MULTI-REGIONAL CLINICAL TRIALS
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COLLABORATIVE

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Research Interrupted: Early Clinical Trial Termination and Participant Withdrawal/Discontinuation from Trials

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Premature Clinical Trial Termination

Trial termination refers to situations in which a trial is permanently stopped before its planned completion, with participants no longer enrolled in the study and, in some cases, their participation halted mid-trial. Studies may be terminated early for scientific reasons, such as safety concerns or an interim conclusion that the study intervention is unlikely to be effective. They may also be stopped early for non-scientific reasons, including low participant enrollment, funding loss, business dynamics or decisions, or investigator departure. Empirical data suggests that early termination occurs in 12-31% of trials, with two-thirds of terminations being due to non-scientific reasons; poor recruitment is the most common cause, accounting for 40-57% of terminations.[1,2,3] The COVID-19 pandemic caused widespread trial suspensions and increased early termination rates, and more recently, approximately 3.5% of NIH-funded trials lost grant funding, affecting an estimated 74,000 participants.[4]

Early study termination has several consequences. Scientifically, it often prevents the realization of generalizable knowledge, yielding insufficient data for meaningful statistical analyses. Early termination also involves significant waste and opportunity costs, with investments from participants, funders, and institutions made in vain. Participants often face interruptions of care, loss of access to beneficial interventions, and risks that may be

[1] Kasenda B, Von Elm E, You J, et al. Prevalence, Characteristics, and Publication of Discontinued Randomized Trials. JAMA. 2014;311(10):1045. doi:10.1001/jama.2014.1361

[2] Speich B, Taji Heravi A, Schönenberger CM, et al. Nonregistration, Discontinuation, and Nonpublication of Randomized Trials: A Systematic Review. JAMA Netw Open. 2025;8(9):e2524440. doi:10.1001/jamanetworkopen.2025.24440

[3] 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. Briel M, ed. PLOS ONE. 2015;10(5):e0127242. doi:10.1371/journal.pone.0127242

[4] Patel VR, Liu M, Jena AB. Clinical Trials Affected by Research Grant Terminations at the National Institutes of Health. JAMA Intern Med. 2026;186(1):126. doi:10.1001/jamainternmed.2025.6088

unjustified in light of the study's failure to realize the wider benefits of generalizable knowledge.

While current regulations address participants' right to withdraw and require informing individuals that their participation could be ended without their agreement, they do not address ethical standards for when and how termination decisions should be made, mechanisms to ensure scientific value is extracted from terminated trials, and what investigators owe participants following termination.

The opening presentations reflected on post-termination responsibilities and their likely distribution across multiple stakeholders, including sponsors, funders, and study teams. While IRBs should review relevant early terminations to ensure participants are transitioned safely off studies, investigators and sponsors will ultimately be responsible for helping participants access other resources. Further, transparent communication to participants about termination and its implications is crucial, as is prospective allocation of resources for orderly trial closeout. However, the robustness of current practices on these points is unclear.

The opening remarks considered possible prevention and mitigation measures. Sponsors and funders currently conduct feasibility assessments before trial initiation, and investigators and study teams engage in recruitment planning and forecasting. Yet early study closures persist at high rates, underscoring the need for sustained discussion of best practices. More stringent checks to ensure realistic enrollment projections may be needed. IRBs may also have a bigger role to play. It is common for IRBs to review enrollment plans, but it is unclear whether they make an effort to identify, prevent, or require changes to studies at high risk of terminating early, or whether they have the information or resources to identify such studies or take effective actions. While consent form development begins with sponsors and investigators, IRBs can and should provide a check on disclosure practices and ensure that participants are adequately informed about the possibility of early termination. Institutions should establish processes to prevent early termination due to investigators retiring or departing mid-study, and to avoid excessive recruitment competition between concurrent trials.

Attendees agreed that minimizing the number of studies that terminate early is a shared responsibility, with no single entity holding all the information or power to accomplish this on their own. Despite this, there is a notable absence of systematic efforts to collect data on early study closures or identify termination predictors across the research ecosystem. Institutions may feel they lack leverage or adequate resources to prevent these situations, and the NIH, despite funding a large number of trials, lacks a centralized system to proactively monitor enrollment and termination risks. On the other hand, some industry

sponsors have developed internal policies requiring early termination decisions to be reviewed by an ethics committee, where financial considerations are separated from scientific ones.

