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# Investigators' sense of failure thwarted transparency in clinical trials discontinued for poor recruitment

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## Abstract

**Background and Objective:** When a randomized clinical trial (RCT) prematurely discontinues, it is essential that stakeholders do the right thing to ensure that lessons can be learnt and trust in clinical research is maintained. There is, however, a lack of evidence exploring this issue. This study aimed to examine clinical trial stakeholders' practices following trial discontinuation due to poor participant recruitment and their views on implications of such discontinuation.

**Methods:** Individual semi-structured qualitative interviews were conducted with 49 clinical trial stakeholders from Switzerland (n = 39), Germany (n = 9) and Canada (n = 1) between August 2015 and November 2016.

**Results:** After interviews with 49 clinical trial stakeholders (75% male presenting), it was found that stakeholders were aware of the risks of premature trial discontinuation wasting limited resources, adversely impacting scientific evidence, and having negative personal and professional implications. However, barriers continue to undermine transparency regarding trial discontinuation in practice, with it being reported that most investigators of discontinued trials are failing to notify stakeholders or publishing their results. Investigators sense of failure and associated negative emotions were identified as a key reason why investigators are not more transparent following discontinuation.

**Conclusion:** The decision to notify stakeholders and publish results of a discontinued clinical trial should not rest solely on individual investigators but come from a systemic approach. However, until health research proactively requires the dissemination of results of all clinical trials, much will rest on individual investigators being motivated to do the right thing. Support programs might be helpful for investigators involved in discontinued trials and promote transparency and learning lessons. 

*Keywords:* Randomized controlled trials; Trial discontinuation; Participant recruitment; Transparency; Trial stakeholders; Implications; Qualitative research

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**What is new?**

- Premature discontinuation of clinical trials due to poor recruitment leads to waste of limited resources, adversely impacts scientific evidence, exposes participants to risks despite no knowledge gain, and has negative personal and professional implications for trial investigators.
- Trial investigators' sense of failure and associated negative emotions hinder investigators to transparently notify stakeholders of trial discontinuation or to publish the data and learnt lessons from discontinued trials.
- Clinical trial stakeholders are typically aware of negative implications of trial discontinuation, but as long as systemic measures to promote transparency are lacking, it rests on individual investigators being motivated to do the right thing.

## 1. Introduction

Randomized clinical trials (RCTs) are a cornerstone in the evaluation of preventive and therapeutic healthcare interventions. However, empirical evidence suggests that 20%–25% of initiated RCTs are prematurely discontinued; with poor participant recruitment being the most frequent reason [1–4]. Furthermore, trial discontinuation due to poor participant recruitment appears much more prevalent with investigator-initiated clinical trials (IICTs) than with industry-initiated trials [1,2]. Such premature trial discontinuation constitutes a huge waste of scarce research resources, and threatens to undermine patients' and the public's trust in clinical research.

Publishing the results of clinical research has been described as an "ethical imperative" [5], and non-publication of discontinued trials may lead to replication of unsuccessful approaches and compromise the results of systematic reviews and meta-analyses that inform clinical decision-making and health care policy. Previous research indicates that furthering scientific knowledge and helping other patients are two key motivators for participants to consent to being involved in clinical trials [6], and the International Committee of Medical Journal Editors argues that "patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions" [7]. The Declaration of Helsinki also makes it clear that clinical trial investigators are required to not only register their clinical trials but publish or otherwise make publicly available their results [8,9]. However, a retrospective review of archived protocols in Switzerland, Germany, and Canada between 2000 and 2003 found that 58% of trials discontinued due to insufficient recruitment remain unpublished [1]. A recently published evaluation of oncology trial results reporting over 10 years also found that discontinued trials were less likely to report results compared with completed trials [10]. An analysis of all registered trials completed at German university medical centers between 2009 and 2013 found that only 39% published their results in a timely manner (less than 24 months after completion), and 26% of trials had still not published results more than 6 years after study completion [11]. Furthermore, previous qualitative research with clinical investigators indicate that many investigators are "generally unaware of the implications for the evidence base of not reporting all outcomes and protocol changes" [12].

