should always be referenced in the protocol. [...]" • "The committee has learned that in Sweden,, protocol [...] was not approved. [...] The committee would like to receive an explanation regarding this negative decision." • "The committee has noted that information regarding [...] the publication policy is missing. Please add this information in accordance with [...]."

This classification system was adapted from Van Lent et al,[10] during a pilot phase of the current study. All extracted REC comments and stipulations in our study were classified using these categories. Details regarding classification rules are provided in **Supplementary Material S1**.

Table 2. Trial characteristics stratified by completion status and recruitment failure

	Entire cohort		Completed		Early terminated		Recruitment failure	
Variable	**n = 198**	**%**	**n = 96**	**%**	**n = 69**	**%**	**n = 31**	**%**
Sponsor								
Investigator	143	72.2	70	72.9	45	65.2	27	87.1
Industry	55	27.8	26	27.1	24	34.8	4	12.9
Subsidising party (other than the sponsor)								
None	92	46.5	44	45.8	40	58.0	12	38.7
Industry [a]	38	19.2	21	21.9	8	11.6	5	16.1
Other [b]	68	34.3	31	32.3	21	30.4	14	45.2
Centres								
Single centre	73	36.9	44	45.8	16	23.2	9	29.0
Multicentre	125	63.1	52	54.2	53	76.8	22	71.0
Medical field								
Internal medicine	37	18.7	19	19.8	13	18.8	5	16.1
Oncology	36	18.2	12	12.5	14	20.3	5	16.1
Neurology & neurosurgery	28	14.1	15	15.6	9	13.0	0	0.0
Psychology & psychiatry	31	15.7	14	14.6	10	14.5	6	19.4
Other [c]	66	33.3	36	37.5	23	33.3	15	48.4
Overarching purpose								
Treatment	149	75.3	75	78.1	52	75.4	22	71.0
Prevention	15	7.6	7	7.3	6	8.7	4	12.9
Feasibility (pilot)	20	10.1	8	8.3	5	7.2	3	9.7
Other [d]	14	7.1	6	6.2	6	8.7	2	6.5
Study design								
Single arm	28	14.1	12	12.5	9	13.0	5	16.1
Parallel	140	70.7	72	75.0	45	65.2	23	74.2
Crossover	13	6.6	7	7.3	4	5.8	1	3.2
Other [e]	17	8.6	5	5.2	11	15.9	2	6.5
Intervention								
Drug [f]	108	54.5	55	57.3	40	58.0	15	48.4
Device	18	9.1	8	8.3	6	8.7	3	9.7
Behavioural & digital health innovations	41	20.7	21	21.9	13	18.8	9	29.0
Other [g]	31	15.7	12	12.5	10	14.5	4	12.9
Phase								
1	10	9.3	3	5.5	7	17.5	1	6.7
2	36	33.3	14	25.5	13	32.5	7	46.7
3	32	29.6	19	34.5	11	27.5	2	13.3
4	14	13.0	8	14.5	5	12.5	4	26.7
Other [h]	16	14.8	11	20.0	4	10.0	1	6.7
Not applicable	*90*		*41*		*29*		*16*	
Arms								
1	37	18.7	14	14.6	16	23.2	6	19.4
2	125	63.1	69	71.9	35	50.7	20	64.5
≥3	36	18.2	13	13.5	18	26.1	5	16.1
Allocation								
Randomised	153	95.0	80	97.6	49	92.5	23	92.0
Non-randomised	8	5.0	2	2.4	4	7.5	2	8.0
Not applicable	*37*		*14*		*16*		*6*	
Blinding								
Open	72	47.1	32	40.0	23	46.9	10	43.5
Blinded	81	52.9	48	60.0	26	53.1	13	56.5
Not applicable	*45*		*16*		*20*		*8*	
Comparator								
Active	53	32.9	27	32.9	13	18.8	9	36.0
Placebo	56	34.8	34	41.5	18	26.1	6	24.0
No intervention	52	32.3	21	25.6	22	31.9	10	40.0
Not applicable	*37*		*14*		*16*		*6*	

