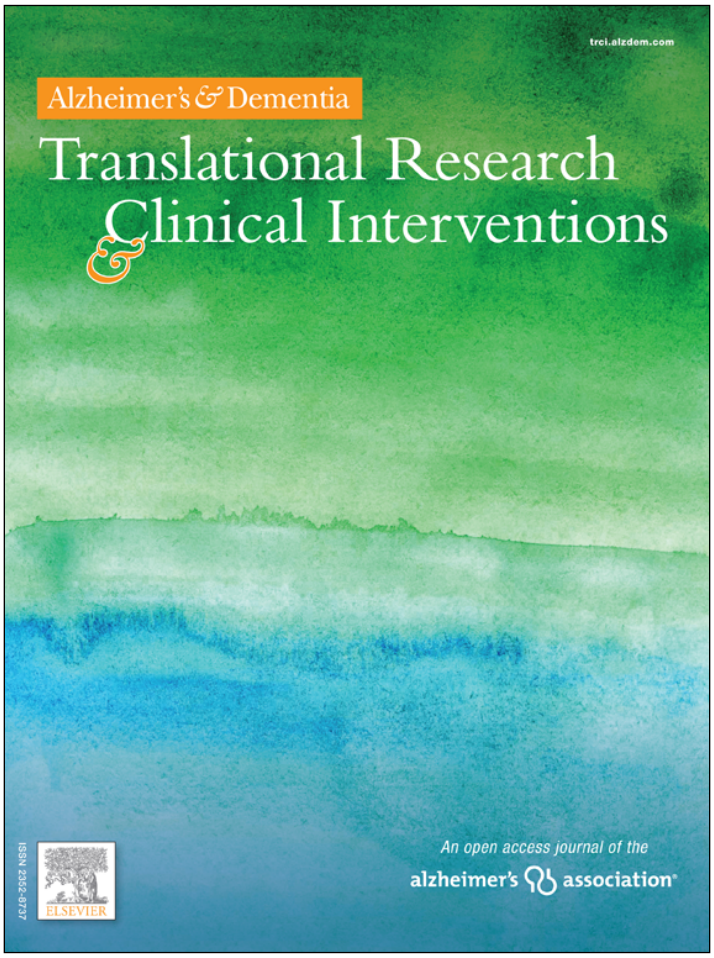

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Alzheimer's & Dementia

Perspective

Concise informed consent to increase data and biospecimen access may accelerate innovative Alzheimer's disease treatments

Ann M. Hake[a], Penny A. Dacks[b], Stephen P. Arnerić[c,*], CAMD ICF working group[1]

[a]*Eli Lilly and Company, Indianapolis, IN, USA*
[b]*Alzheimer Drug Discovery Foundation, New York City, NY, USA*
[c]*Coalition Against Major Diseases (CAMD), Tucson, AZ, USA*

Abstract

Introduction: Informed consent forms that restrict the distribution of data and samples have been an impediment to advancing Alzheimer's disease (AD) understandings and treatments. The Coalition Against Major Disease public-private partnership developed concise addenda to responsibly broaden data access of informed consent forms.

Methods: Coalition Against Major Disease members identified key elements for ensuring data and biospecimen access, and patient privacy protection according to applicable US law. Collaboration with the Alzheimer's Association established the understandability and relevance of the addenda with AD patients and Care Partners.

Results: Two key findings are (1) patients with dementia and Care Partners were shocked that their data and samples are not broadly shared and (2) with diverse feedback, two concise addenda were created to enable data and sample sharing both within and outside future sponsored studies (see Boxes).

Discussion: Increasing the access of valuable anonymized patient-level clinical trial data has the potential to inform the foundational and regulatory science required to deliver innovative treatments for AD.

Keywords: Alzheimer disease; Biospecimen; Consortia; Databases; Data sharing; Drug development tools; Informed consent; Regulatory sciences

1. Introduction

HeLa cells were one of the most important tools in medicine in the 20th century, vital for developing the polio vaccine, gene mapping, in vitro fertilization, and more. The original researchers at Johns Hopkins shared the cells freely and extensively for research. With time, a major industry was developed around the cells that were being bought and sold by the billions. *He*nrietta *La*cks, the woman who had unknowingly contributed those cells in 1951 remained unknown, when her legacy family was unable to afford health insurance. Central to the outrage expressed by her family is that the cells were taken and used without her informed consent.

Informed consent forms (ICFs) are now a central requirement of clinical research in the United States, intended to ensure that prospective participants understand the risks and benefits of the study and the purpose of the research before they agree to participate. This straightforward goal has been complicated in recent decades as ICFs have evolved into lengthy and technical forms designed to protect both the patients and the sponsors of the research study [1].

