



DR LLOYD STEELE (Orcid ID : 0000-0003-4745-1338)

PROFESSOR CARSTEN FLOHR (Orcid ID : 0000-0003-4884-6286)

Article type : Research Letter

The prevalence of and reasons for discontinuation of atopic eczema trials on ClinicalTrials.gov: a cross-sectional analysis

Running head: Discontinued trials in atopic eczema

Lloyd Steele¹ and Carsten Flohr²

Affiliations

¹Department of Dermatology, Royal London Hospital, Barts Health NHS Trust, London;

²Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, King's College London and Guy's & St Thomas' Hospital NHS Foundation Trust, London, UK.

Corresponding author: Dr Lloyd Steele

Email: Lloyd.Steele@nhs.net

Word count: 750

Table count: 1

Figure count: 0

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJD.18858](https://doi.org/10.1111/BJD.18858)

This article is protected by copyright. All rights reserved

Funding

There was no funding for this study.

Conflicts of interest

None

Research waste is a major issue in atopic eczema.¹ One contributor is the premature discontinuation of trials. Although termination of trials is essential when participants are exposed to harm, many trials terminate for potentially avoidable reasons.^{2,3} Such avoidable trial termination presents many issues. These include ethical issues, from the wasted time and effort of voluntary participants; financial issues, from the use of finite resources; and scientific issues, arising from publication bias.³ These issues can be mitigated in part by publishing the results from terminated trials on trial registries.

This study aimed to assess what proportion of trials registered on ClinicalTrials.gov for atopic eczema were discontinued, the reasons for this, and whether results were published if recruitment had commenced (with a one-year grace period).

A cross-sectional analysis was performed of the ClinicalTrials.gov database, which is the largest publicly-available, individual registry of clinical trials. We searched for ‘clinical trials’ pertaining to ‘eczema’ and terms suggested by ClinicalTrials.gov: ‘atopic dermatitis’ and ‘atopic dermatitides’ (date of last electronic search 23-May-2019).

Three types of trial status on ClinicalTrials.gov were considered discontinued: trials which commenced recruitment, enrolling participants, but later discontinued (“terminated”); trials which discontinued before commencing recruitment (“withdrawn”); and trials which were active but had not updated the study record for two or more years (“unknown”).⁴

Trial discontinuation and reported reasons are presented as frequencies and percentages. Multivariable logistic regression was used to assess associations between discontinuation reason and the following variables: phase of trial (1 and 1/2, 2 and 2/3, 3, and 4), funder (industry, non-industry), participant age group (adults, children, both), and intended recruitment (<50, 50-249, 250 or more).

The search identified 653 trials, of which 90 (13.8%) were discontinued. These consisted of 35 (5.4%) terminated, 27 (4.1%) withdrawn, and 30 (4.6%) unknown studies. 2251 patients were recruited to the 35 terminated studies, of which 1646 were aged <18 years. This figure may be an underestimate as some “unknown” studies may have commenced recruitment.

Reasons given for withdrawn and terminated trials are shown in Table 1. The reasons often considered most valid for discontinuation - safety and/or results of interim analyses meeting pre-determined thresholds – were present in only 13% of studies. A reason for discontinuation was not provided in 23% of studies, which increased to 48% when including “unknown” studies. Reasons for trial discontinuation were significantly different by funder ($p=0.037$; Table 1), but not age group of participants ($p=0.677$), study phase ($p=0.284$), nor intended recruitment ($p=0.253$).

For trials that commenced recruitment, 14/30 (48%) did not publish results. These studies recruited 807 participants, of which 340 were aged <18 years.

This study identified that approximately one in seven atopic eczema trials registered on ClinicalTrials.gov were discontinued, involving at least 2251 participants. In the majority of cases discontinuation appeared avoidable, and the most common reasons for discontinuation were recruitment related or sponsor decision.

A strength of this study is that it provides the first assessment of trial discontinuation in atopic eczema. A limitation of this study is that only atopic eczema trials in the ClinicalTrials.gov database were searched, and thus it is an incomplete sample which is not fully representative of the clinical trial landscape. A further limitation was that we relied on sponsor self-identification of trial status, and thus misclassified studies may have been missed.