Number of primary outcomes								
1	136	68.7	69	71.9	46	66.7	26	83.9
2	41	20.7	21	21.9	14	20.3	3	9.7
≥3	21	10.6	6	6.2	9	13.0	2	6.5
Planned interim analysis	45	22.7	17	17.7	18	26.1	5	16.1
Target sample size (median [IQR])	100	[53.5 - 240]	100	[49.5 - 200]	110	[64 - 300]	100	[60 - 275]
Any form of recruitment projection reported in protocol [i]	85	42.9	39	40.6	30	43.5	15	48.4
Detailed recruitment projection reported in protocol [j]	35	17.7	17	17.7	13	18.8	7	22.6
Number of eligibility criteria (median [IQR])	14	[9 - 24]	13	[8 - 23]	18	[9 - 27]	15	[9 - 19]
Inclusion of vulnerable patient groups	36	18.2	15	15.6	13	18.8	7	22.6
Participant reimbursement [k]	107	54.0	54	56.2	42	60.9	17	54.8
Investigator reimbursement [l]	79	63.2	35	67.3	31	58.5	12	54.5
Not applicable	*73*		*44*		*16*		*9*	
Individual participant duration in months (median [IQR])	9.0	[3.1 - 14.5]	8.0	[3.0 - 12.0]	9.0	[3.3 - 18.0]	9.0	[3.1 - 13.2]
Planned trial duration in months (median [IQR])	26.0	[17.0 - 39.9]	24.0	[15.0 - 36.0]	30.1	[18.0 - 37.8]	30.1	[23.0 - 42.0]
Planned end date ≥ 01-03-2020 (start COVID-19 regulations in the Netherlands)	56	28.3	19	19.8	21	30.4	11	35.5
Year REC approval was obtained								
2015	40	20.2	22	22.9	18	26.1	10	32.3
2016	57	28.8	34	35.4	11	15.9	3	9.7
2017	52	26.3	22	22.9	18	26.1	8	25.8
2018	49	24.7	18	18.8	22	31.9	10	32.3

[a] Industry category also includes trials that had a combination of industry and other subsidizing parties.
[b] Other includes any non-commercial subsidizing party such as foundations, non-profit organizations, etc.
[c] Other includes anaesthetics, emergency medicine, general surgery, gynaecology, immunology, infectious diseases, ophthalmology, paediatrics, public health, rehabilitation medicine, radiology, rheumatology, urology.
[d] Other includes aetiology and supportive care (interventions aimed at supporting/improving existing treatments)
[e] Other includes sequential (e.g., dose-escalation), adaptive, cluster trials
[f] Drug intervention also includes vaccines and biologicals
[g] Other includes dietary interventions, combination products, radiation, surgical interventions and interventions that did not fit into any of the listed categories
[h] Medicinal product trials that did not fit in phase 1-4 and were classified as 'other phase' by the principal investigator
[i] Whether any form of recruitment projection was mentioned in the protocol (e.g., recruitment phase duration, recruitment rates per month or year, information regarding the availability of the target population)
[j] Whether the protocol reported more than just a single statement regarding recruitment, and provided at least a combination of information regarding recruitment phase duration, recruitment rates and/or availability of the target population
[k] Whether participants were reimbursed for participating in the trial (e.g., a static amount, reimbursement of travel costs and/or hotel costs, coupons, etc.)
[l] Whether (sub)investigators of participating centres in multicentre trials were financially reimbursed to participate in the trial (e.g., reimbursement per included participant or per centre).

Table 3. Termination reasons

Termination reasons	n = 88 [a]	%
Recruitment failure	31	35.2
Strategic/organisational reason	8	9.1
Benefit	3	3.4
Harm	3	3.4
Futility	11	12.5
External evidence	1	1.1
Limited resources	8	9.1
COVID-19 pandemic	13	14.8
Other [b]	2	2.3
Not mentioned	8	9.1

[a] In total 69 trials were early terminated, of which 17 trials mentioned a combination of two (n = 15) or three reasons (n = 2, summing up to 88 reasons mentioned): Twelve recruitment failure trials listed other reason(s), including external evidence (n=1), COVID-19 pandemic (n=6), organizational (n=1), limited resources (n=2), COVID-19 & limited resources (n = 1), COVID-19 & other (n = 1). Three trials with limited resources also listed COVID-19 pandemic. Two trials mentioned both futility and harm as reasons. [b] Other: regulatory approval took longer than expected, development of software and medical device took longer than expected.

