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European Prevention of Alzheimer's Dementia Consortium

Grant Agreement n°115736

D8.1 Initial ethics policy review and information governance framework

WP8 – Ethical, Legal and Social Implications

V2.0
[Final]

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 EPAD - 115736	D8.1 Initial ethics policy review and information governance framework		
	WP8 – Ethical, Legal and Social Implications		Version: v2.0 – Final
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Description of the deliverable	The deliverable outlines and provides guidance on ethical, legal and social implications arising from the EPAD project.
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¹ If “Other” type of dissemination level, please inform the PMO team (mgt@ep-ad.org) accordingly.

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DEFINITIONS²

- Partners of the EPAD Consortium are referred to herein according to the following codes:
 - **Janssen.** Janssen Pharmaceutica NV (Belgium)
 - **UEDIN.** The University of Edinburgh (United Kingdom)
 - **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
 - **BBRC.** BarcelonaBeta Brain Research Centre (Spain)
 - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
 - **KI.** Karolinska Institutet (Sweden)
 - **VU-VUMC.** Stichting VU-VUmc (Netherlands)
 - **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
 - **MRC.** Medical Research Council (United Kingdom)
 - **BERRY.** Berry Consultants LLP (United Kingdom)
 - **UNIGE.** Université de Genève (Switzerland)
 - **RUMC.** Stichting Katholieke Universiteit (Netherlands)
 - **CU.** Cardiff University (United Kingdom)
 - **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
 - **QUINTILES.** Quintiles, Ltd (United Kingdom)
 - **AE.** Alzheimer Europe (Luxemburg)
 - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
 - **APHP.** Hôpital de la Salpêtrière (France)
 - **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
 - **ULEIC.** University of Leicester (United Kingdom)
 - **IXICO.** IXICO Technologies Ltd (United Kingdom)
 - **ARACLON.** Araclon Biotech S.L (Spain)
 - **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
 - **Eisai.** Eisai Inc (United States)
 - **SARD.** Sanofi-Aventis Recherche & Développement (France)
 - **NOV.** Novartis Pharma AG (Switzerland)
 - **BI.** Boehringer Ingelheim International GmbH (Germany)
 - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
 - **HLU.** H. Lundbeck A/S (Denmark)
 - **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
 - **AC Immune.** AC Immune SA (Switzerland)
 - **Biogen.** Biogen Idec, Inc (United States)
 - **Amgen.** Amgen NV (Belgium)

² To be completed with terms and abbreviations related to the actual content of the document


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- **Pfizer.** Pfizer Limited (United Kingdom)
- **UCB.** UCB Biopharma SPRL (Belgium)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

- LCS – EPAD Longitudinal Cohort Study
- PoC – EPAD Proof of Concept trial
- PC - Parent Cohort
- TDC – EPAD Trial Delivery Centre

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EXECUTIVE SUMMARY³


The EPAD project raises a number of important ethical issues, many of which are novel. The document covers questions related to the EPAD longitudinal cohort study (LCS) and proof of concept trial (PoC). The accompanying deliverable D8.2 covers EPAD’s relationship with parent cohorts. Together the deliverables form an overarching guidance document which encompasses the entire EPAD journey from parent cohort to trial and beyond. **This document is for guidance and to support the development of study governance, protocols and ethics review submissions. It does not replace the need for ethical review procedures.** It has been developed in consultation with other workpackages within the EPAD delivery cluster. Its content will necessarily evolve as the EPAD project develops, and will be reviewed and updated in D8.4 (M36) and D8.5 (M60).

This document identifies issues and sets out recommendations for the project in the following areas:

- Informed consent through the EPAD journey
- Return of results and disclosure of Alzheimer’s risk
- Incidental findings
- The experience of participation in EPAD
- Data sharing and governance
- Continuity between LCS and PoC

The recommendations are summarised in the following section. The remainder of the document then provides the background and reasoning behind the recommendations in each of these areas.

³ Maximum 2,000 characters (including spaces).

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SUMMARY OF RECOMMENDATIONS

Informed Consent

See [section 2](#)

General

- Informed consent is the voluntary agreement to participate in research. It is an ethical and a legal precondition for enrolling people as participants in the EPAD project.
- Informed consent is part of a broader responsibility of EPAD researchers to inform, update and communicate with EPAD participants.
- Consent and information sheets should be drawn up in collaboration with WP8.
- EPAD national leads and PIs within EPAD are responsible for ensuring that all relevant local and/or national legal and regulatory requirements are met.

Staged consent


- In order to prevent the ‘fish trap phenomenon’ (see page 20), EPAD should always and explicitly present information about the entire EPAD journey to (potential) EPAD participants.
- EPAD should adopt a staged consent model which feeds relevant, indispensable and ‘material’ information bit by bit along the EPAD journey and asks for informed consent whenever important decisions need to be made by EPAD participants.

Informed consent is a continuous process

- The EPAD project is extended over time and multi-staged. Informed consent within EPAD is a continuous process, not a one-off event.
- EPAD participants and study partners should be informed of relevant changes within EPAD that could influence their decision to participate. If these occur between Trial Delivery Centre (TDC) visits they should be notified through targeted contact.

Withdrawal from EPAD by research participants

- EPAD participants and their study partners may withdraw consent at any time.
- A study partner cannot withdraw consent on behalf of the EPAD participant.
- EPAD participants and study partners who would like to withdraw are not obliged to give a reason for their withdrawal

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Assignment of a study partner

- The study partner will act as an informant for the research team, not as a proxy consentor.
- Since the study partner is also taking part in EPAD, it is essential that they receive specific information about their role and function and sign a separate informed consent form.
- Personal information about the EPAD participant cannot be disclosed to the study partner without the explicit consent of the EPAD participant.

Capacity to consent


- EPAD participants' capacity to consent must be monitored and registered during the course of EPAD.
- If there is reason to doubt capacity - and only when there is reason to doubt – an independent healthcare professional should conduct a more formal assessment of the EPAD participant's capacity to consent.
- The local TDC PI is responsible for a proper policy to formally assess decision-making capacity (when in doubt), including monitoring and registration.

Recruitment from EPAD Register to EPAD-LCS

- Initial first contact with participants from PCs will be established by PC teams (see D8.2)
- When potential EPAD-LCS participants agree to be contacted by EPAD, they will visit a TDC, where a formal face-to-face informed consent conversation will take place with an EPAD researcher. They will receive written and verbal information about the EPAD-LCS and EPAD in general. This should include that participating in EPAD may involve learning information about AD risk at a later (PoC) stage and involve information about what this means.
- If the potential EPAD-LCS participant decides to participate in the EPAD LCS, written informed consent will be obtained.

Recruitment from EPAD-LCS to PoC trial

- When an EPAD-LCS participant is eligible for participation in a PoC trial, he/she should be actively approached with written information about the proposed trial by a member of the EPAD team, and will then be invited to come to the Trial Delivery Centre (TDC).


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- At the TDC, a face-to-face informed consent conversation will take place, during which the potential EPAD-PoC participant will have the opportunity to ask questions.
- If the potential EPAD-PoC participant decides to participate, written informed consent for participation in the PoC trial will be obtained.

Return of results and disclosure

See [section 3](#)

- At recruitment for the LCS, the question of 'why have I been contacted for this research' should be answered in terms of the characteristics shared by all EPAD LCS participants.
- EPAD's policy on the return of individual results should be clearly communicated through the consent process²³ and EPAD should consult EPAD-LCS participants on revisions to this policy.
- Some results from LCS examinations should be actively disclosed as long as the conditions set out in section 3.4 are met.
- EPAD LCS examinations should be communicated on specific request and EPAD TDCs should be aware of the legal requirements for providing access to data. (3.4.2)
- On recruitment for a PoC trial, EPAD-LCS participants should be informed of the specific marker(s) on the basis of which they are invited to take part in that trial. This should be discussed in a face to face meeting.
- A discussion of the implications of disclosure and the provision of educational material should take place **before definite inclusion in the LCS**. The provision of educational material should be separated from the taking of consent to allow potential EPAD participants time to engage with and discuss the materials in detail.
- Because any invitation to take part in a PoC trial potentially discloses information related to risk status, potential EPAD participants should be informed at the time of enrollment into the cohort that they may later be approached about joining trials that will require learning the results of genetic, blood or imaging tests conducted within the LCS that measure their risk of developing Alzheimer's dementia.
- Because the purpose of the LCS is as a readiness cohort for the PoC there is no opportunity for LCS participants to avoid learning their AD risk status through PoC recruitment. Potential participants who do not want to know their risk status should not be included in the LCS.
- Education materials related to disclosure should be drawn up by the EPAD Education and Writing Taskforce, established by WP4 and coordinated by WP8.


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- Any risk disclosure within the course of EPAD should be registered in the investigator files by the person disclosing any relevant information.
- TDCs should monitor EPAD participants for up to a year after disclosure of genetic or biomarker results. A procedure should be in place to contact participants and actively offer support, possibly as part of the research visit. TDCs should also use validated self-report questionnaires to detect anxiety, depression and distress. EPAD participants should also have the opportunity to contact a member of the research team in their country with questions about their results or if they are in need of psychosocial support.
- The criteria for returning results to EPAD-LCS participants after they have taken part in a trial are in principle the same as for other EPAD-LCS participants. Regular updates on biomarker status will not be routinely given, as it will be often unclear how to interpret changes that are independent of changes in cognition.
- When people participate in a second, subsequent EPAD PoC trial the disclosure process should consider what information has already been communicated, and EPAD participants should be helped to make sense of the interrelationships between different risk factors.

Incidental Findings

See [section 4](#)

- Incidental findings can and should be anticipated. EPAD must set up a protocol in advance for the detection, management and communication of incidental findings.
- Incidental findings of (high) clinical importance should be reported to research participants but EPAD should offer a qualified opt-out option to participants.
- Where possible, the potential for detecting incidental findings should be minimized.
- All research scans should be screened for abnormalities by specially trained researchers.
- In all TDCs, expert radiologists should be available for consultation when potential incidental findings are flagged during routine review.
- EPAD should consider the set-up of a multidisciplinary expert panel at the level of the TDC to make decisions regarding the handling of unanticipated incidental findings
- EPAD TDCs should make arrangements with local hospitals or medical centres about referrals to help ensure timely and high-quality clinical follow-up in case of (potentially) serious incidental findings detected at the TDC.
- The protocol should be reviewed by a (local) research ethics committee.

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- The protocol should be communicated to EPAD participants as part of the informed consent process.