[1]Authors of the ICF—see acknowledgments for details and affiliations.
*Corresponding author. Tel.: +1-231-740-0268; Fax: +1-520-382-1389.
E-mail address: sarneric@c-path.org

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Box 1
Informed consent form addendum to ensure future data and sample sharing

Overview

The information collected in this study will be used to:

- see if the study drug works and is safe;
- compare the study drug to other potential or approved therapies;
- examine the relationship of the data and samples to that of other diseases;
- develop new tests;
- improve the design of future studies;
- advance the understanding of health and disease; and
- accelerate other activities (e.g., creation of clinical tools that improve the delivery of innovative treatments by advancing basic and regulatory science).

You will not be identified in any publication from this study or in any data files shared with other researchers. Your identity will be protected as required by law.

When the information from this study is shared outside the study site, the information that identifies you will be removed. In addition, the sponsor, like other sponsors, provides access to clinical data that have been further deidentified so that outside researchers can use these data. Information that could directly identify you will not be included.

Your rights: data and samples

You have the right to decide whether to participate in the study. If you decide to participate in the study, the following are groups with whom your study team may share your data and samples to improve new treatments or the conduct of clinical trials:

- Health authorities throughout the world (e.g., Food and Drug Administration, European Medicines Agency, and other governing bodies that review clinical trials).
- Institutional Review Boards that oversee and review the ethics of the research.
- The study sponsor and those working for or with the sponsor, which may include affiliates of the sponsor located in your country or other countries.
- Other groups: Examples of which include academic, government, or industry researchers; public-private partnerships; and/or external research collaborations. These entities will have oversight committees that will supervise the ethical use of the data and samples.

At no time will the data or samples be allowed to be sold by an individual or group for profit.

Your data and samples will be deidentified or anonymized. This means that your data or samples will not be linked with information that would allow any person or organization to determine that the data directly corresponds to you.

The health information you contribute will be protected by U.S. federal law (the Health Information Portability and Accountability Act).

New results obtained with your data and samples will be reported back to the sponsor and the results made publicly available.

You have the right to withdraw your permission for us to use or share your information up until the time that your data and samples are deidentified and pooled together into a database. Your data and samples will be used and shared as described in this form.

Potential benefits and risks

Benefits

Allowing your deidentified data and samples to become available to research and regulatory organizations could advance new treatments. By giving approval now for your data and samples to be shared for research purposes, your valuable contributions have the best chance to be used as effectively as possible for research not only today but also in the future as new research questions and technologies emerge.

Risks

Your deidentified or anonymized data may be shared for research purposes. Because your data and samples are deidentified (anonymized), the potential is extremely small that a person or organization could determine that it belongs to you.

However, anonymity cannot be absolutely guaranteed. Experts in reidentification may in very rare cases be able to reverse the processes used to protect your identity and confidentiality.

Withdrawal of consent

I understand I can withdraw permission to collect data/samples at any time but data already collected and pooled into the database will continue to be used. The study doctor/staff will discuss this with you.

Consent

I give permission to use and share my data and samples as described in this document.

The scope of research purpose has expanded for any given study. With technological advances for more than the past 50 years, the data and samples collected in one study can often be used for secondary research purposes, reducing the costs, time, and patient burden needed to develop effective therapies.

Many ICFs do not discuss secondary research purposes or corresponding data sharing, leaving the research participant uninformed and the data/samples lost in storage or destroyed. The need to share data and samples from clinical research has been increasingly recognized, with some leading groups describing it as an ethical obligation to the participants who may have put themselves at risk in interventional clinical trials [2–5]. In 2015, the National Academy of Sciences recommended the development of "templates for informed consent for participants that enable responsible data sharing" while explaining the potential risks to privacy, the protections deployed to mitigate this risk, and the conditions in which data sharing may occur [3]. An addendum to the ICF template that highlights the choice of expanded data and biospecimen sharing was recently developed by the Coalition Against Major Diseases (CAMD).

CAMD is one of 14 public-private-partnerships of the Critical Path Institute, dedicated to delivering on the vision of the US Food and Drug Administration's (FDA) Critical Path Initiative. CAMD convenes diverse stakeholders (academia, non-profit patient advocacy or research foundations, industry, and regulatory agencies) to collaboratively create tools and methods to advance new treatments for various stages of Alzheimer's disease (AD) and related neurodegenerative diseases. Many projects rely on the sharing of data or samples and, in some cases, could not be accomplished because ICFs had been used that did not include potential data sharing. At the same time, CAMD members from non-profit and for-profit entities strongly maintain the need to use data and samples in a manner consistent with the participant's consent.