Recruitment Failure

Investigator-sponsored trials were more likely to experience recruitment failure than industry-sponsored trials (RR: 2.93, 95% CI: 1.23 – 9.54). Longer ethics review duration (per month, RR: 1.12, 95% CI: 1.03 – 1.22) and comments on privacy and confidentiality (RR: 1.31, 95% CI: 1.05–1.62), subject selection (RR: 1.73, 95% CI: 1.03 – 2.89) and non-categorizable issues (RR: 1.61, 95% CI: 1.10 – 2.36) were also associated with recruitment failure. Neurology/neurosurgery trials were less prone to recruitment failure than those in internal medicine (OR: 0.10, 95% CI: 0.00 – 0.98). Both phase 2 and phase 4 trials, compared to phase 3, showed increased risk, though estimates were imprecise due to very few observed recruitment failure events for phase 2 – 4 trials (phase 2, RR: 3.89, 95% CI: 1.05 – 25; phase 4, RR: 4.62, 95% CI: 1.03 – 31). Individual participant duration was weakly associated with recruitment failure (i.e., very small effect size).

Sensitivity analyses

Inclusion of trials with ongoing or unclear status

Results were largely consistent with the main analysis when trials with ongoing or unclear status were included as either completed or terminated early, with minor shifts in effect sizes and confidence intervals (**Tables S1-S4**).

Early termination due to preventable reasons

Early termination due to preventable reasons (i.e., recruitment failure, limited resources, organizational and strategic, other and unclear reasons) was associated with the number of ethics review comments (per comment, RR: 1.03, 95% CI: 1.00 – 1.06), the total comment text length (per 100 words, RR: 1.09, 95% CI: 1.02 – 1.17), and specific comments on privacy and confidentiality (RR: 1.25, 95% CI: 1.06 – 1.47) and participant information sheets (RR: 1.06, 95% CI: 1.02 – 1.09) (**Tables S5-S6**). Increased target sample size and longer individual participant durations were significant, but had small effects.

Discrepancy between target and achieved sample size

Several characteristics were associated with deficits between the achieved and target sample size, including multicentre designs (13.5% participant deficit in comparison to single centre, 95% CI: 1.6%

Table 4. Ethics review characteristics for each trial stratified by completion status and recruitment failure

Variable	Entire cohort n = 198	%	Completed n = 96	%	Early terminated n = 69	%	Recruitment failure n = 31	%
Review duration in months (median [IQR])	4.6	[3.3 - 6.6]	4.0	[2.9 - 6.2]	4.8	[3.6 - 6.5]	5.4	[3.9 - 6.7]
Number of review rounds								
1	16	8.1	10	9.4	4	5.8	1	3.2
2	116	58.6	60	62.5	41	59.4	19	61.3
3	48	24.2	21	21.9	19	27.5	8	25.8
4	15	7.6	6	6.2	4	5.8	2	6.5
5	2	1.0	0	0.0	1	1.4	1	3.2
6	1	0.5	0	0.0	0	0.0	0	0.0
Live meeting	8	4.0	2	2.1	3	4.3	1	3.2
Total number of comments raised during ethical review (median [IQR])	5	[3 - 9]	5	[3 - 9]	6	[4 - 10]	7	[4 - 9.5]
Total text length (number of words) of all comments (median [IQR])	231	[129.5 - 403.5]	207	[112.25 - 371.5]	307	[146 - 466]	304	[155 - 481]
Protocols with comments in each category								
1 Proportionality	33	16.7	16	16.7	13	18.8	5	16.1
2 Minimisation of risks and burdens	11	5.6	7	7.3	2	2.9	0	0.0
3 Privacy and confidentiality	51	25.8	15	15.6	26	37.7	13	41.9
4 Patient safety	40	20.2	20	20.8	14	20.3	6	19.4
5 Recruitment process	35	17.7	15	15.6	13	18.8	5	16.1
6 Information sheet and consent form	150	75.8	73	76.0	53	76.8	26	83.9
7 Subject selection	10	5.1	6	6.2	3	4.3	3	9.7
8 Protection of vulnerable subjects	10	5.1	6	6.2	1	1.4	1	3.2
9 Methodology and statistical considerations	86	43.4	41	42.7	28	40.6	15	48.4
10 Product information	54	27.3	29	30.2	19	27.5	4	12.9
11 Supporting documentation	59	29.8	23	24.0	28	40.6	11	35.5
12 Facilities and research staff	24	12.1	11	11.5	7	10.1	4	12.9
13 Financial aspects	12	6.1	5	5.2	4	5.8	3	9.7
14 Editorial, inconsistencies and formalities	57	28.8	27	28.1	21	30.4	9	29.0
15 Other / non-categorizable	31	15.7	11	11.5	13	18.8	7	22.6