The group discussed challenges in enrollment and recruitment that can lead to early termination. These include increasingly saturated US academic and community sites, which can lead to recruitment competition and a lack of investment in clinical trial infrastructure. Another recurring issue is PI departure mid-study, without succession planning. Successors are often reluctant to assume responsibility due to liability and reputational concerns related to the predecessor's data and performance. It was recommended that having a co-investigator at the outset is a practical mitigation strategy.

One attendee noted institutional measures designed to minimize these challenges, and another person noted that at least some sponsors monitor enrollment monthly, with trials that fail to meet 60% of their enrollment targets being placed on corrective action plans. There was interest in identifying early predictive markers of recruitment shortfalls, including metadata. Attendees noted that multiple factors could influence a study's likelihood to meet enrollment targets, including disease severity and prognosis, the nature of the intervention, available alternatives, site accessibility, and study design. It was also noted that AI-assisted analysis of terminated versus completed trials could further help identify relevant characteristics and factors.

The second speaker presented their company's effort to develop an ethical framework for determining their responsibilities in studies that terminate early. The framework incorporates multiple foundational assumptions relevant to the topic. These include the ideas that industry sponsors have a dual responsibility to innovate and deliver new products for unmet medical needs; that guidance on this topic should be timely and pragmatic to inform difficult prioritization and operational decisions; that resource stewardship is essential, as human and financial resources are finite and sustainability is imperative; that industry must navigate expectations from a wide range of stakeholders, including patients, advocates, regulators, payers, communities, and investors; and that it is crucial to be mindful of operational complexity, particularly for larger companies with global operations, where individual decisions can have a ripple effect across multilayered structures.

The framework was developed with reference to complex use cases, such as rare pediatric disease, that require complex manufacturing processes to produce the investigational product, multi-site trials spanning countries with different regulatory requirements, and programs that miss their primary endpoints but benefit a subpopulation. The framework includes guiding principles, ethical considerations, questions about governance and

activation time points, and a process for identifying high-risk programs. A key insight from this work is that identifying and discussing the possibility of termination early in the development process can enable effective contingency planning. Ultimately, the framework aims to avoid harm to trial participants, ensure fairness in the treatment of current and future participants, foster trust through proactive engagement and transparency, and emphasize responsible resource allocation and stewardship. It provides guidance to teams supporting patients, caregivers, healthcare providers, and future researchers, particularly when access to an intervention will be interrupted.

The third speaker provided insight into an NIH Department of Bioethics working group that arose in response to the early closure of numerous NIH-supported research studies since 2025. Listening sessions were held with extramural staff to understand the impacts of NIH-funded research studies being stopped early due to changes in or premature termination of NIH funding. At the time, NIH policies only addressed trial closure for safety, efficacy, and futility, but none addressed termination of research due to changes in funding.

The aim of the working group was to author and disseminate a report outlining how to close trials responsibly. The group organized the guidance around core research ethics principles or values. For each value, the group identified how trial closure may compromise it and points to consider for mitigation. For example, with respect to the principle that the risk/benefit balance of research must be favorable, the group considered how premature closure before data collection is complete can prevent the primary research question from being answered and can increase risk to participants and third parties. Proposed mitigation strategies included completing the trial as planned when possible, pivoting to address a revised research question using data already collected, sharing data or other information that may be valuable to other researchers, and arranging post-trial care for participants.

The group was faced with two open conceptual questions. The first regards the scope of continued spending on participant safety following grant modification. The group proposed that participant safety spending should include, at a minimum, preventing and treating adverse events caused by the intervention, long-term monitoring and management, minimizing risks associated with discontinuation, and ensuring participants do not disengage from the study without first receiving clinically actionable information.

The second open conceptual question concerns implicit commitments made to participants during the trial. The working group's stance was that participants have reasonable expectations that extend beyond the written informed consent and that exist regardless of what is explicitly stated. This raised the question of how implicit commitment should be defined and how it can be honored when trials close unexpectedly—a topic that warrants

further work.