Box 2
Abbreviated informed consent form addendum to ensure future data and sample sharing

Use of data and samples for additional research outside this clinical trial

Your rights: data and samples

You have the right to decide whether to participate in the study. If you decide to participate in the study, the following are groups with whom your study team may share your data and samples to improve new treatments or the conduct of clinical trials:

- Health authorities throughout the world (e.g., Food and Drug Administration, European Medicines Agency, and other governing bodies that review clinical trials).
- Institutional Review Boards that oversee and review the ethics of the research.
- The study sponsor and those working for or with the sponsor, which may include affiliates of the sponsor located in your country or other countries.
- Other groups: Examples of which include academic, government, or industry researchers; public-private partnerships; and/or external research collaborations. These entities will have oversight committees that will supervise the ethical use of the data and samples.

2. Methods

In January 2016, CAMD assembled a working group of individuals from industry, advocacy, and information technology backgrounds to draft addenda that would enable broader responsible data sharing. Because ICFs are often criticized as lengthy (e.g., 15–40 pages), technical, and difficult to understand [4], the addenda were designed for clarity and brevity with direct oversight from patient communication experts at the Alzheimer's Association and Sage Bionetworks, the creator of eConsent (http://sagebase.org/governance/econsent). A key objective was to create a clear language that ensures future data and sample sharing that was less than two pages.

Recognizing that AD is progressive and ICFs are intended for the patient, it was vital to incorporate input from individuals living in the early stage of the disease and their Care Partners. To that end, the draft was presented for review to the Alzheimer's Association National Early-Stage Advisory Group (AAESAG) and to their Care Partners.

The Advisory Group comprised individuals from across the United States living with early stage AD, other dementias, or mild cognitive impairment (MCI) and includes younger-onset individuals. "Early stage" refers to people, irrespective of age, who are diagnosed with AD or related disorders and are in the beginning stage of their disease. In this stage, individuals can still participate in give and take dialogue and express their wishes for the future. Advisors bring a unique perspective to key efforts of the Alzheimer's Association. Through their work as national spokespersons, Advisors raise awareness of AD, advocate to increase funding for AD research, and provide input about programs and support services for people in early stage AD or related dementias.

National engagements have included presentations to the Social Security Administration, FDA, Office of Minority Health, and the Special Committee on Aging. In addition, Advisors have successfully participated in the FDA's Patient Representative Program and the National Alzheimer's Project Act Advisory Council on Alzheimer's Research, Care, and Services.

3. Results

Overall, the groups expressed strong support for data sharing as outlined by the Addenda. Indeed, both groups expressed surprise, even anger, at the thought that samples and data were not being used to their fullest extent. One person living with AD stated, "To me this is a no-brainer. I am just learning now that this data was tossed out the window. I am shocked." Another individual expressed, "I am getting emotional. It makes me angry to think that they could be using this [data] to find a cure." Similarly, a Care Partner stated, "It's a waste and extremely sad to think that samples are destroyed." At the same time, both groups desired information regarding how the samples and data would be controlled and protected. They also gave helpful feedback on language that they felt was too vague.

Two documents were created: a more complete addendum containing the key elements of informed consent that would enable future data and sample sharing and an abbreviated addendum. Both documents (Boxes 1 and 2) are intended to augment pre-existing ICFs with clear, concise language that would be consistent with recent FDA guidance for informed consent [6]. These documents are tailored for studies and applicable laws in the United States. Essential features include as follows:

- Research purposes that encompass not only the present study but also possible secondary research goals such as "compare the study drug to other potential or approved therapies," "improve the design of future studies," and "advance the understanding of health and disease." The research purposes were intentionally not restricted to any single disease due to the many examples where data and samples collected for one disease may be useful to another.
- Data and samples will not be sold for profit. This concern was reiterated as an important concern by the AAESAG members and Care Partners.
- Specific examples of groups with whom the study team may share data and samples, with reassurance that these groups will have oversight committees to supervise the ethical use of the data and samples.
- Potential benefits and risks, specifically the fact that anonymity cannot be guaranteed.
- Methods used to mitigate the risk to privacy.

4. Discussion

Because of the long length of existing ICFs, it is often missed by the patient and caregiver that the data and samples collected in the sponsored study will never be used outside the sponsored study to continue to advance research. CAMD engaged those living with early stage AD (i.e., the AAESAG) to understand the experience of those living with it. In doing so, we believe it helped focus on what is important for them to enhance quality of life and to prepare for the needs of those not yet affected by the disease. CAMD consortium members hope that these addenda will serve the needs of researchers and research participants of future clinical studies to enable the use of biospecimens and data for secondary research purposes that could accelerate the development of effective therapies for AD and other chronic diseases in need of effective treatment.