– 25.4%), phase 2 trials (19.5% participant deficit in comparison to phase 3, 95% CI: 0.2% – 38.8%), longer individual participant durations (0.8% deficit per month, 95% CI: 0.3% – 1.4%), and longer planned trial durations (0.4% deficit per month, 95% CI: 0.0% – 0.8%) (**Tables S7-S8**). Neurology and neurosurgery trials were associated with a negative deficit, and thus a surplus of participants (-19.5% deficit in comparison to internal medicine trials, 95% CI: -34.5% to -4.6%).

COVID-19 pandemic

Of 198 trials, 56 (28.3%) had a planned end date ≥ March 1, 2020. Proportions of early termination were comparable between the two groups (pre-COVID regulations: 33.8% vs. 37.5% during or after), but more trials were still ongoing in the group with a later planned end date (2.1% vs. 25%, **Table S9**). For both

groups, recruitment failure was the most frequent mentioned reason for early termination (35.2% vs. 35.5%, **Table S10**). Overall, predictors of early termination and recruitment failure in trials with pre-COVID planned end dates were similar to those identified in the main analysis, with minor shifts in effect sizes and wider confidence intervals, except for trials with two arms (vs. single arm, RR: 0.56, 95% CI: 0.35 – 0.95), and comments on inconsistencies and formalities (RR: 1.21, 95% CI: 1.04 – 1.41), which indicated an association with early termination (**Tables S11-S12**).

Table 5. Association between trial characteristics and early termination or recruitment failure

	Early termination		Recruitment failure	
Variable	**RR**	**95% CI**	**RR**	**95% CI**
Investigator vs. industry sponsorship	0.82	0.57 - 1.20	2.93	1.23 - 9.54
Subsidising party				
None (reference)				
Industry [a]	0.58	0.28 - 1.01	1.21	0.41 - 2.96
Other [b]	0.85	0.55 - 1.24	1.88	0.94 - 3.84
Multicentre vs. single centre	1.89	1.24 - 3.14	1.40	0.71 - 3.02
Medical field				
Internal medicine (reference)				
Oncology	1.33	0.76 - 2.36	1.23	0.40 - 3.80
Neurology & neurosurgery	0.92	0.45 - 1.78	0.10 [i]	0.00 - 0.98 [i]
Psychology & psychiatry	1.03	0.52 - 1.94	1.60	0.55 - 4.63
Other [c]	0.96	0.58 - 1.69	1.63	0.65 - 4.07
Overarching purpose				
Treatment (reference)				
Prevention	1.13	0.50 - 1.88	1.78	0.59 - 3.84
Feasibility (pilot)	0.94	0.38 - 1.68	1.33	0.35 - 3.23
Other [d]	1.22	0.57 - 1.99	0.96	0.17 - 2.76
Study design				
Single arm (reference)				
Parallel	0.90	0.56 - 1.70	0.83	0.39 - 2.24
Crossover	0.85	0.28 - 2.01	0.38	0.02 - 2.01
Other [e]	1.60	0.89 - 3.11	0.53	0.08 - 2.11
Intervention				
Drug [f] (reference)				
Device	1.02	0.46 - 1.75	1.36	0.35 - 3.52
Behavioural & digital health innovations	0.91	0.53 - 1.42	1.68	0.77 - 3.41
Other [g]	1.08	0.59 - 1.71	1.15	0.35 - 2.83
Phase				
1	1.91	0.95 - 3.62	1.50	0.07 - 14.18
2	1.31	0.71 - 2.51	3.89	1.05 - 24.64
3 (reference)				
4	1.05	0.40 - 2.30	4.62	1.03 - 30.50
Other [h]	0.73	0.23 - 1.74	1.00	0.05 - 9.68
Number of study arms				
1 (reference)				
2	0.63	0.42 - 1.01	0.96	0.46 - 2.43
≥3	1.09	0.69 - 1.75	0.81	0.26 - 2.41
Randomised vs. non-randomised	0.57	0.31 - 1.05	0.53	0.16 - 1.76
Open vs. blinded	0.84	0.54 - 1.32	0.97	0.46 - 2.11
Comparator				
Active (reference)				
Placebo	1.07	0.60 - 1.97	0.51	0.19 - 1.30
No intervention	1.64	0.94 - 2.97	1.03	0.46 - 2.35
Number of primary outcomes				
1 (reference)				
2	1.00	0.60 - 1.53	0.38	0.09 - 0.99
≥3	1.50	0.85 - 2.25	0.59	0.11 - 1.71
Planned interim analysis vs. none	1.31	0.86 - 1.88	0.71	0.26 - 1.56
Target sample size (increments of 100 participants)	1.01	1.01 - 1.02	1.01	0.99 - 1.04