The reported trial termination (5%) and overall discontinuation (14%) rates observed in this study were lower than have been reported in other fields (11-12% and 19%, respectively).^{2,3} This may reflect a lower risk inherent to atopic eczema trials compared to other specialties.⁵ The non-publication rate (48%) observed was consistent with most other studies of terminated trials (28-55%).^{2,3}

Approximately half of discontinued trials did not specify a reason for discontinuation, despite this being advocated by CONSORT.⁶ The most common reason given was recruitment issues, which have previously been cited as the major cause of trial discontinuation.^{2,5} The next most common reason was sponsor decision. The commercial interruption of ongoing medical research is not unprecedented, and some authors have argued that this is an ethical violation that goes against the Declaration of Helsinki,^{7,8} as the interests of subjects do not prevail over those of society. In atopic eczema trials, we observed that more than 50% of participants were children (compared to 12.5% for all research),⁵ which may potentiate the ethical issues.

Terminating trials prematurely, without a valid or stated reason, is ethically unfair to patients who willingly take part and who may be exposed to risk through participation. Recruitment, as the major cause of trial discontinuation, should be carefully considered prior to study commencement to reduce the observed rates of trial discontinuation. When a trial is discontinued, the reason for this and any results obtained should be disclosed in order to maximise the study's societal value and reduce publication bias.

REFERENCES (8)

- 1 Flohr C, Weidinger S. Research Waste in Atopic Eczema Trials-Just the Tip of the Iceberg. *J Invest Dermatol* 2016; **136**: 1930-3.

Pica N, Bourgeois F. Discontinuation and Nonpublication of Randomized Clinical Trials Conducted in Children. *Pediatrics* 2016; **138**.

Williams RJ, Tse T, DiPiazza K, Zarin DA. Terminated Trials in the ClinicalTrials.gov Results Database: Evaluation of Availability of Primary Outcome Data and Reasons for Termination. *PLoS One* 2015; **10**: e0127242.

US National Library of Medicine (2019) Glossary of Common Site Terms URL <https://clinicaltrials.gov/ct2/about-studies/glossary>

Guinn D, Wilhelm EE, Shoulson I. Reasons for Premature Conclusion of Late Phase Clinical Trials: An Analysis of ClinicalTrials.gov Registered Phase III Trials. *Ther Innov Regul Sci* 2019: 2168479019830648.

The CONSORT Group (2010) 14b. Reason for stopped trial URL <http://www.consort-statement.org/checklists/view/32--consort-2010/103-reason-for-stopped-trial> [accessed on May 24, 2019]

Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. *JAMA* 2003; **289**: 2128-31.

Boyd K. Commentary: Early discontinuation violates Helsinki principles. *BMJ* 2001; **322**: 605-6.

Table 1. Reasons for trial discontinuation by funder and overall for terminated and withdrawn eczema trials.

Reason for trial discontinuation	Non-industry funded n (%)	Industry-funded n (%)	All studies n (%)
Not stated	8 (26%)	7 (21%)	15 (23%)
Recruitment issues	8 (26%)	6 (18%)	14 (22%)
Sponsor (strategic/business) decision	0 (0%)	12 (36%)	12 (19%)
Interim analysis results	2 (6%)	3 (9%)	5 (8%)
Funding issues	4 (13%)	0 (0%)	4 (6%)
Safety issues	1 (3%)	2 (6%)	3 (5%)

Moved study location/investigator moved	2 (6%)	1 (3%)	3 (5%)
Limited time / clinical capacity	1 (3%)	1 (3%)	2 (3%)
Ethical approval lapsed	2 (6%)	0 (0%)	2 (3%)
Study materials expired	2 (6%)	0 (0%)	2 (3%)
Other	1 (3%)	1 (3%)	2 (3%)

“Other” included “contractual issues” (n=1) and “patients would improve naturally due to weather conditions” (n=1).