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PERSPECTIVE

Early termination of pivotal trials in Alzheimer's disease—Preserving optimal value for participants and science

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Abstract

Participants in Alzheimer's disease late-phase clinical trials are frequently confronted with a situation of early termination. We discuss measures to protect the perceived value of study participation and to maximize the scientific value under such circumstances. A communication strategy should ensure that trial participants maintain a positive relationship with the research team and have their informational needs optimally met. Measures to maximize the scientific value may include data/sample sharing, strategies for personalized medicine, as well as scientific follow-up. Critical for the success of such a concept are networks of excellence, extending models of existing initiatives like Global Alzheimer's Platform Foundation Network (GAP-Net).

These networks could fundamentally strengthen the role of clinical investigators if they decide on their involvement in trials based upon their estimation of the scientific value and benefit for the participants, actively contribute to scientific analyses, and mediate optimal communication among the relevant trial stakeholders.

1 | INTRODUCTION

1.1 | Interim analyses and early termination

The major reasons for interim analyses in Alzheimer's disease (AD) are to stop study subjects from exposure to unnecessary risk and inconvenience, and to direct resources toward more promising strategies.[1] However such analyses also have the inherent risk of drawing a wrong decision based on an incomplete data set, with potential detrimental consequences for millions of patients.[2]

The discussion of whether futility analyses are useful and how they should be performed is beyond the scope of this article—we aim to illustrate how the benefit of an early terminated trial can be maximized. Many of our recommendations can also be used to improve the scientific output of clinical trials in general.

For the purpose of this perspective paper we refer to null trials when they do not demonstrate a significant treatment effect (null finding) and to negative trials when there is evidence that the intervention may have caused more harm than benefit (negative finding). We want to stress the scientific importance of trials when they indicate the absence of a treatment effect or point out a risk of an investigative product that has not been previously noted.

1.2 | Measures to minimize the risk for null or negative trials

Reasons for null or negative trials in AD and potential strategies to increase the likelihood for success have recently been reviewed in detail.[3,4] Reasons include inadequate understanding of the complex AD pathology, wrong selection of main treatment targets, inappropriate drug dosages, as well as methodological issues.[3] Especially the conduct of robust phase II programs—who should ensure target engagement, adequate dose selection, and indicate a clinical benefit—could help to reduce the risk of null or negative findings in phase III, which clearly would be the gold standard, but it is not the focus of the current publication and we will not elaborate further. Establishing an accurate diagnosis with the help of biomarkers may increase as well the

likelihood of success.[4] Furthermore, it could be helpful to determine measurement error before the start of a trial and use a trial simulator to guide endpoint selection as well as trial design. In this context, a longer trial duration could increase the likelihood of detecting a given treatment effect.[5]

1.3 | Preserving benefit for patients and science in case of early termination is important

Although newer trials have implemented some of the aforementioned recommendations, early termination is still a frequent event. Since 2015, four phase III programs studying beta-site amyloid precursor protein cleaving cnzyme (BACE) inhibitors, including the CNP 520 arm of the Generation Trials, were prematurely and permanently discontinued.[6–10]

With respect to anti-amyloid monoclonal antibody therapies, the studies on crenezumab (CREAD 1 and 2) were terminated early, whereas the solanezumab (Expedition III) study was completed but did not demonstrate efficacy. Subjects that participated in the SCarlet RoAD and the Marguerite RoAD phase III trials on gantenerumab were offered the chance to participate in open-label extension trials with a titration to higher doses.[11]

Thus, if a patient enters a phase III clinical trial on AD there is high risk that he or she will be confronted with a situation of early termination after an interim analysis which can, as was the case of some of the BACE Inhibitors, even indicate negative effects on cognitive function. Stopping trials on the basis of interim analyses raises important interconnected issues involving communication with participants as well as extracting optimal value from the data gained. We discuss approaches to more thoroughly educating participants on the value of interim analyses as a basis for early termination of the trial as well as collaborative approaches to gaining the greatest degree of knowledge. The stronger the case that even trials that are terminated early provide important knowledge, the stronger the case for participation in trials that have a likelihood of early termination.

2 | PRESERVING THE VALUE OF A TRIAL FOR TRIAL PARTICIPANTS VIA OPTIMAL COMMUNICATION

Clinical trials are only possible with the consent of patients and their partners willing to dedicate their time and accept the uncertainty with respect to risks and benefits. Meeting their informational needs may be critical for the perception of a trial as well as for the scientific quality, especially in the case of early termination.