Previous research and anecdotal evidence also suggest that research ethics committees and participants are often not informed about the decision and the reasons for trial discontinuation [1,13]. According to the Declaration of Helsinki, ethics committees are entitled to monitor the progress of approved studies, and researchers should notify ethics committees of changes to the protocol and submit a final report to the committee including a summary of the studyś findings and conclusions [8]. However, the study of archived protocols in Switzerland, Germany, and Canada also found that ethics committees were informed about discontinuation due to insufficient recruitment, futility, or harm only in 32%, 43%, and 57% of cases, respectively [1]. Research ethics committees spend considerable resources on reviewing protocols of planned studies. However, many of them are under-staffed and their members serve on a voluntary basis. The fact that ethics committees may not be able to proactively follow-up approved RCTs systematically due to limited resources undermines feedback loops for quality management and monitoring of problems.

While it is important that efforts are made to reduce the number of RCTs that are discontinued, it is also essential that when a RCT does prematurely discontinue, stakeholders do the right thing and transparently report what has happened to ensure that lessons can be learnt and trust in clinical research is maintained. There is, however, a lack of evidence exploring this issue. This study therefore aimed to examine clinical trial stakeholders' practices following trial discontinuation due to poor participant recruitment and their views on implications of such discontinuation.

## 2. Methods

The regional ethics committee of Northwestern and Central Switzerland exempted the study from an ethics review in line with Swiss law (EKNZ UBE-15/50). The study methods are presented in accordance with the "Consolidated criteria for reporting qualitative research" (COREQ) [14]; see *Supplementary file 1*.

### 2.1. Research team and reflexivity

*Personal characteristics:* Interviews were primarily conducted by P.S., a female Post Doc in biomedical ethics, and M.B., a male physician and senior scientist in clinical epidemiology. Both interviewers have longstanding experience with qualitative research [15–20].

*Relationship with participants:* The interviewers had already had contact with a number of the stakeholders from previous research studies. Otherwise, no relationship existed between the interviewers and the other participants prior to the study and participants received limited information about interviewers. There was no hierarchical relationship between the interviewers and the study participants.

### 2.2. Study design

The data from this exploratory qualitative study were analyzed using content analysis [21].

*Participant selection:* Stakeholders were selected through purposive sampling to ensure that interviewees involved in discontinued clinical trials were from different backgrounds [22]. Interviewees were primarily identified through our professional networks and through the database of our prior quantitative study on early discontinuation of clinical trials [1]. The prior study included RCT protocols approved by one of six research ethics committees from Switzerland, Germany, or Canada. The collaboration with ethics committees in the three countries was established through the professional network of MB. Interviewees were contacted by email and suitable dates for an interview were found with those willing to participate. A total of 49 clinical trial stakeholders agreed to participate in the study. The majority of interviewees (39/49; 79.6%) came from Switzerland; including 6 trial investigators with personal experience of a discontinued RCT, members of ethics committees (n = 3), clinicians with experience in clinical trials (n = 8), representatives of clinical trial support units (n = 6), patient organizations (n = 2), international pharmaceutical companies (n = 10), public health authority (n = 1), drug regulatory authority (n = 1), cancer research network (n = 1), and funding agency (n = 1). An additional 10 trial investigators with personal experience of a discontinued RCT were also recruited from Germany (n = 9) and Canada (n = 1).

Several interviewees provided multiple perspectives on trial discontinuation depending on their current and/or former professional role, for example, ethics committee members who previously worked as trial investigators. Verbal informed consent was obtained at the beginning of the interview, and was audio recorded and transcribed verbatim. 65 people contacted did not respond or refused to participate because they did not think they were the suitable person or because of workload issues.