Any recruitment projection reported in protocol vs. none	1.07	0.74 - 1.53	1.30	0.68 - 2.47
Detailed recruitment projection in protocol vs. none or unsubstantiated	1.04	0.62 - 1.58	1.31	0.57 - 2.60
Eligibility criteria (increments of 1)	1.01	1.00 - 1.03	0.98	0.96 - 1.01
Inclusion of vulnerable patient groups vs. none	1.14	0.68 - 1.70	1.43	0.62 - 2.80
Participant reimbursement vs. none	1.12	0.78 - 1.65	0.87	0.46 - 1.68
Investigator reimbursement vs. none	0.83	0.57 - 1.24	0.71	0.34 - 1.53
Individual participant duration (per month)	1.01	1.00 - 1.02	1.02	1.00 - 1.04
Planned trial duration (per month)	1.01	0.99 - 1.01	1.01	0.99 - 1.03
Planned end date ≥ 01-03-2020 (start COVID-19 regulations) vs. preceding period	1.37	0.92 - 1.95	1.72	0.86 - 3.21

RR: risk ratio (univariable); CI: confidence interval. [a] Industry category also includes trials that had a combination of industry and other subsidizing parties. [b] Other includes any non-commercial subsidizing party such as foundations, non-profit organizations, etc. [c] Other includes anaesthetics, emergency medicine, general surgery, gynaecology, immunology, infectious diseases, ophthalmology, paediatrics, public health, rehabilitation medicine, radiology, rheumatology, urology. [d] Other includes aetiology, supportive care (interventions aimed at supporting/improving existing treatments). [e] Other includes sequential (e.g., dose-escalation), adaptive, cluster trials. [f] Drug intervention also includes vaccines and biologicals. [g] Other includes dietary interventions, combination products, radiation, surgical interventions and interventions that did not fit into any of the listed categories. [h] Medicinal product trials that did not fit in phase 1-4 and were classified as 'other phase' by the principal investigator. [i] Due to 0 events for this category, an odds ratio and 95% CI was estimated using exact logistic regression

Table 6. Association between characteristics of the ethics review and early termination or recruitment failure