Early involvement of patients and partners, for example, via focus groups or delegates from patient organizations, may be useful to assess the understanding of the trial design and the patient information material. They could provide input on how they would like to be informed in case of early termination and which information they want to receive with respect to individual level and group level data. In addition, the use and acceptance of digital devices may be discussed, as these could be used for communication including recruitment and retention, informed consent process, data collection, and analytics.[12]

HIGHLIGHTS

- Early termination of clinical trials in AD is still frequent despite improved trial design
- Communication is critical to protect the perceived value for trial participants
- Data and Sample sharing adds to the scientific value of a clinical trial
- Academic experts in AD shall have a strong influence on scientific trial aspects
- Networks of academic trial centers could ascertain optimal trial conduct and scientific value

2.1 | Subjects may perceive a benefit from trial participation—thus the scenario of early termination needs to be carefully anticipated

During the informed consent procedure, subjects are usually informed about the possibility that a trial is stopped upon the decision of the sponsor.

Investigators need to assess the capacity of the subjects to provide consent, which also includes an assessment of the understanding of the trial. This assessment provides an opportunity to identify and to address therapeutic misconception according to Applebaum.[13]

Irrespective of therapeutic misconception, central motivational aspects of many trial participants and their trial partners are the hope that the trial participation may be beneficial for them and that their participation will be beneficial for medical research.[14,15] Positive effects of participation in trials in AD are perceived even in the absence of a therapeutic effect.[16]

Participants in AD trials mention positive aspects of disease monitoring, support, coping, mental stimulation, feelings of value, and positive personal experiences.[15] Thus early termination in case of futility or even safety issues may have a negative impact, or lead to disappointment in trial participants.

In our view, the possibility of a negative or null finding should be discussed in detail during the informed consent process, and the scenario and circumstances of an early termination should be anticipated. The goal is to prepare the trial subjects for this potential scenario. By carefully addressing the scientific value that a trial with a negative or null finding might have, the perceived value of study participation could be preserved.

2.2 | Communication in case of early termination shall be timely and personal

From our experience, early termination in pivotal trials is frequently communicated to the general public via press release, and almost simultaneously to the site investigators. Thus participants and

investigators do not have an advantage in information access. Investigators need to ensure that participants are informed in a timely manner and be able to optimally meet their information needs.

Here, a strategy, either site specific or centrally provided by the sponsor, should be in place beforehand. Clearly the content of such a communication cannot be foreseen. Therefore, a strategy may be generic, for example, informing the patients within a timely manner on the termination and already scheduling a second conversation with the principal investigator. We believe that it is crucial to provide an opportunity for the patients to ask questions after being confronted by various sources of information and enable a personal contact.

Ideally, a communication statement for the investigators is prepared by the sponsor and information is provided to the participants in a personal contact through their site investigators. Here it is critical to maintain a positive relationship, as the positive influence of research on participants in AD studies seems to be closely connected to positive encounters with the researchers.[17]

Ideally, researchers should also be able to meet the requests for individual-level study results.[18] Participants in focus groups consisting of research participants have indicated that they want information relevant to their needs and priorities, including individualized findings, and endorsed having a personal physician deliver sensitive or negative research findings.[19] From our experience, participants especially want to know their group allocation and their individual cognitive test results over time, which in AD can be helpful tools to guide future clinical decisions.

Sponsors could facilitate this information by providing graphical individual trajectories of the test assessments. We propose that sponsors, together with experienced clinicians and patient representatives, discuss which trial data are of potential clinical value and include a feature that enables sharing of such data in their data management system. It shall not be mandatory to provide such information; however, information should be available upon request in a consumable and appealing manner. Alternatively, the site investigators could directly construct such trajectories.

MDs may face beliefs of study participants that the situation of the subjects could worsen with the interruption of the study drug. In this context it is important that they are familiar with the heterogeneity of clinical course and can explain that rapid progressive or stable courses also occur under natural conditions. We were neither able to identify empirical data on how early termination is perceived by study participants nor official guidelines on communication. We want to encourage activities toward that direction. We found one study that described the use of telephone conferences to inform participants about interim results in a study on early Parkinson's disease.[20] The authors valued the approach for fostering connections between participants and study leaders.

Addressing communicational aspects might be especially important in the context of trials where disclosure of AD biomarkers occurs or when a negative benefit to risk profile becomes evident. Of interest, an HIV-1 vaccine trial was terminated due to futility, and subsequent analyses revealed increased HIV infection susceptibility in a subgroup. When participants were interviewed, their strongest criticism was about perceived delays in unblinding and gaps in information dissemination and not about the undesired outcome per se.[21] Data about how communication is perceived in case of early termination and what impact it has on well-being and attitudes toward the trial or research in general could systematically be gathered at a visit following the event of early termination, for example, via a questionnaire already anticipated in the study protocol for such an occasion.

When negative or null results are communicated, strong feelings of disappointment among participants, trial partners, sponsors, as well as trialists may occur. Such feelings should in no case derail the effort to maximize trial integrity by ensuring the necessary follow-up procedures. In this context a focus on the scientific value also of negative or null trials from the very beginning may enhance compliance with study visits.