*Setting:* Interviews were held between August 2015 and November 2016. The interviews were conducted in person or via a telephone call. All interviews were conducted in English. Only the interviewee and the researcher were present during the interview. Overall, 75% (37/49) of stakeholders were male presenting, and 25% (12/49) were female presenting.

*Data collection:* A researcher-developed semi-structured interview guide was developed for each group to guide the discussion (see *Supplementary file 2*). Based on the first two interviews that did not show any problems, it was decided that no further piloting or adaptation of the interview guides was necessary. No repeat interviews were carried out. Interviews were audio recorded, no field notes were taken. Interviews lasted an average of 50 minutes (range 40–70 minutes). After 49 interviews the question about data saturation arose and it was concluded that saturation was reached in the content and attitudes expressed by the interviewees [23]. Transcriptions of the interviews were returned to all interviewees with an invitation for them to review the transcription and send any corrections or clarifications; three responses were received with minor corrections to syntax.

### 2.3. Data analysis

Using the interview transcriptions in their original language, P.S. and M.B. performed content analysis [21] with the assistance of the qualitative software MAXQDA. Analysis commenced while interviews were ongoing. Initial themes identified common across participants as well as those unique to individuals were labelled using a process of open coding. Findings are presented as higher- and lower-level categories in a coding frame (Table 1, Table 2). The other investigators [S.M., B.E., E.v.E.] reviewed the initial analysis to clarify and refine codes, and conversations among the investigators continued until coding differences were resolved and consensus was achieved.

## 3. Results

A total of five key themes were identified regarding interviewees' practices following trial discontinuation due to poor participant recruitment and their views on implications of such discontinuation (Table 1, Table 2, Fig. 1). *Supplementary file 3* provides online Tables 3–7 with example quotes for each theme and subtheme.

### 3.1. Practices following trial discontinuation

#### 3.1.1. Reporting trial discontinuation to stakeholders

Only six of 16 investigators who had to discontinue trials due to low recruitment reported to have notified the responsible ethics committee, while only two said that they had informed trial participants. The other investigators indicated that they had not notified the responsible ethics

**Table 1.** Practices following trial discontinuation

| Theme | Sub-theme |
|---|---|
| Reporting trial discontinuation to stakeholders | Reporting discontinuation to patients |
| | Reporting discontinuation to ethics committees |
| | Reasons for not reporting trial discontinuation |
| | Strategies to improve reporting of discontinued trials |
| | Obligation to report discontinued trials |
| Publishing data/lessons learnt from discontinued trials | Challenges in publishing the results |
| | Alternatives to make the data available |

**Table 2.** Views on implications of trial discontinuation

| Theme | Subtheme |
|---|---|
| Waste of valuable and scarce resources | Loss of return on investment |
| | Reducing the pool of eligible/willing patients |
| Impact on knowledge production and scientific evidence | Unanswered research questions |
| | No knowledge gain despite participants being exposed to risks |
| | Room for (mis-) interpretation/spin of inconclusive results |
| | Loss of lessons learnt |
| Personal and professional implications for investigators | Demoralization of research professionals |
| | Diminished opportunities to participate in future trials |