The experience of EPAD participation


[See Section 5](#)

- EPAD PIs should establish and seek to minimise the risks associated with participating in the research
- EPAD TDCs should monitor the burden of taking part in EPAD research and put in place procedures for anonymous feedback
- The LCS protocol should make it clear whether people who have previously been considered as screen failures will be excluded and definitively cease to participate or can be recontacted as inclusion criteria change, and if so, if they will be re-screened.
- The EPAD participant information sheet should make it clear that EPAD is a public-private partnership, and that the research may result in financial gain for private partners.
- Engagement with Parent Cohort (PC) PIs should make it clear that EPAD may have implications for the retention of their participants and should work to minimise these.
- TDCs should establish a procedure for dealing with enquiries from those not currently in a parent cohort
- EPAD WP4, WP6 and WP8 should work together to establish a clear plan for ongoing feedback and communication with EPAD participants. This should include establishing a clear plan for the communication of aggregate results from LCS and PoC findings and ensuring that at least two EPAD participants are represented within the EPAD steering group

Data sharing and governance

See [Section 6](#)

- Procedures related to data storage, sharing and access must conform to all relevant national and European legislation
- Consent to data sharing between the EPAD LCS and the PC should not be a *sine qua non* for participation in the LCS.


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- The EPAD data access committee should be set up at an early stage to establish procedures for access requests and monitoring and to ensure that data are ready and available to be shared at the earliest possible opportunity.
- It is desirable that all relevant stakeholders, including EPAD participants, be included in decision making relating to data sharing and re-use beyond the project. The data access committee should include representation from at least two EPAD participants.
- The PoC informed consent process include a component about data sharing between the EPAD PoC and the EPAD LCS.
- Consideration should also be given to sustainability, ensuring that EPAD data remains available after the conclusion of the project and is available for long-term future use.

Continuity between LCS and PoC

See [Section 7](#).

- Although separate consent will be needed for each PoC study, from the perspective of an EPAD participant who takes part in both the EPAD LCS and a PoC trial, many features of the study will remain constant. Consequently, the studies should be seen and managed as a continuum.
- There is no reason for an EPAD participant to leave the LCS to take part in a PoC study
- WP4 should ensure continuity between LCS and PoC procedures and data, to avoid placing an unnecessary burden on EPAD participants and wasting EPAD resources on repeated assessments.
- However, consent for data sharing between the LCS and PoC should not be a sine qua non for participation in the PoC.
- EPAD should record participation in PoC trials and be vigilant about whether some EPAD-LCS participants are being contacted disproportionately to take part

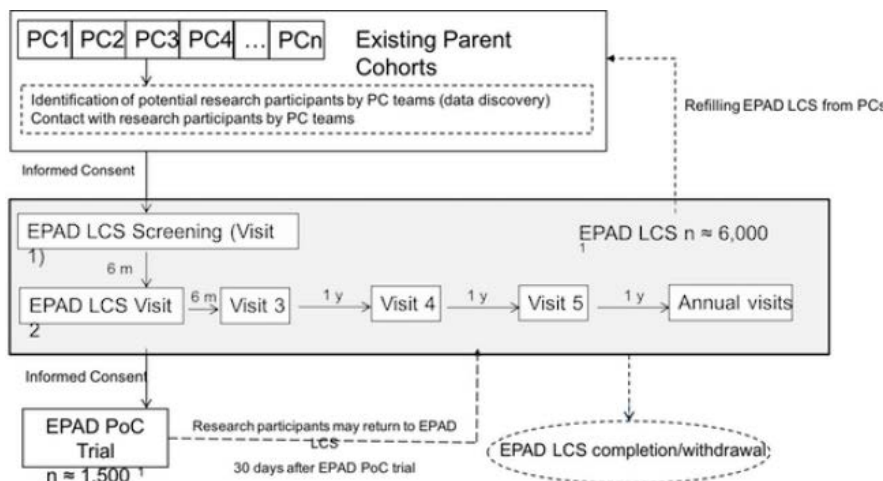
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1. SCOPE

1.1. The EPAD project

The EPAD project aims to develop a standing clinical trial platform for secondary prevention trials in Alzheimer’s disease. It includes three phases


- Virtual register
- Longitudinal cohort study (LCS)
- Proof of concept trials (PoC)



¹ Once recruitment is completed, at any given time there should be approx. 6,000 research participants in the EPAD LCS and approx. 1,500 in the EPAD PoC, hence the need to replenish each as participants are lost through attrition.

Figure 1: The structure of the EPAD project

The virtual register consists of metadata from cohort studies across Europe. These cohort ‘fingerprints’ will be used to facilitate the recruitment of a heterogeneous cohort of participants, the EPAD LCS. The EPAD LCS is a prospective, multicentre cohort study designed to develop longitudinal models for AD covering the entire disease course and develop an infrastructure to facilitate the identification of research participants and for clinical trial recruitment. EPAD LCS participants will range from asymptomatic volunteers drawn from population-based parent cohorts to individuals without dementia who may be receiving medical care for early cognitive problems.

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The EPAD LCS is planned to include 6,000 individuals, and this number will be maintained over time by continuous recruitment of new participants as existing participants leave the cohort. The EPAD PoC is planned to include around 1500 participants in a number of study arms.

1.2. Ethical issues associated with EPAD


The EPAD project raises a number of important ethical issues which are explored in this document and the accompanying deliverable D8.2. Together these form an ethics guidance document which encompasses the entire EPAD journey from Parent Cohort to Proof of Concept trial and beyond. **This document is for guidance only and does not replace the need for ethical review procedures.** Its content will necessarily evolve as the EPAD project develops, and will be reviewed and updated in D8.4 (M36) and D8.5 (M60).

The background to the document is provided by national and international frameworks for the conduct of ethical research in biomedical science, in dementia research and in the development of platforms for data sharing¹⁻⁵ and interpretations of these^{6,7}. In the context of dementia research, relevant background is provided by the work of the Nuffield Council on Bioethics⁸ and Alzheimer Europe⁹. Other relevant guidance includes that provided in the Nuffield Council's report on the collection, linking and use of data in biomedical research¹⁰ and the Global Alliance for Genomics and Health's framework for the responsible sharing of genomic and health-related data¹¹. Finally, relevant background is provided by the growing body of empirical work on secondary prevention of Alzheimer's dementia and the development and use of big data approaches to biomedical research. This work is discussed where relevant within the guidance document.

In addition to the wealth of relevant ethical guidance relevant to the project, it is important to note that the EPAD project will operate across regulatory jurisdictions within Europe. As such, study and trial arrangements must conform to national and international ethical regulations⁴, including those related to informed consent and data governance. This may need to be reflected in local changes to the study protocol, consent and disclosure procedures. It will also need to evolve to reflect regulatory changes, notably in relation to the impending EU Data Protection Regulation.

Responsibility for ensuring that EPAD adheres to local regulatory frameworks ultimately lies with national leads and EPAD TDCs, and will involve working with local ethics review boards.

⁴See the International Compilation of Human Research Standards <http://www.hhs.gov/ohrp/international/>

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The EPAD ethics guidance document provides background to these discussions. It considers six areas in which issues arise in relation to the project. These are:

- Informed Consent
- Risk Disclosure
- Incidental Findings
- Participation
- Data Sharing and Governance
- Continuity between LCS and PoC

Each section outlines relevant ethical principles and the issues arising in relation to EPAD and provides recommendations on best practice.

1.3. Future development: ethical issues associated with EPAD PoC trial design

EPAD is based on the development of a standing trial platform. Many of the implications of this are covered in the other sections of this document, particularly related to the safety of participants, including the risks and burdens involved in participation (see section 5). However, this document does not currently cover in detail the issues associated with the development of clinical trials involving adaptive randomization. As this design is not to be used in EPAD, these issues will not apply. Nevertheless, such adaptive trial design is likely to become more common in the future, and it is important to note that the development of such adaptive trials in other settings has prompted an emerging ethical debate¹²⁻¹⁷. EPAD WP8 will revisit the issue of the ethical implications of trial design as the EPAD PoC protocol and trial design are finalized, contributing to providing an updated section in D8.4.

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2. INFORMED CONSENT

2.1. Introduction


Informed consent is the voluntary agreement to participate in research. It is an ethical and a legal precondition for enrolling research participants in the EPAD project. Informed consent is meant to promote control and self-determination among research participants, but should not unduly burden participants or hamper the conduct of research. Informed consent is part of broader responsibility of EPAD researchers to inform, update and communicate with research participants. This section proposes a staged model for informed consent for EPAD and outlines the ethical and practical conditions for an adequate set-up of the informed consent process.

The EPAD project spans multiple jurisdictions, and European nations differ in their demands concerning informed consent for medical research^{18–20}. It is beyond the scope of this document to outline in detail the modes of actions required within the six or more jurisdictions involved. Rather, it discusses the moral, instrumental and legal roles of informed consent within EPAD and provides general directions for ensuring the ethical requirements of informed consent can be met. However, **it remains the responsibility of national leads and PIs within EPAD to ensure that all relevant local and/or national legal and regulatory requirements are met.**

2.2. Background

Informed consent has three roles: moral, legal and instrumental.

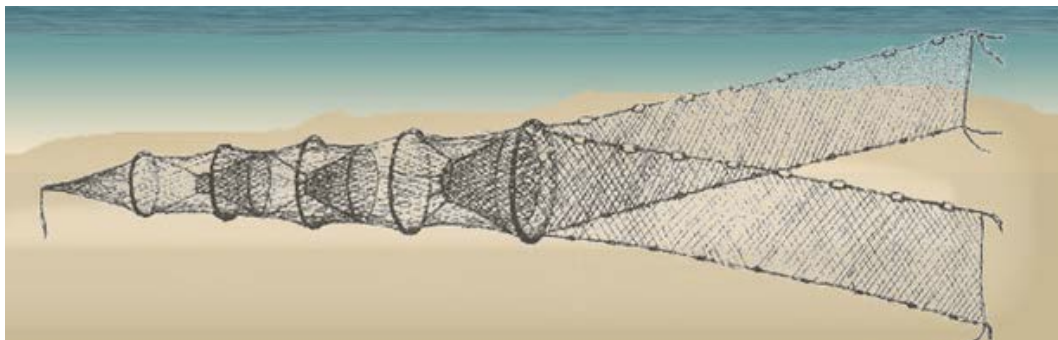
- The *moral* role of informed consent in the EPAD project is focused on research participants' self-determination and self-governance. Firstly, informed consent serves to protect against involuntary research participation, but also against deceit, inducement and misleading communication. As such it is an expression of respect for autonomy. Secondly, informed consent within EPAD aids future research participants to protect themselves against the possible harms associated with participation (e.g. receiving unwanted risk information, harms of taking compounds of which efficacy is not yet established).
- From a *legal* point of view, EPAD must ensure that informed consent is in place at all relevant stages of the EPAD journey. From a legal point of view, the informed consent process and adjacent forms lay down the agreed upon rights and responsibilities of participants and researchers within EPAD.