2.3 | Participation in alternative trials shall be supported

Subjects who have participated in a futile trial may want to enter additional research programs. Exclusion from such programs could be perceived as a disadvantage as it reduces their opportunities for action.

Here an inclusion is generally feasible for subjects on placebo; thus the information on allocation should be communicated in a timely manner. Specialized study centres that have a portfolio of diverse studies could enable a swift transition from one trial to another. Sponsors may want to exclude participants from the intervention arms of previous trials to reduce additional variability.

However also an inclusive strategy could be of strong scientific interest as treatment combinations may constitute a way forward in AD.[22]

One example would be sequential testing of drugs, for example, an anti-tau drug trial in subjects who had previous anti-amyloid treatment. Sponsors and investigators could support such trials by developing clinical research protocols that allow inclusion of subjects from former interventional arms.

Another possibility for keeping subjects associated with trials would be to extend the use of platform trials. The opportunities and challenges for expediting drug development in AD by using platform trials were recently discussed by the European Union/United States Clinical Trials in Alzheimer's Disease (EU/US CTAD) task force. The task force acknowledges the success of the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) in building up a global network of trial sites and to develop a platform, which offers the possibility of testing multiple drugs and targets in parallel, using a pooled placebo and control group as well as adapting the trial in response to biomarker findings.[23] This clearly indicates the possibility of multinational networks working together in conducting trials.

3 | OPTIMIZING THE SCIENTIFIC VALUE OF A TRIAL OUTSIDE THE PRIMARY OUTCOMES

3.1 | Data and sample sharing to increase research efficiency

There is a growing consensus that data sharing is paramount to scientific research. The International Committee of Medical Journal Editors believes that responsibly sharing data from clinical trials is an ethical obligation.[24] Sharing individual patient level data would increase the efficiency of research and development, and guide future projects.[25] In the field of AD, sharing of active treatment arm data would allow study of the effects of targeted pharmacological interventions, for example, amyloid removal, on other physiological parameters, for example, functional MR-measurements. Thus, data sharing would justify the use of considerable resources and add to the value of clinical trials. Obstacles to overcome include time and resource constraints, insufficient patient consent, confidentiality issues, lack of permission to share data, lack of credit for analyses based on shared data, and the concern that competitors may benefit from analyses based on shared data.[26] Articles dealing with best practice guidance about trial data sharing have been published in recent years, for example, Ohmann et al. in 2017.[27] Platforms that facilitate the sharing of patient level data have emerged. The Yale University Open Data Access (YODA) Project has facilitated access to clinical trial data since 2013.[28] As of July 20, 2021, more than 20 AD trials including the phase III trials on Bapineuzumab (NCT00574132, NCT00575055) were listed on this platform. Clinicalstudydatarequest.com, a platform used by several industry sponsors, lists over 30 trials in the field of AD. Vivli, which aims to link existing data platforms but also to host data,[29] lists 61 studies in the field of AD but there is overlap with the aforementioned platforms. Detailed guidance on how data can be accessed and the data sharing policy are available on the respective websites (please see Table S1 for web links). In addition, data sharing has led to the successful creation of drug-development tools and methodologies.[30] The Coalition Against Major Disease created an Online Data Repository for AD studies conducted by different sponsors, which was a key component in the successful development of a clinical trial simulation tool for mild and moderate AD[31] (please see Table S1).

To examine whether the considerable efforts for data sharing are scientifically justified one study examined publications that reuse randomized controlled trial data from YODA, Vivli, and clinicalstudydatarequest.com up to December 2019. The authors identified 89 reuses, with secondary and meta-analyses being the vast majority. They found no differences in social attention for the publications arising from reuse compared to matched publications in the same journals.[32]

We believe that the use and impact of data sharing could be increased if sharing occurs on a platform dedicated to AD and related diseases, hosted by a combined industry-academia network with a genuine interest in analyzing the data. The goal would be that all clinical trial data in the field will be shared through a single platform, which is anchored in the consciousness of the research community. Investigators deciding about engagement in a trial, and competent authorities shall be attentive to this sharing strategy. Harmonization of consent procedures and outcome assessment would facilitate data sharing. As progress in AD biomarkers is moving fast, we suggest that a biobank is linked to the data, and additional samples are collected with consent for scientific use, for example, post hoc genotyping, when new genetic variants become evident. Oversight by dedicated scientists in the field would enable the acquisition of harmonized state of the art data sets and complementary samples. A specialized platform would also facilitate the integration of specialized analytical tools. This is important in a model where data are not downloadable and used only in the environment of the platform to better control data access. Value enhancement of health or knowledge and favorable risk-benefit ratio are among the aspects that make research ethical.[33] Only if the scientific community succeeds in sharing all clinical and biomarker data in a highly usable and used format, will this optimize the risk-benefit ratio of any clinical trial in AD. If data potentially relevant for millions of AD patients remain unused, value enhancement remains below its potential.