The working group affirmed that participants should be fully informed about the possibility of early termination, not only at the point of termination but during the trial. Participants in terminated trials will typically benefit from a detailed follow-up that explains what happened and why. Participants often feel a sense of collaboration and sacrifice when involved in trials, which can lead to expectations that they be kept informed. Post-termination communication should include why the termination decision was made, what participants should expect regarding future trial opportunities, and an expression of gratitude and, when appropriate, regret. Participants in ongoing modified trials also have a right to understand the nature of the modifications, including whether the study will address a different question, carry less social value, or impose new requirements. These participants should be given the option to continue in the study under these new conditions or withdraw.

The discussion shifted to data and specimens collected in trials that terminate early, and whether they can or should be used for secondary research purposes. One member argued that early termination may breach the original research contract with participants, with downstream implications for how secondary use of data and samples should be governed. Another member shared that some industry consent forms include clauses anticipating discontinuation, suggesting that it would be helpful to address secondary use of data and biospecimens in those clauses.

Participant Withdrawal/Discontinuation from Clinical Trials

The Bioethics Collaborative then shifted to focus on individual participant withdrawal or early discontinuation from trials. This can happen when a participant decides to stop participating in the study on their own. It can also happen when a participant is discontinued by the investigator or sponsor, either because the participant meets individual withdrawal criteria or for other reasons.

Canonical research ethics documents (e.g., the Common Rule, FDA Informed Consent Guidance, 21 CFR 20.25(a)(8), CIOMS, and the Declaration of Helsinki) recognize the fundamental ethical idea that participation in clinical research is voluntary and that participants have the right to withdraw at any time. This must be explicitly communicated to participants during the informed consent process. In addition, informed consent must also address the anticipated circumstances under which a participant may be discontinued without their consent. Regulatory guidance further states that generic statements that allow the investigator or sponsor to withdraw a participant at any time appear inadequate, and that

investigators must specify the circumstances that may trigger termination.[5] Despite this, anecdotal evidence suggests that many consent forms do not adhere to this standard.

Individual participant withdrawal is common, with rates of 20-25% commonly cited across trials. The primary reasons for withdrawal include safety concerns, individual preferences, and noncompliance with study expectations. Safety-related withdrawal includes adverse events and worsening disease and/or co-morbidities. Withdrawal on the basis of individual participant preference is usually related to the burdens of participation, including time demands, travel requirements, and study complexity, as well as loss of interest, lack of perceived benefit, logistical challenges (e.g., relocation or employment conflicts), and financial toxicity (e.g., loss of insurance or unreimbursed expenses). Compliance-related withdrawals, as initiated by the investigator, stem from participant non-adherence to the protocol, missed appointments, and use of prohibited medications or substances, among others.

While withdrawal is typically presented as all-or-none—with participants either remaining in the study and committed to all study expectations, or leaving the study and being committed to none—it need not be. There do not appear to be any regulatory or ethical principles that prohibit more nuanced approaches, such as allowing participants to forego some planned study procedures while remaining amenable and committed to others. When participants express a desire to withdraw, thoughtful, shared deliberation should be the ideal, with the research team attentive to the participant's reasons, addressing any issues that can be corrected, and respecting aspects of the study the participant finds unduly burdensome.

For participants who show openness to continuing on the study with modified expectations, at least three options could be presented: (1) withdrawal from the study intervention alone, with a commitment to continued follow-up, safety monitoring, and data collection, which may include some procedures (e.g., blood draws, periodic imaging); (2) withdrawal from both the study intervention and any procedures, with non-intrusive follow-up and data collection still permitted, perhaps via telephone calls or other remote check-ins; and (3) complete withdrawal from all study participation with no further contact. Consent forms or other educational materials could address different withdrawal scenarios and clarify the right to withdraw generally, or notify participants that the investigator intends to have a detailed discussion with them about the available options should they wish to withdraw.

At the point of withdrawal or discontinuation, investigators also have responsibilities to

[5] U.S. Food and Drug Administration. Informed Consent: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors. FDA; August 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

participants. These include discussing what will happen with previously collected data and/or samples, as well as the participant's preferences regarding any plans for future data collection, such as EHR data access; plans for ongoing safety monitoring and adverse event reporting; arrangements for transitions in care where appropriate; and the participant's willingness to be contacted for future research. If the participant is willing, the research team may also explore their reasons for withdrawal, including which aspects of participation or the study design they found burdensome, and whether and how the research team might have better addressed those burdens. Such efforts can help contribute to more systematic evaluations of the reasons for withdrawal and the development of evidence-based corrective actions and mitigation strategies.