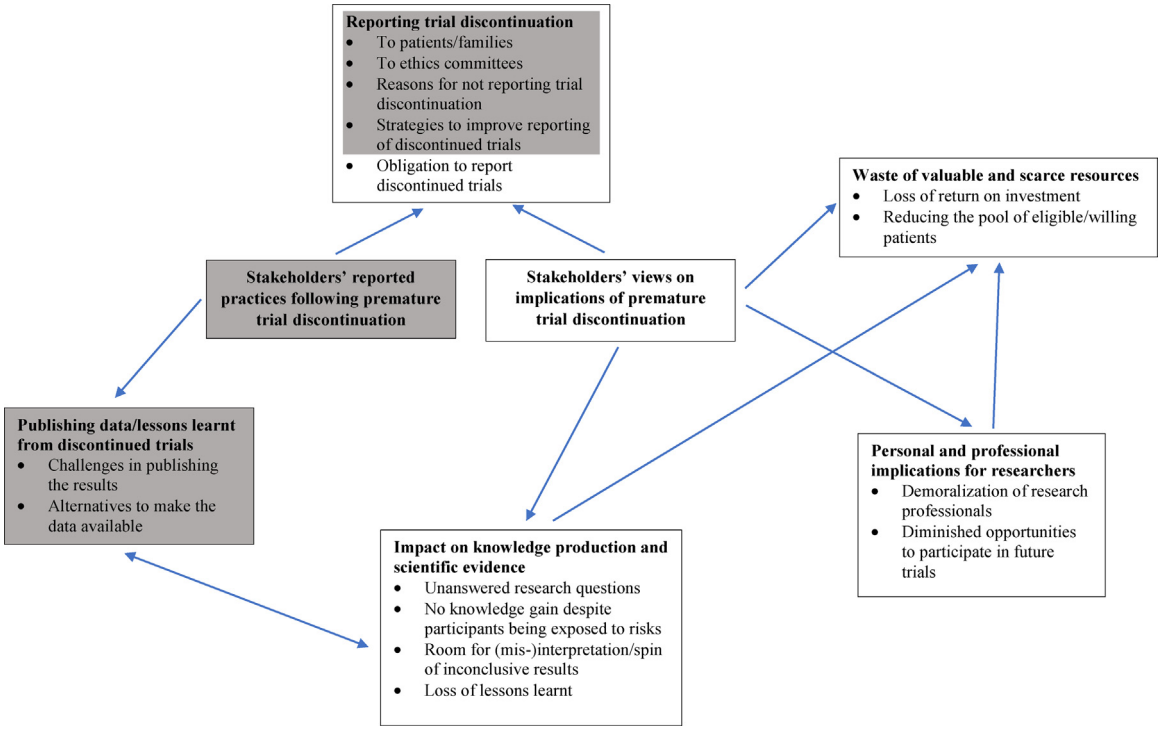


**Fig. 1.** Stakeholders' views on the implications of and practices around premature trial discontinuation.

committee or trial participants or could not recall what they had done. A sense of failure, together with desire to move on to the next project and high administrative burden, were key reasons given for not notifying stakeholders of discontinuation. Some investigators thought that proactive enquiries on trial progress from the responsible ethics committees and trial participants would likely have prompted them to report discontinuation.

In contrast, all non-investigator interviewees (eg, representatives of clinical trial units, ethics committees, pharmaceutical companies) stressed the importance of notifying not only ethics committees, but also funders

and regulatory authorities of the discontinuation, and documenting it in trial registries. They believed that many investigators, especially those affiliated with the academic research centers, are unaware of their ethical obligation to report trial discontinuation and identified the need for improved training regarding this issue. A few of them characterized this failure to report trial discontinuation as unprofessional behavior on the part of the investigators and as lack of oversight by ethics committees. More proactive monitoring of trial progress by research ethics committees and funding agencies, and improved training of trial investigators with respect to ethical obligations after trial discontinuation, were suggested as ways to improve reporting practices (see online Table 3 for selected quotes).

#### *3.1.2. Publishing data/lessons learnt from discontinued trials*

Only a minority of investigators with experience of discontinued trials reported publishing their findings in peer-reviewed journals. Several interviewees highlighted that finding a journal willing to publish the results from discontinued trials is far more challenging than publishing studies disproving a hypothesis due to low power and inability to draw meaningful conclusions. A few pointed out that these data could or should be made available in trial registries or open data repositories so that they can be included in meta-analyses. However, a few were critical of this approach stating that 'one cannot expect gold out of trash' and raising questions on the overall quality of trial conduct if it could not recruit the required number of study participants. Finally, several interviewees felt that a discontinued trial due to low recruitment often produces a sense of failure among investigators, making them reluctant to reflect on the valuable lessons learnt and sharing those with wider research communities through other outlets such as conference sessions, academic blogs, or short communications/letters in scholarly journals (see online Table 4 for selected quotes).