3.2 | Addressing disease heterogeneity by fostering precision medicine

AD is a heterogeneous disease with respect to important parameters like distribution of pathology, age at onset, global cognitive status, disease duration, apolipoprotein E (APOE) genotype and biomarker levels.[34] The EU/US/CTAD task force discussed the value of targeted trials in AD and explicitly mentioned a biomarker adaptive threshold design and an adaptive signature design to address disease heterogeneity.[35] Adaptive strategies that can be implemented in phase III clinical trials include response adaptive randomization, sample-size reassessment, seamless designs, and adaptive enrichment strategies, which are comprehensively reviewed elsewhere.[36] In particular, adaptive enrichment designs that allow for the eligibility criteria to be changed, thereby restricting trial entry to patients who may benefit from the new treatment could be used to address disease heterogeneity.[37]

Ultimately, the strategy to address disease heterogeneity is precision medicine, with its goal to determine the most effective therapeutic approach for the individual. Systems pharmacology has been described as an integrative interdisciplinary disease modeling paradigm that aims to explore and predict the entire effect of a drug, providing the final biological output through body systems, with the goal of developing pathway-based, biomarker-guided targeted therapies.[38] We believe that it should be a central scientific aim of phase III trials in AD to foster precision medicine, which will enhance disease understanding and help to define innovative biomarker outcomes. Thus, we suggest that specialists in precision medicine strategies, who also have an in-depth knowledge of AD biomarkers, should be involved in trial design to define the relevant biomarker and sampling strategies.

3.3 | Subgroup analyses may guide current and future studies

Related to precision medicine is the detection of heterogeneity in treatment effects, which means understanding how a treatment's effect varies among patients to guide individual treatment decisions. However, the most common strategies, which divide patients sequentially into different groups based on single characteristics (eg, sex, age) and sequentially test whether the treatment effect varies among these groups tend to yield false-positive results. In addition, claims of effect consistency can be misleading due to lack of power to detect subgroup effects.[39]

Subgroup analyses may be performed as interim analyses or after a regular study closure. It has been argued that in pivotal trials of AD the trial should be stopped at interim only for safety reasons.[2] This would provide a complete data set as a solid basis for subgroup analysis.

Subgroup analysis can be confirmatory, exploratory, or aimed at subgroup discovery, which employs data mining and machine learning algorithms to identify subgroups to help the design of future trials.

In a recent article, the European Federation for Statisticians in the Pharmaceutical Industry and Statisticians in the Pharmaceutical Industry have evaluated plotting of standardized effects, bias adjusted bootstrapping, as well as subgroup identification based on differential effect search for subgroup detection in confirmatory clinical trials and found that these perform favorably when compared to traditional approaches.[40] In addition, with respect to subgroup discovery, strategies to address multiplicity, control model complexity, and to achieve bias-corrected reliable treatment effects for subgroups have been described in detail.[41] In our view, strategies for subgroup discovery should also be applied to phase III clinical trial data and made publicly available, either to guide decisions with respect to the current or to inform future trials. Subgroup analyses will also benefit from the availability of a common data platform for AD clinical trials as this might aid validation of subgroup effects.

3.4 | Additional scientific follow-up is valuable

A great example for the scientific value of follow-up-studies is the phase IIa clinical trial on the active immunization with aggregated amyloid beta (Aβ) 1-42 (AN1792) together with the adjuvant Q21. Clinical follow-up indicated beneficial effects in patients who had generated an antibody response and even a cerebrospinal fluid (CSF) tau decrease in antibody responders,[42] as well as hints for reduced functional decline over a longer follow-up period.[43] This supported the view that Aβ immunotherapy could be a useful target for the treatment of AD.

Long-term neuropathological follow-up revealed that most subjects with active vaccine showed evidence of plaque removal, and that post-mortem plaque scores correlated with post-vaccination antibody titers. In addition, plaque-free regions displayed fewer tau-containing dystrophic neurites and cell bodies.[44] This illustrates the scientific power of clinical trials if follow-up is continued in a stringent research setting.

3.5 | Multinational networks shall strengthen the role of the investigators and function as scientific hubs

A central recommendation to overcome barriers to the development of AD therapeutics was to realize economies of scope between research and drug development by establishing a network of comprehensive AD centers to promote the understanding of AD mechanisms and to speed the translation of this knowledge to the clinic.[45]

Initiatives pursuing the aforementioned recommendation are the GAP-Net[46] and was the European Prevention of Alzheimer's Dementia (EPAD) Consortium. Currently, according to their websites, GAP-NET includes over 80 trial sites in North America, whereas EPAD had about 39 involved institutions, about half of which were academic sites. Both initiatives made significant progress with their goal to provide trial-ready cohorts for clinical trials in AD.[47,48] EPAD terminated in October 2020 and its cohort of over 2000 participants will continue being followed in the context of IMI Neuronet. Thus, the scientific community shows considerable efforts to facilitate drug development in AD.