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- Besides a moral and legal role, informed consent within EPAD also serves an *instrumental* role. An adequate informed consent process builds trust and commitment among research participants and helps maintain participation rates.

An adequate informed consent process is also a way to prevent the ‘fish trap’ phenomenon from occurring.

Fig. 1: The fish trap phenomenon




A fish swims into the first space of the trap. In that first space, he is free to swim around for a while and then leave. If he goes into the next space, however, the chances of the fish finding its way back become slimmer. The further the fish goes into the trap, the less likely he is to be able to escape. By the time the fish has entered the third or fourth space of the trap, he is beyond return.

EPAD runs the risk of becoming a fish trap for its participants. EPAD starts by asking participants from parent cohorts (PCs) whether they are interested in learning about the EPAD project. This seems like a small step. Then, EPAD will ask whether they are willing to undergo additional tests and examinations as part of the EPAD-LCS. Then, they will be asked to participate in a phase II trial, which aims at testing drugs to delay the onset of Alzheimer’s disease. As a result, they may also come to find out their risk of Alzheimer’s disease.

Once started on the route of EPAD, it may eventually become more difficult – and more irrational - to go back. EPAD will not want to lure participants into a fish trap. Participants should not be ‘eased into’ learning their risk status for Alzheimer’s disease or participation in drug trials.

Although in each stage of the EPAD journey, informed consent is given for that specific stage, information about the totality of EPAD and the EPAD journey should always and explicitly be made available to participants. This information should include information about the EPAD LCS and PoC stages, about the consequences and implications of participation, about the choices to be made in the next stages of the project, and about the

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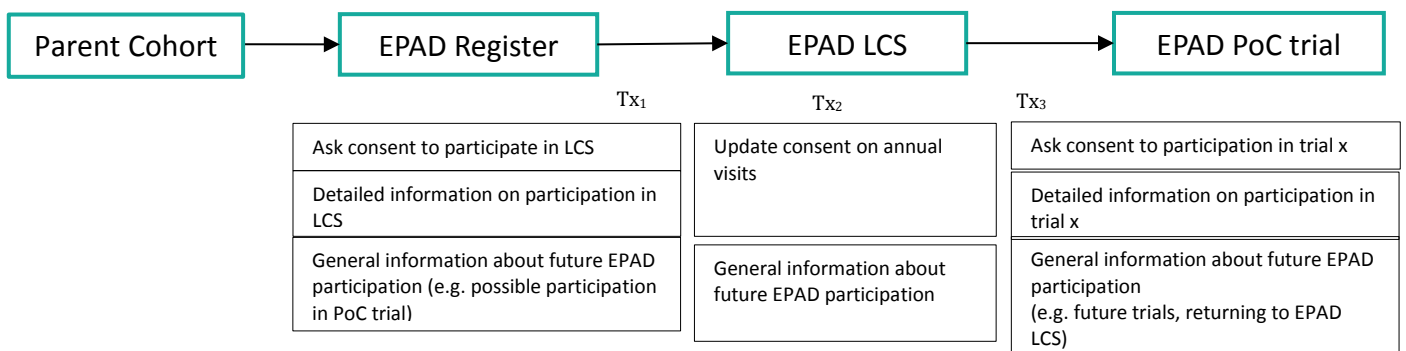
future of EPAD. Informed consent – although given for a specific stage of EPAD – would not be *informed* consent without the provision of general information about the ‘totality’ of EPAD.


2.3. Staged consent model

EPAD will recruit potential participants from pre-existing Parent Cohorts (PCs) across Europe to enter into a longitudinal cohort study (LCS) and possibly a Proof of Concept trial (PoC trial). The EPAD project is extended over time and multi-staged, and as research participants and data will move from one stage to the next, informed consent will need to be asked at multiple time points for multiple tasks or activities by multiple persons. Therefore, **staged consent is the preferred decision making model**. Staged consent feeds relevant/indispensable/‘material’ information – bit by bit, along the EPAD journey - to (future) research participants and asks informed consent at every moment in which important decisions need to be made by research participants.

EPAD should distinguish between asking informed consent for specific tasks or activities and ongoing information provision to and communication with research participants. **Although informed consent is given for a specific stage of the EPAD journey, information about the ‘totality of EPAD’ should always and explicitly be made available to (future) participants during the informed consent process.** This information includes information about the consequences and implications of participation, about the choices to be made in the next stages of the project, and about the future of EPAD. Informed consent – although given for a specific stage of EPAD – would not be *informed* consent without the provision of general information about the ‘totality’ of EPAD.

Fig. 2: Staged consent within EPAD



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2.4. Understanding consent within EPAD

2.4.1. *Informed consent as a continuous process*

The EPAD project is extended over time and multi-staged. Therefore, it needs to be emphasized that **informed consent within EPAD is a continuous process, not a one-off event.**

Participation in the LCS entails annual visits to the Trial Delivery Centre for research procedures. During these visits the participants are informed about new developments within the EPAD project and asked specifically if they wish to continue participation. Also participation in the PoC-trials entails regular visits to the Trial Delivery Centres for research procedures. During these visits participants are also informed about new developments that could influence their decision.

If there are relevant changes within EPAD that could influence participants’ decisions to participate in EPAD in-between TDC visits, participants and study partners should be updated by EPAD through targeted contact.


All written information within the course of EPAD concerning recruitment and (continuous) informed consent should be drawn up in collaboration with the EPAD writing and education taskforce constituted from WP4, WP6 and WP8.

EPAD should consider the use of a validated questionnaire to check the level of understanding of the benefits, risks and burdens assumed by the participants.

2.4.2. *Withdrawal from EPAD by research participant*

EPAD research participants and study partners may withdraw consent at any time. A study partner cannot withdraw consent on behalf of the research participants. Participants and study partners who would like to withdraw are not obliged to give a reason for their withdrawal.

Through the entire course of EPAD research participants may request the destruction of their previously collected samples. However, in the PoC studies, the withdrawal of consent should not affect, in principle, the activities carried out and the use of data obtained based on consent before the decision to withdraw.

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The protocol for the PoC-trial needs to include relevant provisions to ensure safe termination and appropriate safety follow up (with consent from participant) for the withdrawn research participant.


The research participant and his/her study partner will be informed about the possibilities for withdrawing their consent from EPAD, the consequences and conditions stated above. This information will be stated in the information sheets for participants and study partners of the EPAD LCS and PoC trial.

2.4.3. Study partner during EPAD project

The study partner is a common phenomenon in Alzheimer's disease trials, where the research participant might lack the capacity to participate in a trial without proper support. The study partner is generally tasked with supporting the research participant, assisting him or her on visits to the research centre, and updating researchers about the participant's disease progress. However, the goal of the EPAD project is the development of drugs for secondary prevention of Alzheimer's Dementia. EPAD will recruit asymptomatic or mildly symptomatic participant and is therefore unlikely to be confronted with people who lack the capacity to be in a trial or a cohort study without support from a study partner.

Research participants enrolled in the EPAD LCS will thus be capable of providing informed consent, and **Accordingly, the role of the study partner will not be to provide proxy consent for participation in EPAD.**

EPAD does, however, require the involvement of study partners as informants. On their first visit to the TDC, potential EPAD-LCS participants will be asked to identify someone who is willing in principle to be their study partner. This study partner, i.e. a relative or friend aged at minimum 18 years, may or may not live together with the participant, and is available either for face-to-face or telephone contact with the EPAD staff at the local TDC. Over the course of EPAD, the study partner will be asked to fill in questionnaires. The study partner will therefore function purely as a data source. **Since the study partner is a research participant in the EPAD project, it is essential that the study partner receives specific information about his/her role and function and needs to sign a separate informed consent form for his/her participation in EPAD.** Personal information about the research

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participant will not be disclosed to the study partner without the participant's explicit consent.

2.4.4. Capacity to consent

Capacity to consent is specific to the situation and decision at hand and to a given study protocol. As a general rule, all adults should be presumed able to consent, until proven otherwise. When prospective research participants are capable of making informed decisions, they may accept or decline participation in the research project, without involvement of any third parties.


Participants' capacity to consent to research embodies a minimum of four abilities:

- *Understand* the information relevant to the decision
- *Appreciate* the situation and likely consequences
- Handle information in a *rational* manner and retain it
- Make a *choice* and communicate it.

As stated previously, since EPAD aims at the secondary prevention of Alzheimer' disease, the EPAD-LCS and PoC trials will exclude people not capable of providing informed consent. The onset of clinical dementia or the loss of the capacity to consent are exclusion criteria for the EPAD LCS. While there may be scientific reasons to follow participants who develop mild dementia during the LCS for some time for disease modelling purposes, they should still be capable of providing informed consent themselves. These exclusion criteria will also apply to the EPAD PoC trials: participants with mild dementia will not be invited for an EPAD PoC. As they have no possibility of taking part in an EPAD PoC, participants should not be included in the LCS any longer than necessary.

EPAD LCS participants will thus be capable of giving or withholding informed consent. When they lose the capacity to consent, they will be excluded from the LCS. It is possible that participants with (mild) cognitive symptoms experience fluctuating or diminished decision-making capacity along the EPAD journey. Therefore, it is essential EPAD anticipates this and routinely monitors capacity to consent.

It is of crucial importance that participants' capacity to consent is monitored and registered during the course of EPAD. The researcher will briefly and informally assess the participant's decision-making capacity during every informed consent conversation. This

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brief, informal assessment should not take place once, at time of inclusion, but should be repeated throughout the EPAD journey: at every annual visit at the TDC, at the moment of inclusion in a PoC trial and at all other moments where an updated informed consent is needed. It is recommended, to this end, that all investigator files contain the prompt: *“Is there any reason to doubt capacity to consent?”* **When there is reason to doubt - and only when there is reason to doubt – a health care professional independent from the research team will conduct a more formal assessment of the participant’s capacity to consent.**

The PI of the local TDC is responsible for a proper policy to formally assess decision-making capacity (when in doubt), including monitoring and registration. Currently, no validated instrument can be considered a Gold Standard for the formal assessment of capacity to consent for research. This ethics guide cannot advise on a specific instrument, since there is no consensus in this field. Dependent on local preferences and experiences PIs of TDC’s are advised to incorporate one of the below mentioned instruments in their policy:

- Clinical judgment (based on the four abilities mentioned above: understanding, appreciation, reasoning, expressing a choice)
- MacArthur Competence Assessment tool for Clinical Research (MacCAT-CR)²¹
- The University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)²²

Instruments used should be validated in the language used with participants. If EPAD decides to include in the EPAD PoC trials people who are unable to consent, proxy consent will be required and other protective measures will need to be implemented. These will include:

- Obtaining informed consent from the legal representative or authorized representative (in compliance with applicable, country-specific laws and regulations) when the research participant’s ability to give free and informed consent is compromised or when there is evidence that the participant is not able to understand information and make choices for him- or herself.
 - o The ideal surrogate decision maker or authorized representative should be someone who was appointed by the participant while he/she was still able to consent, possibly through a proxy advance directive.
 - o The surrogate decision maker must be independent of the research team and should have the participant’s best interests in mind. He/she should be available to assist the participant in navigating the consent and research

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process, to monitor the participant’s recruitment, participation, and eventually, withdrawal from the study.