		Early termination		Recruitment failure	
Variable		**RR**	**95% CI**	**RR**	**95% CI**
Review duration (per month)		1.04	0.98 - 1.10	1.12	1.03 - 1.22
Number of review rounds					
	1	0.76	0.26 - 1.51	0.41	0.06 - 2.81
	2 (reference)				
	≥3	1.16	0.78 - 1.67	1.15	0.59 - 2.22
Live meeting vs. no live meeting		1.45	0.69 - 3.05	1.07	0.18 - 6.34
Total number of comments raised		1.02	1.00 - 1.05	1.02	0.97 - 1.06
Text length (number of words) of all comments combined (increments of 100 words)		1.06	1.00 - 1.13	1.06	0.95 - 1.18
Number of comments raised per category					
1	Proportionality	0.93	0.69 - 1.25	0.73	0.43 - 1.23
2	Minimisation of risks and burdens	0.74	0.25 - 2.19	0.25 [a]	0.00 - 1.70 [a]
3	Privacy and confidentiality	1.21	1.05 - 1.41	1.31	1.05 - 1.62
4	Patient safety	0.96	0.65 - 1.26	0.89	0.43 - 1.48
5	Recruitment process	1.01	0.66 - 1.36	0.97	0.42 - 1.73
6	Information sheet and consent form	1.05	1.02 - 1.08	1.00	0.93 - 1.09
7	Subject selection	1.00	0.56 - 1.78	1.73	1.03 - 2.89
8	Protection of vulnerable subjects	0.35	0.07 - 1.79	0.71	0.15 - 3.36
9	Methodology and statistical considerations	1.02	0.90 - 1.16	1.12	0.92 - 1.36
10	Product information	1.00	0.89 - 1.12	0.99	0.72 - 1.35
11	Supporting documentation	1.08	0.95 - 1.23	1.02	0.81 - 1.29
12	Facilities and research staff	0.87	0.55 - 1.38	1.11	0.59 - 2.08
13	Financial aspects	1.07	0.39 - 1.89	1.86	0.51 - 4.08
14	Editorial, inconsistencies and formalities	1.04	0.86 - 1.27	1.01	0.67 - 1.53
15	Other / non-categorizable	1.28	0.97 - 1.68	1.61	1.10 - 2.36

RR: risk ratio; CI: confidence interval

[a] Due to 0 events for this category, an odds ratio and 95% CI was estimated using exact logistic regression.

Discussion

This study explored whether characteristics of research ethics committee (REC) evaluations, as well as trial protocol characteristics assessed during ethics review, are associated with subsequent trial termination. We observed that approximately one-third (34.8%) of the trials in our cohort were terminated prematurely, with recruitment failure being the most common reason (35.2%). Several factors, including multicentre design, extensive REC comments – particularly on privacy and confidentiality issues, and participant information sheets and consent forms – were associated with early termination. While investigator sponsored trials did not terminate early more often than industry sponsored trials as a whole, they did experience recruitment failure more frequently. Recruitment failure was also more frequent in trials with longer ethics review durations, and those receiving REC comments regarding privacy and confidentiality, subject selection, and non-categorizable comments. Furthermore, some characteristics like longer individual participant durations were associated with early termination and recruitment failure, but observed effect sizes were small, suggesting limited relevance.

Comparison with previous literature

Our findings on termination frequency and recruitment failure align with earlier studies, which reported early termination frequencies of 25-30%, with recruitment failure accounting for 37-40% of cases.[1,2] The association between investigator sponsorship and recruitment challenges has also been reported before.[1,7,8] To our knowledge, the relation between REC comments and early termination has not been previously explored. While targeting specific termination reasons directly may seem more intuitive, we chose to classify comments using a broader system (modified from Van Lent et al.),[11] that reflects topics typically assessed during ethics review. Our aim was to explore whether certain ethics review characteristics could serve as early indicators of trials at risk of termination. We hypothesised that both the overall number of comments and those on certain topics, might act as indirect indicators of study quality, potentially predicting early trial termination, even if the associations are not directly causal. In other words, these comments could serve as proxies for underlying issues. Similar to previous studies on REC comments, we found that most comments focused on participant information sheets and consent forms, followed by methodology and statistical considerations.[11-15] Interestingly, comments addressing trial feasibility related issues, such as stringent eligibility criteria, availability of the target population, or recruitment strategies were rarely raised, suggesting there might be opportunities for greater consideration of these aspects during ethics review.