In Switzerland as a first step, eight Alzheimer's Research Centers have joined to develop an online registry of persons interested in participating in clinical trials and observational studies. Citizens can register, provide basic personal data, and express a preference for the geographical location of the center they wish to attend (Geneva, Bale, Lausanne, Zurich, Lugano, Fribourg, St. Gallen). Memory clinic researchers will contact registry participants wherever a trial fits their profile (please see Table S1 for web links to the aforementioned initiatives).

In our view, the European Network of Gynaecological Oncological Trials (ENGOT) could serve as a model for the AD field. ENGOT is a research network of the European Society of Gynaecological Oncology founded in 2007. They promote clinical trials in Europe in women with gynaecological cancer, and one of the scopes are clinical trials in cooperation with industry partners aiming to perform multinational studies with academic groups in Europe. ENGOT has published requirements for trials between academic groups and industry, which we cannot describe in their entirety. The central characteristic is that the network takes a central role in the setup, design, data analysis, as well as publication also in industry-sponsored studies.[49] Furthermore they were able to liaise with the GOG–Foundation, an important US-based institution in the field of gynaecological oncology with the result of joint requirements for trials with the industry.[50]

Recently they evolved a model to perform several phase I/II trials with one or more industry partners within an integrated program. To foster translation, they suggest a parallel academically led biobank together with a joint translational research plan or a translational research plan to be sponsored by an ENGOT group. The entire database of the program should be available for later analyses by academic groups and the scientific board associated with the program.[51]

The Collaboration for Alzheimer's Prevention has argued in a similar direction. They propose that in preclinical AD, all study data and remaining corresponding samples should be made available to the scientific community after certain predefined time points.[52]

3.6 | Our vision–a strong academic network for a strong partnership between academia and industry

We envision a future where industry-sponsored phase III studies in AD will be conducted in an environment dominated by a strong partnership between academia and industry and featuring a common data platform and biobank. The network could feature an agile multinational coordination board of national chapters of dementia centers of excellence, all of which will sign up to a strict code of conduct quality assurance. Performing a trial in this environment shall be regarded a marker of high quality of the trial.

Investigators and scientists from academia will be respected experts with strong expertise in the field of AD pathophysiology and biomarkers and form the academic steering board of the network. Following the ENGOT model, the academic steering board will appoint trial steering committees for individual trials that will work as partners of the industry sponsor. The network may also provide sponsors with resources, for example, template protocols, harmonized procedures for data acquisition, and biosample collection procedures.

After predefined scientific analyses by the sponsor and the trial-specific academic network committee, the joint database and biobank shall be open to scientific analyses outside the network, as agreed between academics and the industry partners.

The network may interact with patient organizations and decide upon involvement in clinical trials, based on the estimated scientific value and the anticipated burden and benefit for the participants. The network may also provide statements that could aid competent authorities in their decisions and could be involved in informing the public about the content and the scientific background. The goal would be to disseminate independent information complementary to the informed consent procedure, and to create interest and a scientific knowledge base for patients and their partners for the decision on trial participation.

4 | A BENEFIT FOR ALL RELEVANT STAKEHOLDERS

We believe that our suggestions may lead to a significant benefit for all stakeholders of AD clinical trials. The position of clinical researches will be strengthened when they can directly provide input to the scientific trial aspects and share their experience on patients' and trialists' needs with the industry. Communication with patients will be facilitated, which will also facilitate study conduct. Investigators may benefit directly from publications arising from collaborative efforts, which would be an additional incentive for academic sites for the participation in clinical phase III studies, as well as for the development of centers of excellence for the disease and trial conduct.

Patients and their partners are assured that their informational needs are optimally met and that the individual and scientific value of study participation is maximized. They would have access to comprehensive trial-specific scientific information.

The pharmaceutical companies may benefit from building trust of trial participants and society in general, which may increase the interest in study participation and thus facilitate timely recruitment. Scientific gain will speed up the drug-development process and may pave the way toward new treatment strategies or new indications for specific "personalized" subpopulations. In addition, the formation of networks as strong partners could reduce costs and time for setting up a trial structure. Sponsors may rely on high-quality data provided by the centers, especially when the centers are monitored for data quality, start-up times, trial conduct, protocol compliance, recruitment rates, and retention of patients in trials as in case of GAP-NET.[46]

The broader scientific community will benefit through the availability of highly harmonized data sets.

An optimized scientific output as well as an optimal individual value will satisfy these important aspects for the competent authorities as well as for the public. Competent authorities could directly consult with the network of investigators on critical trial aspects.