- When making decisions, he/she should take into account the participant’s wishes, values and beliefs, and advance directive (if it exists).
- The research participant should have received information about the PoC trial in a way that is adequate in view of their capacity to understand it and shall, as far as possible, take part in the informed consent procedure.
- The participant’s wish to refuse participation in or to withdraw from the clinical trial must be respected at any time; objection or resistance to participation must be taken as a refusal or withdrawal and must be honoured.

2.5. Recruitment from PC to EPAD Register

Refer to D8.2

2.6. Recruitment from EPAD Register to EPAD-LCS

2.6.1. Process of contacting participants from PCs

See D8.2


2.6.2. Process of recruitment and informed consent into EPAD-LCS

For the EPAD-LCS, informed consent from research participants is required.

Initial first contact with participants from PCs who are potentially eligible for EPAD LCS will be established by PC teams, designated by the PIs of the respective PCs. EPAD will not approach eligible research participants from PCs directly.

A potential participant will receive information material from his/her PC team. This should include:

- A front letter about the reason for contacting them (without disclosing previously acquired biomarkers or other test results) and asking whether they would be interested in being contacted by EPAD
- The LCS information sheet (including a general introduction of the EPAD project)
- A return slip including a consent to be contacted by EPAD and contact details of the prospective participant.

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Only after a positive response from the potential participant will EPAD contact that person. Note that this confirmation by the potential participant is not a consent to participate in EPAD, only a consent to being contacted by EPAD. After contact by EPAD, the future participant is asked to visit the nearby TDC, where a formal face-to-face informed consent conversation will be arranged. There, the prospective participant will receive oral information about participation in EPAD LCS specifically and about EPAD generally (on top of the already received written information). Attention needs to be given to the aspects of the study which are compulsory for participation and which are optional during participation in the EPAD LCS.


Clear information should be provided on the relation between EPAD LCS and EPAD PoC trial: participants are potentially entering on a trajectory that may involve trial participation later on and learning their AD risk status. Educational information should be developed by the EPAD writing and education taskforce to provide participants with a clear idea of what this might mean.

Information for participants should further emphasise that informed consent for EPAD LCS does not imply consent for the EPAD PoC trial; eligibility for EPAD LCS does not imply eligibility for the EPAD PoC trial; trial participation is subject to a separate informed consent form.

Potential EPAD LCS participants should also be informed that they may be deselected from EPAD LCS after the first screening/baseline visit. It should additionally be made clear that participants can continue to be involved in their PC, and it is possible to withdraw from EPAD LCS without being forced to withdraw from PCs.

During this conversation the potential participant should have the opportunity to ask questions. There is no obligation for the prospective participant to decide at that time, as every person should be allowed reasonable time to consider his/her participation. No minimum or maximum time limits are defined.

If the potential participant eventually decides to participate, written informed consent will be obtained. Two copies of the informed consent form are signed and dated: one is given to the research participant. Annex 1.1 shows the specific tasks/procedures a research participant needs to consent to before participation in the LCS can take place. This implies that the LCS information sheet needs to include information about these specific tasks/procedures and the LCS informed consent forms needs to include these aspects.

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See Annex 1.1: Recommended Informed consent EPAD-LCS


2.7. Recruitment from EPAD-LCS to PoC trial

Participants will be enrolled in the EPAD-LCS. Some LCS participants, but by no means all, will take part in a PoC trial. They will first be assigned to an intervention cohort. After assignment to an intervention cohort, the participant will be randomized to either the active intervention or a placebo. Participants will be blinded to the latter randomization, but will be informed about the intervention cohort they are assigned to.

When a research participant is eligible for participation in a PoC trial, he/she will be actively approached with written information about the proposed trial by a member of the EPAD team, and will then be invited to come to the Trial Delivery Centre (TDC). There should be sufficient time between the receiving of the written information materials and the visit at the TDC, so that the research participant can process and discuss the provided information. At the TDC, a face-to-face informed consent conversation will take place, during which the potential participant will have the opportunity to ask questions. The prospective participant need not decide at that time, as he/she should be allowed enough time to consider his/her participation. No minimum or maximum time limits are defined. During this face-to-face conversation attention needs to be given to the aspects of the PoC trial which are compulsory for participation and which are optional during participation in the trial. Clear information will be provided on the relation between EPAD LCS and EPAD PoC trial: consequences of participation in the PoC for participation in the EPAD LC, returning to the LCS etc.


There is a difference between ‘disclosing’ information that is required to obtain informed consent for the PoC trial on the one hand, and presenting and repeating information about ‘the totality of EPAD’ on the other hand. In order to avoid misinforming or misleading research participants, it is important to continue to provide information about the entire EPAD project, most notably prior to important decisions to be made by research participants, such as the decision to participate in a PoC trial.

If the potential participant decides to participate, written informed consent for participation in the PoC trial will be obtained. Two copies of the informed consent form are signed and dated: one is given to the research participant. Annex 1.2 shows the specific

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tasks/procedures a research participant needs to consent to before participation in the PoC trial can take place. This implies that the PoC information sheet needs to include information about these specific tasks/procedures and the PoC informed consent forms needs to include these aspects.

See Annex 1.2: Recommended informed consent PoC-trial

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3. RETURN OF RESULTS AND RISK DISCLOSURE

3.1. Introduction

EPAD research involves the identification of individuals who may be at risk of developing Alzheimer’s dementia to take part in clinical trials and to develop new models of disease enabling more accurate risk stratification. There is a prevailing consensus that biomarkers are currently not suited for diagnostic purposes in clinical practice for asymptomatic or minimally symptomatic individuals, given their uncertain prognostic value, the lack of treatment and prevention options, and the difficult nature of conveying probabilistic risk^{24–27}. The disclosure of genetic and biomarker results in the context of research is, however, the topic of debate^{28,29}.


Arguments for and against disclosure at each stage of the EPAD journey differ. However, it is also important to recognise that the decision on disclosure at one point is affected by what has been or may later be disclosed at other instances in a participant’s journey through EPAD. Disclosure is thus not a one-off event, but has implications throughout the EPAD process. As such, it is critical that EPAD records in the investigator file what information has been disclosed to participants.

3.2. From EPAD register to LCS

Individual participants will be recruited to EPAD on the basis of certain characteristics. However, people across the entire probability spectrum of developing AD will be included in the Longitudinal Cohort Study (LCS). This includes cognitively healthy individuals, people with MCI, and both biomarker negative and positive individuals. The population of the LCS will therefore be heterogeneous.

The EPAD virtual register only reveals count data to EPAD. Identifiable individual level data is only visible to the research team of the PC. Consequently, only PC researchers are aware of on what basis an individual is invited into EPAD. The disclosure or non-disclosure of risk information at this stage is thereby the responsibility of the PC. EPAD cannot disclose any individual-level information related to the reason for recruitment that has not been explicitly shared with the project at this stage.

Nevertheless, informed consent requires that people are informed of the reason for being invited to take part in research. To maintain the entire probability spectrum, the inclusion criteria will change over time (initially based on expert assessment and ultimately by means

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of a flexible algorithm) and recruitment will draw more heavily on specific types of PCs accordingly. **Consequently, the question of 'why have I been contacted for this research' can only be answered in general terms, referring to only those inclusion criteria that are stable over time and shared by all participants: people's ongoing or previous participation in a study (PC) associated with EPAD, their age of ≥ 50 years and not being diagnosed with dementia and reflecting the aim of EPAD to recruit a heterogeneous sample.**

3.3. LCS Screening

See also section 5.4


The first visit to the EPAD Trial Delivery Centre (TDC) involves a screening process after which people may be asked to leave the study (or 'deselected'). The informed consent process prior to this first visit should manage expectations with regard to this possibility. **It should be emphasised that neither inclusion nor exclusion in the LCS reflects specific information about risk status**, as the LCS is a heterogeneous population. Exclusion does not necessarily say anything about one's probability of developing AD; people are included and deselected depending on the need for participants with specific characteristics for disease modelling purposes at that time point (although it is most likely there will be an ongoing need for biomarker positive individuals as those are the ones most likely to be included in the PoC trial).

As in the case of the routine feedback of LCS results, the lack of scientific validity or actionability, the risk of bias and the potential negative impact of risk disclosure suggest that there is no value in communicating a composite probability and individual results routinely at this stage.

3.4. Return of results from examinations in the cohort

The EPAD LCS is a research study, the goal of which is to support the development of research, not to provide clinical care. It is important that this distinction is maintained in the conduct of research and in approaches to the communication of information derived from it^{3,5,23}, not least in the case where research and clinical procedures are conducted by the same individual.

Individuals should consent to the study on the clear understanding that all measures are for research purposes only and not to inform decisions about their health. The tests participants

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undergo within the cohort are thus not a health check, and the duties of the researcher differ crucially from those of the clinician. Nevertheless, arguments associated with the ethical principles of justice, beneficence and respect for persons may support the return of individual research results in certain circumstances^{30,31}.

3.4.1. When should results be returned?

There are four potential occasions at which the return of results may occur during the course of longitudinal research²³:

- return of aggregate results to participants;
- return of incidental findings (IFs);
- feedback at assessment and from laboratory analyses before storage;
- return of individual research results (IRRs)


The first three of these are not discussed in detail here. There is broad agreement that researchers should communicate the aggregate findings of research to participants^{2,31} ([see section 5.3](#)). Incidental findings are discussed in more detail [in section 4](#).

In terms of the feedback of results from assessments, guidance²³ suggests that the return of findings emanating from baseline assessments in population studies (such as height, weight and blood pressure) constitutes a form of ongoing communication and feedback and should occur as soon as possible. If necessary, participants should be advised to contact a physician, in line with the recommendations on incidental findings (IF). Results from initial lab analyses before storage should also be returned if necessary, again in line with the IF policy. The outcomes of cognitive testing will also become available during testing and blinding is impossible. Discussing these results may be helpful to participants with cognitive complaints, or be reassuring for those with concerns.

This policy on the return of results should be made clear in the application to the ethics committee, along with provisions for dealing with potential distress caused by this information.