### *3.2. Views on implications of trial discontinuation*

#### *3.3.1. Waste of valuable and scarce resources*

Interviewees most frequently expressed concern was the resources that are wasted when a trial is prematurely discontinued; particularly in cases of publicly funded investigator-initiated trials. In addition to wasted funds, interviewees referred to other resources that go to waste, including trained personnel, healthcare and laboratory infrastructure, and the time invested by everyone involved in the discontinued trials. It was also highlighted that patients recruited to discontinued trials become unavailable for other trials, which was reported to be especially problematic in case of rare diseases (see online Table 5 for selected quotes).

#### *3.3.2. Impact on knowledge production and scientific evidence*

Interviewees highlighted how prematurely discontinued trials can adversely impact the scientific body of evidence and treatment options for future patients. If a trial is discontinued, the research question is not answered and the collected data is generally not made available to other researchers. Furthermore, interviewees noted that if investigators present a discontinued trial due to low recruitment as a pilot study and publish the results, they risk misinterpreting results and drawing unwarranted conclusions due to low power. Interviewees also thought that investigators' inability or reluctance to publish insufficiently powered studies or lessons learnt risks that others will repeat the same mistakes in planning their trials, which will lead to further waste of scarce financial and infrastructure related research resources (see online Table 6 for selected quotes).

#### *3.3.3. Personal and professional implications for investigators*

All interviewees extensively discussed the demoralizing impact of a discontinued trial on investigators. In addition to inducing a sense of failure, it generates enormous frustration. Despite significant commitment on the part of investigators, it was reported that negative emotions often limit investigators willingness to transparently discuss the reasons for failure or to undertake another trial. Pharmaceutical representatives also noted that in industry-sponsored trials, investigators affiliated with the academic sites that recruit sub-optimally rarely get invited to participate in future trials, thus influencing their careers and limiting their future opportunities in research (see online Table 7 for selected quotes).

## 4. Discussion

This qualitative interview study found that despite stakeholders being aware of the dangers of premature trial discontinuation, barriers continue to undermine transparency regarding trial discontinuation in practice. Investigators' sense of failure and associated negative emotions were identified as a key reason why investigators are not more transparent following discontinuation. Stakeholders expressed serious concerns about the waste of scarce research resources and the negative impact on knowledge production and scientific evidence associated with recruitment failure in clinical trials.

The finding that most investigators of discontinued trials are failing to notify stakeholders or publish their results, supports previous results [1,13]. This lack of transparency constitutes research misconduct [9], and is at odds with the move towards Open Science [24–26]. As it has been acknowledged in the clinical care context, however, the failure to do the right thing after things went wrong, typically reflects wider systemic issues [27–29]. Just as the decision to inform a patient about errors in clinical care should

not be shouldered by individual health care professionals but rather come from a systemic institutional approach, the decision to notify stakeholders and publish results of a discontinued clinical trial should not rest solely on individual investigators but come from a systemic approach. As Meerpohl and colleagues have noted [30], efforts to reduce dissemination bias in clinical research will need actions from various clinical research stakeholders, including funding agencies, pharmaceutical companies, research institutions, researchers, research ethics committees, trial registries, journal editors and publishers, regulatory agencies, health technology assessment institutions, and legislators. Although many of the recommendations Meerpohl and colleagues make are not new, as they note, they have so far not been widely implemented into practice [30]. Among the 47 targeted recommendations addressing 11 key stakeholder groups they make, is the strong recommendation that funders should include a statement on the requirement for the dissemination of results in funding calls, the requirement for applicants to provide a dissemination plan for funded projects, and the requirement that grantees explicitly declare in all funding contracts that results of funded research will be disseminated regardless of the nature of findings. In addition, it is strongly recommended that research ethics committees require that investigators register all clinical trials before the recruitment of the first participant, and provide annual reports describing the dissemination of their study results [30]. Interviewees of this study also called for funders and research ethics committees to monitor trials more closely. Unfortunately, until mentioned stakeholders mandate and enforce the registration [9], publication and dissemination of results of all clinical trials, much will rest on individual investigators being motivated to do the right thing.

