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Sending Out an SOS: Rescuing Research Participants After An Alzheimer's Trial Stops Early

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Early on the morning of March 21, 2019, Nancy Childs awoke and—as is her habit—began scrolling through her news feed. There was bad news for her and her husband Mike. Biogen and Eisai had abruptly halted their Phase III trial of aducanumab to slow cognitive and functional impairment in persons with mild cognitive impairment (MCI) or dementia caused by Alzheimer's disease. Headlines described the trial's early end as "a major setback"[1] and "a blow to hopes for new treatment."[2] Biogen's stock plummeted with the news, posting its worst day in 14 years.[3] The Childs' hopes plummeted as well.

Mike Childs was 64 when he was diagnosed with MCI. He enrolled in the aducanumab trial because it offered "an opportunity that I would get better." For more than two years, Mike and Nancy, his study partner, regularly trekked from their home in New Jersey to the Penn Memory Center in Philadelphia, Pennsylvania. Participating in the trial was "pretty invasive" and "a hassle," but Mike was highly motivated to pursue this opportunity. By early 2019, Mike and Nancy knew that Mike was receiving aducanumab rather than a placebo because he was participating in an open-label extension phase, and he had recently agreed to extend his participation even longer. Mike had "done pretty well" in the trial, and it was "easy" for the couple to ascribe this to aducanumab.

News of the aducanumab trial's sudden end was unexpected and unwelcomed. Several hours would pass before the business day started and a "devastated" Penn Memory Center study coordinator—with whom the couple had developed a close relationship over their years of research participation—called Mike and Nancy to confirm the disappointing news.

Nancy analogized the end of the aducanumab trial and the emotions she and Mike experienced to being in a life raft in the middle of the Pacific Ocean. "There's no land anywhere in sight, no expectation of being rescued [from Alzheimer's disease]. But in the raft, we had people with skills, and provisions, and a plan." After learning the study had closed, Nancy felt like the raft was gone and she and Mike were "left to drown."

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Unfortunately, early trial closure has been a common occurrence in Alzheimer's drug development. In 2019 alone, Roche discontinued Phase III studies of crenezumab; Merck terminated its Phase III trial of verubecestat; Novartis, Amgen, and the Banner Alzheimer's Institute discontinued Phase II/III studies of umibecestat; and Eiasai and Biogen halted Phase III studies of aducanumab and, more recently, elenbecestat. These trials were stopped early after interim analyses suggested that the potential benefits of proceeding no longer outweighed the risks, due either to futility or safety concerns.

Many stakeholders were disappointed when these trials stopped early. For some participants, this disappointment was compounded when they learned about trial closure the way Mike and Nancy Childs did: abruptly and through media coverage. Here, we explain both why this happens and how researchers and study sponsors can do better to minimize the impact of this always unpleasant and sometimes traumatic event.

Participant Notification When Trials Stop Early

The decision to stop a trial early because of futility or harm is complex and requires weighing statistical and ethical considerations. A crucial challenge is to balance the well-being of individual participants enrolled in the trial with the broader social interest in generating reliable data for the benefit of future patients. In the context of Alzheimer's disease, where there is at present no disease-modifying therapy, if a trial is erroneously stopped early, a potentially valuable treatment may be lost. If a trial continues too long, participants may be adversely affected.

Once the extraordinarily difficult decision to stop a trial early is reached, there are numerous logistical challenges. An entire infrastructure has been built over years to advance the research, and now it must be brought to a definitive halt. Chief among these logistical challenges is the notification of hundreds or even thousands of participants at sites scattered across the world. It is essential to notify all enrolled participants for practical and ethical reasons. This seemingly straightforward step is, however, significantly complicated when a trial is sponsored by a public company. Notifying research participants or even study staff before notifying shareholders would run afoul of companies' legal obligations. Securities law makes it a crime for public companies to withhold material information from those with financial interests in the company. The law requires companies promptly disclose information that could affect stock prices.

The U.S. Securities and Exchange Commission recognizes a number of methods companies can use to satisfy the disclosure requirement. They include a "press releases distributed through a widely circulated news or wire service, or announcements made through press conferences."[4] Because the human and financial costs of Alzheimer's disease are so great and because a successful drug would be a blockbuster, when pharmaceutical companies employ a press release to fulfill their disclosure obligation (as many do), the news of trial closure garners significant media coverage. Therefore, even when study sites rush to notify participants (as many do), some individuals will learn the news like Nancy and Mike did. As they browse the web or watch their television, they will discover the trial they have been contributing to for months or even years has been halted.

Doing Better

The informed consent process and documents should make clear to participants that the trial in which they are enrolling may be stopped early for reasons of futility or harm. Some prospective participants may be aware of the recent history of Alzheimer's prevention trials and suspect that this is a possibility. Yet, it would be inappropriate to assume that participants have this particular knowledge. The informed consent disclosure should, therefore, make explicit that trials might be stopped early.

During the consent process, participants can also receive a brief explanation of the pharmaceutical company's legal obligations to notify shareholders should a trial be halted early as context for how participants will be notified. Then, participants may be given the choice to receive any press release issued by the pharmaceutical company about trial closure *at the time it is issued* on the condition that further, personal communication with the study site will follow. While notifying participants via a press release is impersonal and not on its own sufficient to discharge ethical obligations after early trial closure, it would address participants' concerns that they are the last ones to be notified that a trial has been stopped early, comply with current securities law and human subjects regulations, and require a minimal expenditure of time and resources given that the press release could be shared with participants via email or text message.

Should a trial be halted, the press release can acknowledge participants' contributions, as many already do, but should also include an overview of next steps and general instructions for affected participants so as to minimize their uncertainty. For example, participants might be told that a follow-up appointment to close out their participation will be scheduled by the study site. In addition, information about steps that would be taken after early study closure could be outlined in the informed consent documents so that patients have it available for reference.

Pharmaceutical companies should share details about the study's results with participants. Participants and their study partners—whatever their motivations for participating—are doing an important service for the field of Alzheimer's disease research. While there is no legal obligation to share the results of a trial, there is an ethical requirement to inform participants of what is learned from research in which they participated.[5] Negative findings and plans not to market the product do not abrogate this requirement.

Study sites also have ethical obligations to protect and promote participant well-being. Sites build trust-based relationships with participants to foster recruitment and retention. Moreover, the regular rhythm of study visits can foster a closeness and rapport between participants, study partners, and staff. Occasionally, participants reflect how they see members of the study team more often than they see their own children or grandchildren. Thus, the unexpected end of a trial is the loss of a network of trusted and well-liked advisors. For some participants, it may be a sort of trauma, akin to a death or sudden and devastating illness. Sites should, therefore, treat early closure of a trial like they do an adverse event, conducting wellness checks in the days after an announcement, providing

additional supports to participants who would benefit, and connecting them with resources as needed.

Conclusion

Alzheimer's disease uniquely implicates individuals' sense of identity and dignity. The unexpected end of a trial can be, in Nancy Childs's words, "another dimension of loss." Respect for persons requires that we treat participants—and their study partners—in ways that acknowledge identity and promote dignity throughout trials but also when they end.

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