3.4.2. Returning individual research results

In terms of the return of individual research results (IRRs), there is no consensus in the existing literature and guidelines^{23,31,32}. Standard practice in AD research recruiting on the

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basis of biomarkers has been to ensure respect for human subjects and the right to basic information about the findings of the research by informing potential subjects at the time of enrolment that research scans such as PiB amyloid cannot be meaningfully interpreted in a clinical sense and, therefore, individual results would not be disclosed²⁸.


More broadly, there has been a move to recognise an ethical duty to return research results that are seen to be valid, significant and beneficial to participants, while respecting the right of participants to choose not to know³⁰. Studies suggest that many research participants want both aggregated and clinically significant individual study results to be made available to them³³. In addition, recent studies have suggested that a considerable number of individuals likely to participate in AD research would still want disclosure of results in the absence of effective treatment³⁴.

Guidance from the P³G consortium²³ suggests that IRRs should be communicated *if consent is in place, if the findings are analytically valid, they reveal a significant risk of a serious health condition, and finally that they are actionable*. The guidelines also outline a second situation in which results *may* be returned, if the first two criteria are met and the findings reveal an established risk of likely health importance to the participant and have a likely therapeutic benefit.

A finding can be considered actionable "if there is a recognized therapeutic or preventive intervention or other available actions that have the potential to change the clinical course of a disease or condition."¹¹. However, this view on clinical utility is argued by some to be too restrictive³⁵ and (potential) research participants report reasons for wanting their results that relate to both a much broader definition of clinical utility and to personal utility³⁶.

Findings may be actionable in a variety of ways. Given that EPAD assessments across the TDCs will be carried out to a common standard, their findings should be analytically valid, that is, both accurate and reliable across testing occasions. However, the requirement for a result to 'reveal a significant risk of a serious health condition' will be problematic, as the meaning and prognostic accuracy of most biomarkers is not yet clearly established^{25,37}. In contrast, the risk conveyed by the different APOE genotypes is quite well-known³⁸. Uncertainty regarding the validity of APOE genotyping is therefore not a reason against disclosure.

The example of APOE highlights the potential implications of disclosure for the study, notably the potential that the return of results will introduce bias. Knowledge of one's APOE


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genotype has been found to influence participants' cognitive performance³⁹ and health behaviours⁴⁰. It is possible that this could be the case for knowledge of other biomarkers as well. The population of the LCS will be very heterogeneous and the return of results would lead to disclosure of different information to all participants. Consequently, this could introduce bias into the disease-modelling process. Outcome assessors may also be influenced unintentionally by knowledge of a participants' results. Therefore, both participants and investigators should be blinded to APOE genotype and other results from examinations in the disease modelling stage as much as possible.

- **In the case of EPAD we recommend that results from examinations should only be actively disclosed, (i.e. other than on request) if:**
 1.
 - a. written consent is in place, and
 - b. findings are analytically valid, in terms of being both accurate and reliable, and
 - c. they reveal a significant risk of a serious health condition, and
 - d. they are actionable (understood as including a broader conception of clinical utility and personal utility), and
 - e. there is either no risk of bias or blinding to results is impossible, or
 2. They are either baseline assessments or they meet the criteria set out in the attached document on incidental findings.
- **The EPAD policy on the return of results should be clearly communicated during the consent process²³.**
- **To reflect the preferences of participants on the return of results, the EPAD Exec should consult participants once the LCS has recruited and consider revising this policy.**
- **EPAD should consult with local research ethics committees to ensure that EPAD's approach is appropriate to local standards of practice.**

Right to access

Participants may want to see their test results regardless of whether they meet the criteria above or are able to act upon the information received. Requests for subject access to data are covered by international and national legal conventions⁴. These include data protection laws implementing the EU Data Directive, the Oviedo Convention on Human Rights and Biomedicine and the additional protocol regarding biomedical research. During the course of

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the EPAD project, it is likely that the forthcoming EU Data Protection Regulation will come into force.

EPAD TDCs should be aware of the legal requirements for providing access to LCS data and the results of EPAD examinations should be communicated on specific request where required. Suitable provision should be made for this.

However, regardless of legal requirements to provide subject access to LCS data EPAD should make results available on direct request, in order to reciprocate participants' contribution.

EPAD should endeavour to ensure that its procedures for dealing with the disclosure of individual research results and incidental findings are reflected in any further use of material and data resulting from the study *New evidence*


If, during the study new evidence arises that changes the interpretation of previously disclosed results, this should be communicated to participants under the conditions that the evidence is analytically valid and results in a considerable change in risk for the participant.

3.5. Disclosure at trial enrolment

An invitation to take part in a PoC trial raises significantly different issues related to disclosure than at earlier points in the EPAD process. The disclosure of genotype or biomarker status as part of a transparent recruitment process is essential to provide potential participants with the information they need to decide whether or not to participate in a clinical trial²⁹. However, it also raises potential concerns about bias, coercion, the prognostic accuracy of the information communicated, and the impact of this information on individuals and their families.

In the case of trial recruitment, the prognostic accuracy of testing is secondary to the need to provide potential participants with the information required to make an informed judgement on participation. However, **it is important that the information provided within the educational component of any disclosure process makes clear the uncertainties and limitations associated with the information provided.**

As all participants entering a PoC study will receive the same information, the concerns that exist around bias in the context of the LCS are not relevant at this stage. Moreover, Kim et

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al.²⁹ argue that as long as it is scientifically feasible to adopt transparent recruitment, there are no special risk-benefit, informed consent, or fair subject selection issues that require blinded enrolment for secondary prevention studies of neurodegenerative disease that are not recruited from limited populations. They argue that transparent recruitment is neither coercive nor does it represent an undue influence on potential participants.


The evidence that is currently available⁴¹ suggests that there are minimal negative consequences of risk disclosure for individuals, providing appropriate exclusion criteria and counselling processes are in place (see Annex 2). Consequently, **the informed consent process for a PoC trial should make clear to participants the specific reasons why they have been invited to take part.** This reflects current practice in the majority of ongoing secondary prevention trials, including the A4⁴² and API APOe4⁴³ studies (although not the TOMMORROW⁴⁴ study).

3.5.1. *The implications of disclosure at PoC stage for LCS recruitment*

The disclosure of results at the PoC stage may have implications for the information provided to participants at earlier stages in the research process and their ability to exercise their right not to know. As discussed in the guidance on informed consent, participants should be informed at recruitment to the LCS of the overall goals of EPAD, including that the primary objective of EPAD is to develop a standing platform for adaptive secondary prevention clinical trials.

In the case of transparent recruitment, taking part in a trial will mean participants learning that they have one or more factors that are thought or are known to increase risk of developing AD. As described above, these findings are not routinely communicated earlier in the EPAD process because of either an unclear prognostic value, risk of bias or both.

Transparent recruitment to the PoC trials has two implications: first, participants will have to be educated on the meaning of results and consequences of learning them prior to any possible PoC invitation. Second, an invitation to take part in a PoC will inevitably tell participants something about their risk status. Consequently the right not to know can only be exercised by not participating in the project. The informed consent at LCS enrolment will therefore include the willingness to learn test results at recruitment into the PoC. **LCS consent should include educational material related to AD risk and a discussion of risk disclosure and the potential implications of learning risk status at a later stage. The**

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provision of educational material should be separated from the taking of consent to allow potential participants time to engage with and discuss the materials in detail.

3.6. Continued participation within the LCS and re-allocation to a PoC trial


During and subsequent to participation in a PoC trial, participants will continue to participate in the LCS. Following a wash-out period, they may then become eligible to take part in a further PoC trial and may wish to do so.

Post-POC participation in the LCS creates a new set of issues. Firstly, participants who learned information about their potential AD risk linked to a specific marker when allocated to a PoC subgroup will subsequently receive regular investigations for these biomarkers as part of their participation in the LCS. Participants may ask for updates on their biomarker status. In general, however, the meaning of changes in biomarkers independent of changes in cognition will be unclear. Therefore, participants who continue to participate in the LCS will in principle receive results from baseline assessments and cognitive tests only, just like the other LCS participants. The conditions for any communication of these results should be clearly established in both the consent for the PoC trial and the re-consent for the LCS if such consent is deemed necessary.

Secondly, as EPAD is a standing trial platform, it is possible that participants will enter subsequent PoC trials, for which recruitment is based on different markers. To date, the evidence related to disclosure focusses entirely on single factor risk communication – whether APOE or amyloid status^{41,45,46}. In the case of any cycling between LCS and PoC, participants are relatively unlikely to be drawn into trials of compounds targeting the same mechanism, given the difficulties of separating out long-term effects. Consequently, taking part in each new PoC may mean recruitment on the basis of a new biomarker, leading to the accumulation of risk information. The implications of this are not known – on the one hand, it is possible that learning amyloid status after learning APOE may not have any new implications. On the other, it is possible that a series of separately communicated risks, even if each is communicated and understood in a probabilistic manner, will become seen as a certainty. Furthermore, in the APOE/amyloid example, the former may be understood as a prediction of disease and the latter as a confirmation.

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The research team of the TDC should record the number of trials people have participated in and the markers on which their inclusion was based. Hence the discussion of the reason for PoC inclusion can be linked to the results someone received previously and he or she can be helped to make sense of the interrelationships between different risk factors.

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4. INCIDENTAL FINDINGS


4.1. Definition of ‘incidental findings’

An incidental finding is a finding “concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study.”⁴⁷ Incidental findings need not be unexpected or unanticipated. For the purposes of EPAD, incidental findings include findings that are clinically meaningful and actionable, and pertain to medical conditions that are life-threatening or serious. This definition excludes findings of unknown or unclear clinical significance and findings pertaining to medical or other conditions that are not serious.

In EPAD, this definition of incidental findings excludes findings related to dementia or Alzheimer’s disease or risk factors associated with Alzheimer’s disease, as these are the variables of interest, which are within the aims of the study. **Biomarkers or pathological changes related to dementia or Alzheimer’s disease (AD) are under study within EPAD and should not be considered incidental findings.**

4.2. Risks and benefits of incidental findings for research participants

The potential for the detection of incidental findings can be either a benefit or a risk to research participants. Incidental findings may lead to improved health outcomes when research participants and their doctors are made aware of abnormalities that suggest the advent or presence of diseases that can be prevented or treated.⁴⁸ On the other hand, incidental findings may lead to shock and distress, especially when there are no treatment options.⁴⁹ Sometimes the clinical significance of an incidental finding is and remains unclear.⁴⁸ Clinical follow-up may result in (unnecessary) burdens, including anxiety or distress (depending on the manner in which the finding is explained to and interpreted by the research participant), but also potentially time, effort and financial costs to research participants (depending on reimbursement structures within healthcare systems). Finally, having a ‘diagnosis’ may lead research participants to experience adverse consequences in the family and/or societal domains, including insurability and employability.⁴⁹ It is important to note that – also in the context of EPAD – research participants are (otherwise) healthy and free of symptoms. It is unclear whether the risks and costs associated with the feedback of incidental findings are outweighed by the supposed health benefits, which can be absent or questionable.