Research related to clinical trials will provide attractive funding opportunities for funding agencies due to their high clinical relevance and their milieu of highly harmonized and quality controlled scientific data and samples. For the sustained maintenance of a network as an ecosystem for scientific innovation, a basic operational structure of the network needs to be sustainably funded. Such an effort may be attractive for agencies like IMI who also funded EPAD. Two topics of the 2020 IMI2-Call 23 are related to aspects in this article, which is the return of clinical trial data to study participants in a framework compliant with data protection and a platform for accelerating biomarker discovery and validation to support therapeutics development in AD. The Davos Alzheimer's Collaborative has launched a 700 million dollar effort to foster precision interventions in AD, whereby one of the foundational goals is building a global clinical trial infrastructure. (Please see Table S1 for the respective web links.)

Finally, all parties are united in their desire to improve the therapeutic opportunities by high-quality and high-impact research, which can also be achieved in the context of a futile trial.

5 | CONCLUSION

We conclude that in the preparation of phase III trials on AD, the inherent risk of early termination or a null or negative trial should be carefully addressed.

Here the aspects of communicating with trial participants and ensuring optimal scientific value are strongly connected. Patients and their partners should have a positive experience and a feeling of value with respect to trial participation.

In AD, even an overall futile trial or a completed trial that did not demonstrate a significant treatment effect could lead to a strong gain in scientific knowledge that can be leveraged by data and sample sharing as well as additional follow-up. Strong engagement of patients

and their trial partners in the scientific aspects of the trial could strengthen the perception of value and motivate subjects to participate in scientific follow-up. The better we communicate the risk of early termination in advance, are able to meet the arising communicational needs and the stronger we build the case for gaining scientific value, the stronger will be the arguments for continuing or future trial participation for patients and their partners.

Central to effective trial conduct and optimal scientific gain is in our view the extension of already existing network initiatives that not only facilitate trial conduct but also provide strong input in trial design, communicational aspects, as well scientific analyses. Ultimately this will benefit all relevant stakeholders of clinical trials.

We are aware that many of our suggestions are not new and that there are several initiatives headed toward that direction but we hope that our article may reinforce those efforts and bring them to the consciousness of the broad readership of *Alzheimer's & Dementia*.

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CONFLICT OF INTEREST

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REFERENCES

1. Doody R. The role of futility analyses in Alzheimer's disease clinical trials. *Jpad-J Prev Alzheimers*. 2020;7(1):7-7. https://doi.org/10.14283/jpad.2020.1
2. Aisen PS, Raman R. Futility analyses in Alzheimer's disease (AD) clinical trials: a risky business. *Jpad-J Prev Alzheimers*. 2020;7(3):195-196. https://doi.org/10.14283/jpad.2020.20
3. Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou SH. Reasons for failed trials of disease-modifying treatments for Alzheimer's disease and their contribution in recent research. *Biomedicines*. 2019;7(4):97. https://doi.org/10.3390/biomedicines7040097
4. Cummings J. Lessons learned from Alzheimer's disease: clinical trials with negative outcomes. *Cts-Clin Transl Sci*. 2018;11(2):147-152. https://doi.org/10.1111/cts.12491
5. Anderson RM, Hadjichrysanthou C, Evans S, Wong MM. Why do so many clinical trials of therapies for Alzheimer's disease fail? *Lancet*. 2017;390(10110):2327-2329.
6. Wessels AM, Tariot PN, Zimmer JA, et al. Efficacy and safety of lanabecestat for treatment of early and mild Alzheimer's disease the AMARANTH and DAYBREAK-ALZ randomized clinical trials. *JAMA Neurol*. 2020;77(2):199-209. https://doi.org/10.1001/jamaneurol.2019.3988
7. Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. *New Engl J Med*. 2019;380(15):1408-1420. https://doi.org/10.1056/NEJMoa1812840
8. Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *New Engl J Med*. 2018;378(18):1691-1703. https://doi.org/10.1056/NEJMoa1706441
9. Novak G, Streffer JR, Timmers M, et al. Long-term safety and tolerability of atabecestat (JNJ-54861911), an oral BACE1 inhibitor, in early Alzheimer's disease spectrum patients: a randomized, double-blind, placebo-controlled study and a two-period extension study. *Alzheimers Res Ther*. 2020;12(1):58. https://doi.org/10.1186/s13195-020-00614-5
10. Henley D, Raghavan N, Sperling R, Aisen P, Raman R, Romano G. Preliminary results of a trial of atabecestat in preclinical Alzheimer's disease. *New Engl J Med*. 2019;380(15):1483-1485. https://doi.org/10.1056/NEJMc1813435
11. Aisen PS, Cummings J, Doody R, et al. The future of anti-amyloid trials. *Jpad-J Prev Alzheim*. 2020;7(3):146-151. https://doi.org/10.14283/jpad.2020.24
12. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *Npj Digit Med*. 2020;3(1):101. https://doi.org/10.1038/s41746-020-0302-y
13. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception - informed consent in psychiatric research. *Int J Law Psychiat*. 1982;5(3-4):319-329. https://doi.org/10.1016/0160-2527(82)90026-7
14. Grill JD, Karlawish J. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. *Alzheimers Res Ther*. 2010;2(6):34. https://doi.org/10.1186/alzrt58
15. Bardach SH, Parsons K, Gibson A, Jicha GA. From victimhood to warriors": super-researchers' insights into Alzheimer's disease clinical trial participation motivations. *Gerontologist*. 2020;60(4):693-703. https://doi.org/10.1093/geront/gnz096
16. Mastwyk M, MacFarlane S, LoGiudice D, Sullivan KA. Why participate in an Alzheimer's disease clinical trial? Is it of benefit to carers and patients? *Int Psychogeriatr*. 2003;15(2):149-156. https://doi.org/10.1017/S1041610203008834
17. Hedman R, Hellstrom I, Ternestedt BM, Hansebo G, Norberg A. Sense of self in Alzheimer's research participants. *Clin Nurs Res*. 2018;27(2):191-212. https://doi.org/10.1177/1054773816672671
18. Shalowitz DI, Miller FG. Disclosing individual results of clinical research - Implications of respect for participants. *JAMA-J Am Med Assoc*. 2005;294(6):737-740. https://doi.org/10.1001/jama.294.6.737
19. Cook S, Mayers S, Goggins K, et al. Assessing research participant preferences for receiving study results.*J Clin Transl Sci*. 2019;4(3):243-249. https://doi.org/10.1017/cts.2019.427
20. Augustine EF, Dorsey ER, Hauser RA, Elm JJ, Tilley BC, Kieburtz KK. Communicating with participants during the conduct of multi-center clinical trials. *Clin Trials*. 2016;13(6):592-596. https://doi.org/10.1177/1740774516665596
21. Newman PA, Yim S, Daley A, et al. Once Bitten, Twice Shy": participant perspectives in the aftermath of an early HIV vaccine trial termination.