Certain types of REC comments were more frequently raised for terminated trials, and those terminated specifically due to preventable reasons such as recruitment failure. Privacy and confidentiality comments typically addressed issues regarding coding practices, incorrect use of terms like "anonymous" versus "pseudonymous", and data storage regulations (e.g., how long data should be stored by law). Non-categorizable comments mostly addressed the use of outdated versions of Declaration of Helsinki in the protocol. Comments regarding these topics, as well as comments regarding errors or suboptimal language use in participant information sheets, could signal investigator inexperience or a lack of rigor, and may potentially reflect broader trial quality issues. Although rare, comments regarding subject selection mostly addressed requests for clarification and justification of certain eligibility criteria, and were specifically associated with recruitment failure. In contrast to for example privacy and confidentiality comments, subject selection issues (e.g., stringent and/or unclear eligibility criteria) have been suggested as potential reasons for recruitment failure,[5] and may represent an underlying cause in addition to their predictive potential.

Strengths and limitations

This study is, to our knowledge, the first to examine ethics review characteristics in relation to early trial termination. Furthermore, by using archived trial protocols and related study documents to extract trial

characteristics and outcomes, we likely achieved greater accuracy in data collection, and had more variables available, compared to relying solely on trial records. However, several limitations must be acknowledged.

Our sample was restricted to a single REC in the Netherlands, potentially limiting generalisability to other RECs, countries or periods. REC review processes could be subjective and may vary over time due to membership changes. Occasional discrepancies between trial protocols and other study documents may have introduced some misclassification, and for some trials, completion status remained uncertain despite investigator follow-up. Finally, as this was an exploratory study, with no adjustment for multiple testing and a relatively small sample size, results should be interpreted cautiously.

Future directions

While our findings suggest potential for ethics review characteristics to predict early termination, further research is necessary to validate these findings in other settings, including data from different RECs and countries. If validated, this could inform the development of a prediction model to identify trials at risk of early termination due to preventable reasons or recruitment failure specifically. Such a model could be useful for imposing targeted preventive measures to reduce early termination risk. For this model to be applied in practice, REC comments should be routinely categorised, preferably in an automated manner. Natural language models may facilitate this. Furthermore, future research could consider weighting REC comments, as certain issues (e.g., spelling mistakes in the participant information sheet), are unlikely to hold the same importance as others (e.g., sample size calculation errors).

Beyond the role of RECs, funders and other stakeholders could also play a more proactive role in identifying and mitigating feasibility concerns earlier in the research pipeline. Poor design or unrealistic planning due to lack of funding may lead to early termination, resulting both in scientific and financial loss. Prediction models might also support funders in allocating resources more effectively (potentially by funding fewer studies but with more generous financial support to increase the likelihood of success).

Finally, while prediction models may help identify trials at high risk of early termination, predicted risks should not be used as criterion for rejecting ethics approval. It could be considered unethical to approve a trial with a very low likelihood of success, particularly if participant burden and resource requirements are high. However, prediction models are inherently imperfect, providing probabilities rather than certainties. The average chance of success across all trials is still reasonably high, and models are often not capable of reliably identifying trials with truly low likelihood of success. Sole reliance on such models could therefore lead to the unjustified rejection of trials that might otherwise succeed and contribute to patient care and scientific knowledge. Even underpowered trials may provide valuable insights, such as individual benefits for participants, learning benefits to researchers, or pilot data to inform future research. Furthermore, some unmodifiable trial characteristics, such as the medical field or sponsorship, may lead to higher predicted risks, which could inadvertently discourage research in specific areas. Rather than serving as a strict approval criterion, prediction models should support ethics review by helping identify risks and guiding mitigation strategies. RECs could play a role in addressing these risks by implementing validated feasibility checklists,[16] recommending design modifications to enhance feasibility, or referring investigators to specialised research units for support during planning and conduct phases.

Conclusion

Ethics review offers a valuable window for predicting and mitigating early trial termination. This study showed that there is potential for characteristics of the ethics review process to predict early termination, including recruitment failure. Several characteristics, such as multicentre design, investigator sponsorship, ethics review duration, the number of REC comments, including particular comments on privacy and confidentiality, participant information sheets, subject selection, and other issues, were associated with

termination and/or recruitment failure. Identifying trials at risk for early termination before they commence, could allow for targeted interventions, such as thorough feasibility checks or design modifications. Further studies are needed to validate and expand upon our findings.

Online Supplementary Files

The supplementary files referred to in this chapter are available online at http://doi.org/10.1016/j.jclinepi.2025.111832.

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