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Although studies show that **many research participants prefer incidental findings to be reported**,^{50–52} participants are less interested in learning about findings of unclear clinical significance or that are not (very) relevant to health or reproductive issues. **Incidental findings of (high) clinical importance should be reported to research participants.**

4.3. When can incidental findings occur within EPAD?

Incidental findings can be detected when research participants undergo ‘deep phenotyping’ upon entering the EPAD Cohort, and during subsequent annual visits at the Trial Delivery Center (TDC). According to the Study Protocol for EPAD Longitudinal Cohort Study that is currently under development, EPAD participants will undergo physical examinations, cognitive assessments, blood tests, CSF tests, genetic testing, MRI of the brain and PET scans. Through the use of each of these testing modalities, incidental findings can be detected. Given the unclear clinical significance and utility of incidental findings and the risks and burdens associated with their feedback, described above, it is generally acknowledged that incidental findings in research settings had better be avoided. When choosing testing modalities, researchers should choose the modality that is best suited to attain the research goals at hand. When two scientifically equivalent testing modalities are available, the narrower testing modality - with the least odds of generating incidental findings – should be considered preferable. **Where possible, the potential for detecting incidental findings should be minimized.**

Some testing modalities allow for a reduction of the potential for incidental findings through the use of filters (e.g. genetic testing) or targeted techniques (e.g. standard laboratory tests). As a rule of thumb, genome-wide screening or polygenic testing should be avoided when EPAD-researchers are only (or mainly) interested in the APOE gene. Polygenic testing may involve the possibility of detecting genetic findings that are unrelated to AD, the clinical significance of which may be unknown. A developing international consensus claims however that clinically actionable incidental findings should be fed back to research participants.^{53,54}

In some modalities, such as physical examinations or MR imaging, it is much more difficult to minimize the potential for incidental findings by technical means. For instance, as part of the longitudinal cohort study, EPAD will acquire diagnostic-grade MR images of the brain. If incidental findings are present, they are likely to ‘catch the eye’ of trained researchers

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reviewing diagnostic-grade MR images. Trained researchers or clinicians conducting physical examinations of research participants will likewise notice abnormal ‘biomarkers’ or measurements, such as BMI, hypertension or skin lesions. In these testing modalities, incidental findings are unavoidable.

4.4. Moral responsibilities regarding the detection of incidental findings

It is generally accepted that researchers have no moral obligation to actively look for incidental findings.⁵⁵ Researchers should strive to achieve their aim of generating generalizable knowledge,⁷ and not be burdened with conducting ‘health checks’ on research participants. Further, not all testing techniques used in the research setting are suitable for diagnostic purposes, for example: the T2 weighted and FLAIR sequences that will be acquired in EPAD are of diagnostic quality, whereas the fMRI sequences are not. Moreover, research participants are (presumed to be) healthy: they do not have symptoms or complaints, for which they are seeking healthcare. In sum, there is no need – in principle – to seek abnormalities or incidental findings in healthy research participants.

Nonetheless, research participants are likely to expect that brain scans will be ‘looked at’ by research personnel⁵⁶. Likewise, research participants may expect that suspect skin lesions, if present, will be detected by clinically trained research personnel. Expectations among research participants should be leading in questions regarding the detection, management and communication of incidental findings – not only to prevent the harms of false reassurance, but also to maintain trust and commitment to EPAD. Research participants may feel indignant if ‘no one has been looking’ at the scans. When they develop symptoms, seek medical care, and are given a diagnosis in a later stage, they may return to EPAD and fail to understand why no one had noticed the abnormality that was clearly visible on the scan at the time of acquisition. EPAD will wish to avoid such incidents. We recommend that **all research scans should be screened for abnormalities by specially trained researchers. In all TDCs, expert radiologists should be available for consultation when potential incidental findings are flagged during routine review.**

Although EPAD will arrange for routine review (for abnormalities) of all diagnostic-grade research scans (by trained research personnel), EPAD will not accept on a ‘duty to detect’ incidental findings and will not be held responsible for ‘missed diagnoses’.

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4.5. The anticipation of incidental findings

In a large-scale research enterprise such as EPAD, **incidental findings can and should be anticipated**. EPAD intends, for instance, to conduct MRI of the brain in over 6,000 *healthy* volunteers, who may or may not be at risk of developing Alzheimer’s dementia. It is known from previous studies that in around 2-3% of healthy volunteers who undergo MRI of the brain, *clinically significant* incidental findings are detected.⁵⁷ EPAD may therefore expect to find clinically significant incidental findings in the brain in at minimum 120-180 participants. It is important for EPAD to discuss and settle upon a policy for the detection, management and communication of incidental findings beforehand, to avoid *ad hoc* decision-making after the fact.

In large population-based imaging studies, it is best practice to pre-devise lists of anticipatable findings worthy and not worthy of feedback to participants.⁵⁷⁻⁵⁹ In the SHIP Study, in which whole-body MRI is conducted, researchers routinely report “category II findings” from a “list of precedents” or relatively common abnormalities for which clinical management guidelines exist and for which the recommendation to disclose is not affected by individual characteristics (e.g. (old) age or co-morbidity). The latter is to prevent researchers from taking up the role of the physician – building a medical case, making a treatment plan – outside the doctor-patient relationship.

We recommend EPAD to identify possible incidental findings for all tests and examinations to be conducted as part of the EPAD Cohort, and **to decide in advance what incidental findings should or should not be reported to research participants**. This requires the establishment of a working group (or set of working groups) within EPAD that will enlist clinicians with the relevant expertise. The aim of the working group is to devise an EPAD-wide protocol for the handling of incidental findings, that is to be implemented at the various TDCs. EPAD is planning such an effort for neuroimaging, as the Protocol Outline for EPAD-LCS reads: “Clinical findings that are identified through the course of the study e.g. incidental MRI findings will be recorded as AEs and managed through the EPAD-LCS protocol for neuroimaging incidental findings that is based on guidelines from across Europe” on page 5.

The working group may make use of an often-used classificatory system to subdivide possible incidental findings into three categories: urgent referral, routine referral and no referral.⁶⁰ The working group would fill in (something like) the table below:

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Testing modality	Urgent referral	Referral	No referral
Cognitive assessment			
Assessment of functional abilities			
Clinical examination			
Progression to dementia			
Neuroimaging (MRI)	e.g. malignant tumor	e.g. aneurysm > 7 mm, meningioma	e.g. white matter lesion, old brain infarct
Neuroimaging (PET)			
Genetic assessments			
Standard laboratory tests			


Box 1: Based on the Study Protocol for EPAD Longitudinal Cohort Study, Protocol EPAD-UoE-001 of 5 July 2015, which is currently under construction, on page 16, this table is meant to contain all tests and examination EPAD is planning to perform as part of the EPAD Cohort.

4.6. Unanticipated incidental findings

In accordance with current best practices,^{58,59} EPAD should consider the set-up of a **multidisciplinary expert panel** - at the level of the TDC - that will be tasked with decisions regarding the handling of incidental findings that have not been anticipated and have therefore not been addressed in the protocol. These will likely be rare occasions where team discussion will be desirable before the (rare) finding is reported. This panel could also perform reviews and/or updates of the protocol, on a regular basis or upon request.

4.7. The communication of incidental findings

Incidental findings will occur as a result of the tests and examinations within the EPAD LCS. If an EPAD researcher detects an incidental finding, the clinical significance of which is clear (and less severe), such as hypertension, the finding may be reported to the research participant directly by research personnel. The researcher will advise the participant to consult a GP or treating physician.


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If the clinical significance of the finding is not clear, the EPAD-researcher will need to consult a clinician with the relevant (oncological, neurological, neurosurgical, genetic) expertise to **confirm the finding** to avoid false positives and concurrent costs and burdens of unnecessary follow-up and ‘overdiagnosis’.

If the EPAD researcher detects an incidental finding that may have severe health consequences, the researcher may need to consult a clinical expert. (Possibly) severe incidental findings should not be reported to EPAD-participants without the provision of an acceptable level of care, support and guidance. EPAD researchers will refer the participant to a local hospital or medical center for clinical follow-up. **EPAD TDCs should make arrangements with local hospitals or medical centers about referrals to help ensure timely and high-quality clinical follow-up in case of (potentially) serious incidental findings detected at the TDC.**

The national lead or local PI at the TDC is responsible for the communication process to adhere to local or national legal and ethical requirements for the communication of incidental findings. In some countries, researchers may not contact research participants directly, but will need to contact a GP or a hospital-based specialist, who will explain the finding to the participant. In other countries, where this is not the case, research participants might feel bypassed when the finding is reported not to them, but to their GPs. In some countries, research participants must be notified by mail, whereas in other countries, it is customary for physician-researchers to contact participants directly by phone. As part of the informed consent process, research participants should ideally be able to indicate their preferences with regard to the manner of communication of incidental findings and whether or not their treating physician/GP should (also) be contacted in relation to such findings. National leads are responsible for the communication policy to adhere to local laws and guidelines. Where possible, participants’ preferences should be respected.

Feedback of incidental findings to the research participant should be conducted by clinical doctors – or, in countries where this is legally or morally acceptable, by knowledgeable research professionals with adequate communicative skills. These could be either members of the EPAD team itself or affiliated others, e.g. specialists in local hospitals, with whom **prior contact** and agreements have been made about the management and communication of incidental findings within EPAD.

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4.8. Ethical considerations


EPAD places high demands on research participants, *inter alia* in terms of time investment, invasive or uncomfortable procedures, long-term commitment, disclosure (or not) of information related to the risk of developing Alzheimer’s dementia, and uncertainty regarding drug trial participation. The **principle of reciprocity** requires a careful handling of incidental findings on the part of the EPAD-researcher.

To the extent it is possible, EPAD should avoid generating incidental findings for which there are no effective treatment options.

EPAD should offer a qualified opt-out option to participants. This means that participants may indicate (as part of the informed consent process) not to wish to know about incidental findings, and that EPAD-researchers will - in principle - respect the participants’ wishes, unless an incidental finding is detected of which the researcher is (almost) certain that feedback will prevent serious harm to the participant. Offering an opt-out option need not be impractical (i.e. some research groups report positive experiences with such an option), while it respect a ‘right not to know’ in the minority of research participants (estimates range between 3 and 10%) who wish to participate in research (e.g. for altruistic reasons) without receiving back incidentally detected health-related information (unless it concerns something very important).

As part of the informed consent process, **research participants may indicate whether or not they would like to receive back information about incidental findings and whether or not they would like EPAD to report the finding to their GP.** National or local regulations may not in all TDCs allow for giving the research participant the opportunity to choose from these options. Where possible, the opportunity to choose should be promoted. If national or local regulations preclude the opportunity to choose, EPAD will adhere to those regulations.