Although improving trial investigators' training with respect to ethical obligations after trial discontinuation may be helpful, this study found that investigators' sense of failure and associated negative emotions were a key reason why they were not proactively notifying stakeholders and publishing results of a discontinued trial. We are not aware of previous research on the emotional impact that discontinued trials can have on investigators, and the influence this might have on investigators willingness to be transparent. However, it is well established in the context of clinical care that health care professionals can experience a significant emotional impact when things go wrong [31,32]. It has also been argued that a harm-causing error can be such an assault to some health care professionals' sense of competency and adequacy that various protective, self-regarding, and defensive psychological responses can be triggered, which can often lead to open communication being avoided altogether or conducted inadequately [33]. It is possible that something similar is occurring with clinical trial investigators following a prematurely discontinued trial. This is an issue that warrants further research. It may be worth exploring whether developing and implementing support programs similar to those used in clinical care following adverse events [34], might be helpful for investigators involved in discontinued trials and promote transparency and learning lessons. It also calls for a reform of what counts for scientific careers. Dealing correctly with failure should give a positive score.

Sharing the encountered recruitment difficulties with the scientific community is an important contribution to overcome similar problems in the future, since most reasons for recruitment failure could be anticipated in the planning phase of a trial [35,36]. Trial investigators need to be aware of potential risk factors to take preventive action according to the individual trial context. Training programs for trial investigators and staff such as the Quintet Recruitment Intervention could further help minimize recruitment problems and, hereby, contribute to the prevention of resource waste [37,38].

### *4.1. Strengths and Limitations*

The qualitative approach taken in this study allowed for a deeper exploration of a broad range of clinical trial stakeholders' practices following trial discontinuation due to poor participant recruitment and their views on implications of such discontinuation. Analysis of the interviews was also carried out by a research team to minimize systematic bias that can arise if the data had been analysed by only one researcher. However, there were 65 stakeholders (57% of invited) who did not reply to our emails or declined to participate. Whether the views of those people are substantially different from those who were interviewed is unclear. Many explained their refusal with their extremely busy schedules and priority given to other tasks. However, it may also be that openly discussing and analysing failures is not popular in the research community. A second limitation is that we conducted our interviews 5–6 years ago. Although we consider this unlikely, we cannot exclude the possibility that the expressed views by the interviewed stakeholders have changed in the meantime. A third limitation of our study is that we only included interviewees from three high-income countries: Switzerland, Germany, and Canada – with 80% (39/49) of interviewees coming from Switzerland. Although we did not find any obvious differences in viewpoints of interviewees depending on the country in our analyzes, further research involving more interviewees outside of Switzerland is needed.

## 5. Conclusions

The decision to notify stakeholders and publish results of a discontinued clinical trial should not rest solely on individual investigators but come from a systemic approach. However, until the wider system proactively requires the dissemination of results of all clinical trials, much will rest on individual investigators being motivated to do the right thing. Support programs might be helpful for investigators

involved in discontinued trials and promote transparency and learning lessons.

## CRediT Author statement

**Priya Satalkar:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – Original Draft. **Stuart McLennan:** Methodology, Validation, Visualization, Writing – Original Draft. **Bernice Elger:** Writing – Review & Editing, Funding acquisition. **Erik von Elm:** Writing – Review & Editing, Funding acquisition. **Matthias Briel:** Conceptualization, Investigation, Formal analysis, Visualization, Writing – Original Draft, Supervision

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2022.01.024.

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