A concern was raised about the risks of allowing withdrawal to be highly flexible, specifically, in the scenario in which a participant will only remain on a trial if specific burdensome procedures are avoided. The concern was that opting out of individual procedures could undermine the trial's scientific integrity or lead participants to forego scientifically crucial, although subjectively burdensome, interventions. In response, another member suggested that certain procedures be designated proactively as required for continued participation, while others be elective, with this established in the study planning phase and communicated clearly.

One member questioned whether it is acceptable to require, at the outset, that a participant's data remain available even after withdrawal from active participation. It was noted that in FDA-regulated research, the FDA requires that data collected up to the point of withdrawal be used for planned study assessments. In non-FDA-regulated trials, some IRBs may have taken the position that when participants withdraw entirely, this may include withdrawing their previously collected data from use in planned assessments. A proposed alternative was to seek IRB approval for a waiver of consent to conduct record reviews of participants who have withdrawn, although drawbacks to this approach were acknowledged. A member shared that participants in cancer trials who withdraw due to toxicity associated with the intervention are still often enthusiastic about contributing to research and willing to consent to data sharing.

One institution shared that it has developed an IRB-approved withdrawal form that walks participants through all available options in non-pressuring language. Options include continued data collection without intervention, access to medical records only, or complete cessation of all research and data collection. The form also informs participants that they may still be contacted if information relevant to their safety becomes available, even after full withdrawal. The group agreed that being clear about flexibilities concerning withdrawal is

important. It was also noted that this process should ideally not significantly lengthen the initial consent process. Rather, it is enough to inform participants at enrollment that such a conversation will occur if and when they choose to leave the study.

The fourth speaker approached the topic of withdrawal from a trial operations perspective, noting that efforts to minimize the factors responsible for withdrawal should always begin at study design, by assessing participant burden and incorporating site-level input to assess participant impact. Proactive planning can also allow sponsors to equip sites with the flexibility to build individualized plans that account for differing participant needs, including those of caregivers, employment constraints, and transportation barriers. Ensuring sites have the resources to support participants throughout the study is important, particularly for long-term follow-up, which is often ethically crucial to ensure continued participant safety and scientifically essential to the study's objectives. Anecdotally, it was noted that in global oncology trials, for example, losing a single participant per site can eliminate up to 20% of endpoint data. A significant gap was identified in how withdrawal conversations are conducted at the site levels. PIs are rarely equipped with the right talking points to guide discussions about what aspects of a study someone finds burdensome or which aspects they would prefer to forego.

The fifth speaker, rather than approaching withdrawal as a tension between scientific integrity and patient autonomy, proposed reframing it as a patient-centered process focused on understanding what aspects of a study the participant finds burdensome. The speaker noted that their institution has developed an investigator-facing guidance document that walks investigators through withdrawal conversations, encouraging them to address the participant's transition to standard of care and to assess the participant's preferences regarding permission for follow-up data collection and contact for future research opportunities.

Lastly, reconsent at the time of disease progression, not uncommon in oncology research, was discussed. The speaker pointed out that it is an opportunity to have honest conversations about whether continued participation remains aligned with the participant's goals, and whether other options may better serve them. Participants who decline further treatment but continue contributing data are not considered fully withdrawn from the study. The institution distinguishes between active and passive follow-up in its continued review reporting, and members agreed that this distinction is important, as the data differ across other models.

The closing discussion focused on several priorities for moving forward. Members agreed that the research community should invest more in recruitment and enrollment planning, and in developing processes to enable more tailored individual withdrawal plans. Systematizing

the withdrawal process through structured conversations, standardized educational materials, and pre-approved language was identified as a potential deliverable. Lastly, the group acknowledged that no single approach will address the full range of withdrawal challenges given variability across trials and populations, and acknowledged the need for more targeted strategies based on systematic work identifying the most common drivers of early participant withdrawal.