Research participants’ expectations regarding the feedback of incidental findings should align with the practice of handling incidental findings in EPAD. This means, for instance, that when research participants believe that scans will be checked for abnormalities or that “they are okay” when they don’t hear back from the researchers, they should not be (completely) mistaken. Researchers should explain whether or not - and to what extent - they will analyze test results ‘with a clinical eye’.

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5. THE EXPERIENCE OF EPAD PARTICIPATION

5.1. Introduction

The EPAD study raises a number of ethical concerns associated with research participation, some of which are common to clinical trials, others which are novel to the approach adopted. Foremost among these is the basic requirement that research must be preceded by a careful assessment and balancing of predictable risks and burdens to individuals involved in the research with foreseeable benefits to them, to those affected by Alzheimer's dementia and to society as a whole⁶¹. The ethical conduct of research also involves the respectful treatment of individuals who choose not to enrol and the careful ongoing monitoring of those who do⁷. This involves protecting the privacy and confidentiality of research subjects and establishing the opportunity to withdraw, informing subjects of newly discovered risks or benefits and of the results of clinical research, and suitably monitoring participant welfare.


5.2. Study risks, burdens and benefits

Principles of medical research ethics stress that researchers should minimise the risks and burdens associated with research participation, thereby ensuring that these are outweighed by the benefits of conducting the research. Consequently, there should be no other, less risky or burdensome way of answering the questions posed. The risk and burden of participation are key factors in research enrolment and retention. Limiting these contributes to ensuring that research makes the most effective use of resources, and ensuring that research is as good an experience for participants as possible.

5.2.1. Risks

It is important that the risks of participating in the EPAD project are as well-established as possible prior to recruitment and are monitored during the study. It is also important that they are clearly communicated to potential participants in order to enable them to make an informed decision on participation, and that participants are informed on an ongoing basis of any significant changes in the risks associated with participation. Equally, EPAD has a responsibility for monitoring the welfare of research participants.

In the LCS participants will be exposed to physical risks associated with testing procedures. The two most invasive procedures are the lumbar puncture and the taking of blood samples. The first brings with a risk of postprocedural headache, local bleeding and infection. Taking blood samples might cause bruising and infection.

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Participation in the PoC trials will involve, in addition to undergoing testing procedures, the intake of investigational compounds or placebo. The associated risks will differ per compound and should be detailed in the relevant compound appendix. Procedures for dealing with risk should follow GCP. If people experience adverse reactions, it is the responsibility of the investigator to assess the participant's general condition and the seriousness of possible adverse event, to take all necessary actions to protect his/her safety and well-being, and to ensure that he/her receives appropriate treatment; the investigator will decide whether this warrants withdrawal from the study. The consent form for PoC trials should clarify the recommended course of action to study participants in case of trial-related injuries and mention the conditions under which the costs of treatment will be covered (e.g. participant's own insurance; the sponsor's dedicated insurance), including applicable restrictions (e.g. if the participant has not followed the instructions, or the injury is related to a pre-existing disease present prior to the administration of the study drug).


In addition to potential adverse effects from IMPs, PoC participation will involve learning the results of biomarker and genetic testing. The effects of disclosing biomarkers other than APOE genotype are currently unknown. This is discussed in more detail in [section 3.5](#).

In both the LCS and in the PoC, there is a risk that false-positive incidental findings will be identified which have the potential to cause substantial distress. The validation of incidental findings is therefore very important. This is discussed in more detail in [section 4](#).

5.2.2. Burdens

A feature of contemporary Alzheimer's disease research, including EPAD, is the number of tests and measurements deemed necessary to provide a sufficiently detailed picture of disease progression. This potentially represents a significant burden on participants, and is a potential concern in terms of the implications for recruitment and dropout⁶². However, while the risks of participation are routinely assessed and communicated, the burden of research participation is comparatively difficult to establish and is in general relatively poorly defined or assessed⁶³⁻⁶⁵. Burden is a subjective experience, as the experience of undergoing tests will vary between individuals and potentially between test sites in different countries. It can be defined as the participant's "perception of the psychological, physical, and/or economic hardships associated with participation in the research process"^{63(p11)}.

Participation in the LCS and PoC involves repeated visits to the EPAD TDC during which people will undergo both biological tests and an extensive cognitive assessment. These visits

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will be time-consuming, particularly if participants have to travel to get to the TDC. Both the lumbar puncture and the taking of blood samples will by most be considered painful and by some as frightening procedures. An MRI scan may be uncomfortable, in particular for claustrophobic participants. Cognitive assessments are often intensive and may be difficult if someone performs poorly and is aware of this, or is concerned about the results. Moreover, the burden of attending study visits fasted (including not drinking coffee and tea or smoking) may be considerable. Specific to the PoC trials is the burden of having to take an IMP.

There is currently little evidence related to participants' experience of taking part in clinical research⁶³, and no standardised measures of burden. Work to develop such a measure building on existing work⁶⁵ may be a valuable future project for WP8. Regardless, it is important that TDCs put in place procedures for monitoring the effect of research on participants and provide opportunities for anonymous feedback related to this.

5.2.3. Benefits

The EPAD project involves potential burdens and risks for individual participants, while the potential benefits of the research are primarily societal and scientific. These are described in the project proposal, and include the more accurate identification of those at greatest risk of developing Alzheimer's dementia, the formation of new hypotheses for prevention strategies and advancing knowledge on compounds that show promise in modifying AD-related pathophysiological processes and in improving cognitive outcomes.

Nevertheless, there may be some benefits to individual participants related to participation. Participation in the LCS may fulfil participants' desire to contribute to research on AD and AD prevention, and the return of aggregate findings may contribute to feeling this is being achieved. Participants may value the opportunity to receive information related to their general health, and find it reassuring that incidental findings will be returned and they will know if something serious is wrong. The return of results from cognitive assessments may be informative if changes occur. For people experiencing problems with cognition in daily life, test results may contribute to explaining these. In the PoC trials, those assigned to an intervention arm may experience beneficial effects of the compound under study. In addition, learning biomarker status may stimulate beneficial health-related behaviour changes⁴⁰.

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5.3. Communication with participants

Ongoing communication with research participants is an important feature of good research practice. To demonstrate respect and reciprocity, the aggregate findings and progress of research should be communicated on an ongoing basis⁶⁶ to research participants. General research results should be made available in an ongoing manner so as to inform participants of overall findings, and researchers have a duty to actively promote the proper interpretation of research results and the limits thereof. This information should be disseminated in a form accessible to participants – in terms of ease of access, the level of expertise required and language. This may involve newsletters, websites, or other dynamic, interactive communications tools such as blogs and public events²³.

After an individual’s participation in EPAD ends, they should be asked if they wish to continue to receive updates on the results of EPAD research. Participants should also be provided with information about the availability of aggregate results following the end of the EPAD study. In this context, **WP6 should make provision for the archiving and ongoing availability of study results through the EPAD website.**

In addition to outwards communication to EPAD participants, EPAD should also develop mechanisms for receiving feedback and involving participants in decision making related to the project. One mechanism for this will be through regular contact between participants and the TDC. The TDCs should establish a procedure for anonymous feedback on the experience of EPAD participation.

At a project level, EPAD **should consider establishing a panel of participants drawn from across EPAD TDCs.** This panel could nominate a chairperson to engage with the EPAD management structure. It could meet virtually or in person, potentially alongside the EPAD GA and could participate in it. Participant representatives should be made aware and provide informed consent that by taking part in such a panel, they would become identifiable as study participants. Their personal data will remain subject to the same protections as for other participants. In the absence of such a panel, the first wave of participants in EPAD should be asked to provide formal feedback on the project from approach to consent, communication with site staff and through to their experience of testing procedures. This will enable the study to adapt to ensure it is acceptable to study participants while maintaining its scientific integrity and potential impact.

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5.4. Screening and exclusion from EPAD


The establishment of the LCS will involve an initial screening visit, with a six month follow-up at which potential participants will be told whether or not they meet inclusion criteria. This screening process is common practice in the development of clinical trials. However, the inclusion criteria for the LCS will change over the course of the project, according to expert judgment and through the development of a recruitment algorithm. This may mean that individuals initially excluded from EPAD may subsequently become eligible to participate.

Given that the inclusion criteria will evolve over the course of EPAD we advise that participants who are not eligible for the LCS after the screening stage are asked whether they would be willing to be recontacted within the next year, or a period for which their screen results are thought to remain valid, when there is a need for participants with their characteristics to cover the probability spectrum. The investigators should remain blinded as to why specific participants are contacted and if people become eligible, it should be made clear that this is because of changes in the study itself, rather than because of any change in the participant.

Not to include people in the future who are interested in participating and for whom the requisite screening data is available potentially means putting other people through screening unnecessarily, as well as wasting resources. In this context EPAD should be clear on how long it will regard assessments from the baseline as valid, and whether it will be necessary to establish a second, less intensive, track of participation that allows some update of assessments.

5.5. Respect for participant motivations

EPAD is unusual in that many participants will be recruited from existing studies, including population cohorts. Participants in such studies often have specific reasons for agreeing to (and continuing to) take part. On the one hand, this may be an altruistic desire to make a broader contribution to society or medical science. However it may also include personal or familial reasons, such as the experiences of a family member with a disease, or an expectation of a potential health benefit for themselves or family members^{67,68}. These motivations will shape how they engage with new studies such as EPAD, and how EPAD can and should engage with them. This may be particularly important in future waves of recruitment if and when parent cohorts were not initially established for the study of dementia or brain ageing.

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In the case of EPAD, the motivation to participate may also be affected by the incorporation of publicly funded cohorts into partnerships with the private sector⁶⁹. The potential for commercial application may have implications for participants for whom the motivation to join a parent cohort was tied to a collective public good.

The EPAD participant information sheet should make it clear that EPAD is a public-private partnership, and that the research may result in financial gain for private partners.

5.6. Implications for existing studies


Recruitment from parent cohorts may risk jeopardising existing cohorts, as participants may feel that their commitment to research is satisfied by their involvement in the new research. Participation may thus become a zero-sum game, as a gain to EPAD becomes a loss to other research.

This is particularly pertinent in the case of long term parent cohort participation, as involvement in clinical trials or changes in behaviour prompted by the disclosure of risk status may exclude participants from observational studies to which they have a longstanding commitment. It is important practically in terms of the ability to interest the PIs of parent cohorts in EPAD if they are concerned about the effect on their own study.

Engagement with Parent cohort PIs should make it clear that EPAD may have implications for the retention of their participants and should work to minimise these.