Although AD is a progressive disorder that impacts an individual's cognition, "Some cognitively impaired individuals are still able to make informed decisions for themselves about participating in research. Others can no longer make these decisions, and another individual (usually

a family member) serves as a proxy to decide whether the impaired individual would want to be considered for a clinical trial. Sometimes individuals in the early stage of a disease establish an advance directive (a legal document) that specifies whether or not they wish to be considered for clinical research should they no longer be able to decide for themselves [7]." Formal mechanisms are in place to ensure this is done appropriately.

CAMD recognizes that the broad sharing of data raises concerns about inadvertent disclosure of the identity of participants, but such risk is mitigated when data are anonymized and curated using the Health Information Portability and Accountability Act–compliant procedures. Also, although some institution compliance officers may object to the lack of specification in the consent document regarding explicitly which organizations will receive these data and samples, CAMD would counter that most study participants would not object to sharing with any qualified the Health Information Portability and Accountability Act–compliant research partner to advance research on effective treatments. Moreover, as a central feature for all informed consent participants who feel uncomfortable with the approach should be permitted to opt out of participation. This could be documented by a separate participant- (or proxy-) initialed "yes" or "no" box in the instance where the data/sample consent is integrated into the main study ICF or with an addendum ICF.

The addenda specify that the samples and data will not be sold, an important point for many patients that can be guaranteed through the restriction of sharing to organizations with oversight committees. In the example of Henrietta Lacks, the researchers at Johns Hopkins who originally took the cells (without consent) shared it widely and freely with other researchers; yet it cannot be denied that an industry was developed over time around those cells. With informed consent, prospective participants have the ability to weigh the benefits and risks of participating in clinical research. This is part of the risk that each person must weigh and compare it to relative the benefits that they personally receive from it, as well as the potential future benefits it may impart to others. This raises an additional important point regarding the intent of these addenda, which is that they can be tailored to reflect the details of the study. For example, if there were a possibility that samples could be sold or used in the future to generate profit for some researchers, this should be disclosed so that prospective participants can make an informed decision about whether they wish to take part in this part of the study.

The addenda provided do not describe all the elements of an ICF required by the FDA (e.g., it does not describe the interventions required to gather those data, or other potential consequences of these procedures or treatment interventions). Instead, it focuses on the critical elements of data sharing that have been overlooked in the ICFs of many past studies that neither enabled nor restricted data sharing. In principle, such forms should be interpreted from the eyes of the participant—what would those participants have assumed when consenting through the ICF? Judging by the surprise and even anger of the AAESAG members and their Care Partners, it is likely that many research participants assume, unless they are directly told otherwise, that responsible data sharing for secondary research will occur. Research participants have widely varying wishes and expectations but, particularly for patients with severe diseases, data sharing for secondary research appears to often be viewed as a moral imperative rather than an unexpected risk [3]. In practice, many forms that omitted discussion of data sharing are interpreted as a barrier to such sharing. It is ironic that a document intended to protect study participants may instead become a reason to counter the wishes and expectations of those who willingly give their time and potentially risk their health to advance future innovative treatments.

Finally, some journals' editors have recently drafted guidelines that data from clinical trials should be shared as a requirement for study publication [8]. These important guidelines represent a major step forward for the field, but they are neither mandates nor public policy. As a clinical trial community, we have a responsibility to focus attention on those whom we are trying to treat and remember that, ultimately, the decision to share their valuable data resides with those who give consent.

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FaegreBD; Richard Meibach, Novartis; Karen Morgan, Boehringer-Ingelheim; Dagmar Thies, Boehringer-Ingelheim; George Vradenburg, USAgainstAlzheimer's; Megan Zosch-Canniere, Roche).

RESEARCH IN CONTEXT

1. Systematic review: This article highlights that unless informed consent forms specifically enable data sharing beyond the specified sponsored study, many studies restrict the distribution of de-identified data and samples. This reality is typically buried in the long (15-40 page) documents created.
2. Interpretation: Both patients and care-givers are often shocked to learn of this restriction, and would rather see their valuable de-identified data used.
3. Future Directions: Use of the concise addenda developed in this Perspective can increase the access of valuable, anonymized data, to inform the foundational and regulatory science required to develop innovative treatments for AD, or potentially, other chronic diseases.

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