Vaccine. 2011;29(3):451-458. https://doi.org/10.1016/j.vaccine.2010.10.076

22. Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. *J Alzheimers Dis*. 2019;67(3):779-794. https://doi.org/10.3233/Jad-180766
23. Aisen PS, Bateman RJ, Carrillo M, et al. Platform trials to expedite drug development in Alzheimer's disease: a report from the EU/US CTAD task force. *Jpad-J Prev Alzheimers*. 2021;8(3):306-312. https://doi.org/10.14283/jpad.2021.21
24. Taichman DB, Sahni P, Pinborg A, et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. *Ann Intern Med*. 2017;167(1):63-65. https://doi.org/10.7326/M17-1028
25. Green AK, Reeder-Hayes KE, Corty RW, et al. The project data sphere initiative: accelerating cancer research by sharing data. *Oncologist*. 2015;20(5):464-U24. https://doi.org/10.1634/theoncologist.2014-0431
26. Rockhold F, Bromley C, Wagner EK, Buyse M. Open science: the open clinical trials data journey. *Clin Trials*. 2019;16(5):539-546. https://doi.org/10.1177/1740774519865512
27. Ohmann C, Banzi R, Canham S, et al. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. *Bmj Open*. 2017;7(12):e018647. https://doi.org/10.1136/bmjopen-2017-018647
28. Ross JS, Waldstreicher J, Bamford S, et al. Overview and experience of the YODA Project with clinical trial data sharing after 5 years. *Sci Data*. 2018;5:180268. https://doi.org/10.1038/sdata.2018.268
29. Bierer BE, Li R, Barnes M, Global SimIA. Neutral platform for sharing trial data. *New Engl J Med*. 2016;374(25):2411-2413. https://doi.org/10.1056/NEJMp1605348
30. Karpen SR, White JK, Mullin AP, et al. Effective data sharing as a conduit for advancing medical product development. *Ther Innov Regul Sci*. 2021;55(3):591-600. https://doi.org/10.1007/s43441-020-00255-8
31. Romero K, Ito K, Rogers JA, et al. The future is now: model-based clinical trial design for Alzheimer's disease. *Clin Pharmacol Ther*. 2015;97(3):210-214. https://doi.org/10.1002/cpt.16
32. Anthony N, Pellen C, Ohmann C, Moher D, Naudet F. Social media attention and citations of published outputs from re-use of clinical trial data: a matched comparison with articles published in the same journals. *BMC Med Res Methodol*. 2021;21(1):119. https://doi.org/10.1186/s12874-021-01311-z
33. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA*. 2000;283(20):2701-2711. https://doi.org/10.1001/jama.283.20.2701
34. Ferreira D, Nordberg A, Westman E. Biological subtypes of Alzheimer's disease: a systematic review and meta-analysis. *Neurology*. 2020;94(10):436-448. https://doi.org/10.1212/WNL.0000000000009058
35. Vellas B, Carrillo MC, Sampaio C, et al. Designing drug trials for Alzheimer's disease: what we have learned from the release of the phase III antibody trials: a report from the EU/US/CTAD task force. *Alzheimers Dement*. 2013;9(4):438-444. https://doi.org/10.1016/j.jalz.2013.03.007
36. Park JJH, Thorlund K, Mills EJ. Critical concepts in adaptive clinical trials. *Clin Epidemiol*. 2018;10:343-351. https://doi.org/10.2147/Clep.S156708
37. Simon N, Simon R. Adaptive enrichment designs for clinical trials. *Biostatistics*. 2013;14(4):613-625. https://doi.org/10.1093/biostatistics/kxt010
38. Hampel H, Vergallo A, Perry G, et al. The Alzheimer's precision medicine initiative. *J Alzheimers Dis*. 2019;68(1):1-24. https://doi.org/10.3233/Jad-181121
39. Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ-Brit Med J*. 2018;363:k4245. https://doi.org/10.1136/bmj.k4245
40. Dane A, Spencer A, Rosenkranz G, Lipkovich I, Parke T, Anal PEWGS. Subgroup analysis and interpretation for phase 3 confirmatory trials: white paper of the EFSPI/PSI working group on subgroup analysis. *Pharm Stat*. 2019;18(2):126-139. https://doi.org/10.1002/pst.1919
41. Lipkovich I, Dmitrienko A, D'Agostino RB. Tutorial in biostatistics: data-driven subgroup identification and analysis in clinical trials. *Stat Med*. 2017;36(1):136-196. https://doi.org/10.1002/sim.7064
42. Gilman S, Koller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology*. 2005;64(9):1553-1562. https://doi.org/10.1212/01.WNL.0000159740.16984.3C
43. Vellas B, Black R, Thal LJ, et al. Long-term follow-up of patients immunized with AN1792: reduced functional decline in antibody responders. *Curr Alzheimers Res*. 2009;6(2):144-151. https://doi.org/10.2174/156720509787602852
44. Nicoll JAR, Buckland GR, Harrison CH, et al. Persistent neuropathological effects 14 years following amyloid-beta immunization in Alzheimer's disease. *Brain*. 2019;142(7):2113-2126. https://doi.org/10.1093/brain/awz142
45. Scott TJ, O'Connor AC, Link AN, Beaulieu TJ. Economic analysis of opportunities to accelerate Alzheimer's disease research and development. *Ann N Y Acad Sci*. 2014;1313:17-34. https://doi.org/10.1111/nyas.12417
46. Cummings J, Aisen P, Barton R, et al. Re-Engineering Alzheimer's clinical trials: global Alzheimer's platform network. *J Prev Alzheimers Dis*. 2016;3(2):114-120. https://doi.org/10.14283/jpad.2016.93
47. Ritchie CW, Muniz-Terrera G, Kivipelto M, Solomon A, Tom B, Molinuevo JL. The European Prevention of Alzheimer's Dementia (EPAD) longitudinal cohort study: baseline data release V500.0. *J Prev Alzheimers Dis*. 2020;7(1):8-13. https://doi.org/10.14283/jpad.2019.46
48. Walter S, Langford OG, Clanton TB, et al. The trial-ready cohort for preclinical and prodromal Alzheimer's disease (TRC-PAD): experience from the first 3 years. *Jpad-J Prev Alzheimers*. 2020. https://doi.org/10.14283/jpad.2020.47
49. du Bois A, Reuss A, Pujade-Lauraine E, et al. European Network of Gynaecological Oncological Trial Groups' Requirements for trials between academic groups and industry partners-first update 2015. *Int J Gynecol Cancer*. 2015;25(7):1328-1330. https://doi.org/10.1097/Igc.0000000000000478
50. Vergote I, Coleman RL, Pignata S, et al. Joint ENGOT and GOG foundation requirements for trials with industry partners. *Int J Gynecol Cancer*. 2019;29(7):1094-1097. https://doi.org/10.1136/ijgc-2019-000441
51. Concin N, Ray-Coquard I, Glasspool RM, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and industry partners - a new Model D for drug and medical device development. *Int J Gynecol Cancer*. 2020;30(6):730-734. https://doi.org/10.1136/ijgc-2020-001464
52. Weninger S, Carrillo MC, Dunn B, et al. Collaboration for Alzheimer's Prevention: principles to guide data and sample sharing in preclinical Alzheimer's disease trials. *Alzheimer's Dement*. 2016;12(5):631-632. https://doi.org/10.1016/j.jalz.2016.04.001

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