5.7. Recruitment Exclusion

EPAD involves a novel recruitment strategy which aims to maximise the potential of the resources and relationships accrued within existing research. However, it currently excludes people who are not already members of a cohort study. However, publicity surrounding the project may mobilise interest from people who would like to be involved in research. Local TDCs should establish a procedure for dealing with these enquiries.

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6. DATA SHARING AND GOVERNANCE

6.1. Introduction

This section covers ethical considerations related to the use and re-use of data within and beyond EPAD. Legal and regulatory considerations related to data sharing are covered by the EPAD Project Agreement. The sponsor, legal and regulatory groups within EPAD and the partners involved in data management are responsible for ensuring that procedures for data quality, protection and security comply with local national and international standards.


The terms of the EPAD project agreement state that following the termination of the EPAD project, EPAD data will be made available for sharing beyond the project. The sharing and re-use of data has become an increasingly important focus of ethical concern over the last decade, associated with the establishment of biobanks⁶⁹⁻⁷², the development of international consortia in genetic^{73,74} and neuroscientific^{75,76} research, and the growing availability and power of bioinformatics approaches to health research.

This work has identified a number of important considerations associated with the combination and use of databases in biomedical research, many of which are considered elsewhere in this document, including the return of results to participants, informed consent procedures and participation and withdrawal.

6.2. Ensuring the ethical use and re-use of data

Important background for this document is provided by the 2015 report of the Nuffield Council on Bioethics¹⁰ into ethical issues associated with the collection, linking and use of data in biomedical research and health care and the Global Alliance for Genomics and Health Framework for responsible sharing of genomic and health-related data¹¹. These establish a set of principles for the ethical management and oversight of data sharing in health research.

The Nuffield report argues that the use of data should occur in accordance with a publicly statable set of morally reasonable expectations and should be subject to appropriate governance. These expectations should be established through both recourse to objective moral standards or principles and a legitimate procedure of decision making which includes all morally relevant parties. They suggest four principles, the first of which is respect for persons, in enabling all those who have relevant interests to have an initial say in how their data will be used and subsequently informing them how their data are being used. In addition, they argue the importance of respect for human rights, the involvement of data

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subjects in determining expectations for data use, and accountability for decisions related to data use and security. This latter point is critical, given that despite the best efforts of all parties, the security of data can never be entirely guaranteed.


The principles and the procedure for decision making require the involvement of all those affected by data storage and sharing. This includes research participants or patients, as well as clinicians, researchers and patients' organisations.

6.3. Data sharing beyond EPAD

The terms of the EPAD project agreement provide for a framework for accessing data generated in the EPAD project during and following the termination of the EPAD project, EPAD data will be made available for sharing beyond the project. The structures for doing this will be established and evolve during the course of the project, and will reflect imminent changes in EU data protection regulation. However, it is important that there should be clarity at an early stage in terms of who authorises access to data and their reuse, how the downstream use of data will be monitored and how participants will be able to refuse or withdraw consent for their data being shared.

Procedures for data sharing should follow the principles set out by the Global Alliance for Genomics and Health¹¹ framework. This includes making sure that data sharing is transparent, with clearly defined and accessible information provided on the purposes, processes, procedures and governance frameworks for data collection, use and exchange, including where data are transferred to third parties or across international borders. It should also be clear to what extent to which individuals and data are identifiable – particularly on the basis of EPAD genetic and imaging data – and whether there are limits to anonymity or confidentiality of data. Establishing a framework for sharing EPAD data also involves ensuring that research complies with applicable privacy and data protection regulations at every stage of data sharing. EPAD should be in a position to provide assurances to citizens that confidentiality and privacy are appropriately protected when data are collected, stored, processed, and exchanged. Furthermore, given that neither anonymization nor compliance with consent are likely to offer sufficient privacy protections¹⁰ there should be clear pathway of accountability.

The EPAD data access committee should be set up at an early stage to establish procedures for access requests and monitoring and to ensure that data are ready and available to be shared at the earliest possible opportunity. The data access committee should include representation from EPAD participants. Consideration should also be given

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to sustainability, ensuring that EPAD data remains available after the conclusion of the project and is available for long-term future use.


6.4. Data sharing between LCS and PC

EPAD-LCS participants are not asked to leave their PCs. This condition makes it reasonable for PIs of PCs to consider collaboration with EPAD. For PC PIs, having their participants enrol in the EPAD-LCS may be advantageous, as research data obtained in the LCS can be shared with PCs. During the informed consent process for the LCS, research participants are asked whether or not they agree to the sharing of research data with the PC. This is an optional component within the informed consent process (see Annex 1): research participants remain able to participate in the EPAD-LCS when they do not agree to data being shared.

Consent to data sharing may also benefit the research participant themselves: participants may not need to be asked to undergo the same or similar tests or examinations in both the EPAD-LCS and again in the PC. This should reduce the sum burden of participation. It will be stressed to EPAD participants during the informed consent process that PC participation can be continued. Research participants will also be informed about the risks and benefits of agreeing to data sharing between EPAD and the PC.

6.5. Data sharing between EPAD and the PC

Discussed in D8.2

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7. CONTINUITY BETWEEN THE LCS AND PoC

7.1. Introduction

The EPAD project aims to establish a well-characterised group of research participants interested in principle in participating in secondary prevention clinical trials – a ‘readiness cohort’ and progress them through proof of concept trials. Within the overarching project structure, there are two connected but distinct study protocols. The first is the Longitudinal Cohort Study (LCS) of 6,000 individuals who regularly attend the EPAD trial delivery centres (TDCs) for a battery of psychological and biological assessments. The second provides the basis for proof-of-concept (PoC) clinical trials that will be recruited from the LCS on an ongoing but ad-hoc basis. The exact inclusion and exclusion criteria and study requirements for any PoC trial will be determined in discussion with compound owners.


In certain legal and practical respects, the EPAD LCS and PoC may be considered separate studies. They may not share a sponsor, while individual PoC trials will include different EFPIA partners, and different entities may bear formal responsibility and liability for participant safety, data security, good clinical practice, etc. The LCS and PoC studies will also be reviewed separately by ethics committees or institutional review boards in the various TDC regions, as will individual PoC trials.

While the LCS and PoC are structured and conducted according to different research protocols, the same participants will take part in both. From a participant perspective, they will be essentially the same study – involving the same study sites, the same personnel and the same EPAD branding. Therefore, the studies should be seen and managed as a continuum.

Key ethical considerations in this context are the burden of participation, further to section 5; implications in relation to disclosure, further to section 3; and related to data sharing and reuse, further to section 6.

7.2. Continuity

It is important that there is continuity in terms of the assessments EPAD participants undergo in the LCS and PoC and in the data derived from these. This ensures that no assessments are carried out unnecessarily, and ensures that participants feel that the EPAD project is connected and consistent.

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There is no reason for participants to leave the LCS in order to participate in a PoC and then re-enter subsequently. They will by default continue to be LCS participants and will continue to be invited for annual follow-up visits at the TDC (from 30 days after PoC trial completion onwards), just like any other LCS participant – though not while they are actively enrolled in a PoC. Participants can thus remain enrolled in both arms of the EPAD study at the same time - as indeed, they may also continue to take part in the parent cohort (PC), or choose to participate in other clinical trials. This suggested policy of default continued enrolment is thus in line with the EPAD policy regarding the continuation of participation in the PC: EPAD-LCS participants are not asked to leave their PCs.

Nevertheless, it may be that participation in the LCS and PoC seems to be incompatible. For example, a participant may miss their annual LCS assessment because they are participating in the PoC, which would represent a ‘violation’ of the LCS protocol. However, it is likely that there will be considerable overlap between the assessments carried out in the PoC and the LCS. If the tests required for the LCS are conducted during PoC participation, the data from these should be fed back into the LCS in place of the annual assessment. There is no reason therefore to insist that participants withdraw from the LCS if they take part in a PoC trial. Neither is there reason to conduct the same assessments again on conclusion of the PoC. Repeating the same assessments would place unnecessary burdens on the research participant.

7.3. Data sharing between LCS and PoC

The LCS and PoC studies will be conducted according to different protocols, data derived from the studies may be stored in databases held by different partner companies, and it is possible that the studies may not share a common sponsor. For the purposes of continuity, **it is advised that the PoC informed consent process include a component about data sharing between the EPAD PoC and the EPAD-LCS.**

For scientific reasons, a participant’s LCS record should show that they has enrolled in a PoC, what the PoC entails (i.e. to correct for confounding effects), when the PoC has been completed, and thus when the participant can be contacted for LCS-related activities again, etc. PoC participation will often entail additional (and more frequent) tests and examinations to detect the effects of compound/placebo. If the research participant objects to the transferal of research results to the LCS, LCS researchers are likely to ask the participant to undergo scheduled annual tests and examinations again, after completion of

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the PoC. This may be burdensome for research participants, as they may need to undergo the same or similar tests twice. Moreover, duplication of tests and examinations is a waste of time and resources. The research participant will be informed about the risks and benefits of agreeing to data sharing between the PoC and the LCS.

However, there is no need to oblige research participants to agree to the sharing of research results with the LCS as a precondition to participation in a PoC trial. In parallel to the policy related to the sharing of data with parent cohorts, this component should be optional: participants can still be enrolled in a PoC when they do not agree to data being shared between the PoC and the LCS. Consequently, **consent to data sharing will not be a *sine qua non* for participation in the LCS.**


7.4. ‘Cycling’ and exploitation

Core principles of research ethics are to avoid the over-exploitation of research participants and to minimise their exposure to unnecessary risks and burdens. If members of the EPAD LCS are repeatedly recruited to PoC trials, ‘cycling’ between the two arms of EPAD, there is a clear potential for this cumulative burden to occur. It would not be feasible or necessarily desirable^{77,78} to limit a participant’s opportunity to participate in trials if they desire to do so. However, participants should not take part in two trials simultaneously, and as they study continues, **EPAD should be vigilant about whether some LCS participants are being contacted disproportionately to take part in PoC trials.** The project should monitor the exposure to risks and burdens of participants during the course of the project, and remain aware of the potential for (cumulative) harm. A clear time period should be established between trials and specified within the study documentation.


7.5. Cumulative disclosure and bias

As discussed in section 3, participation in a PoC trial will involve the communication of information about risk status based on genotyping or biomarker results. Repeated participation will potentially involve the communication of various different forms of information/data points. While on the basis of one data point only, it will be difficult for research participants to draw clinically meaningful conclusions about their risk of AD, they could, in principle, reconstruct a picture of their risk of AD on the basis of multiple data points.

This has implications in terms of the potential impact on individuals (see section 3.5). It could also have implications in terms of any potential bias introduced into the LCS by the inclusion

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of people who have been given information related to their risk of developing AD, information that may affect their cognitive testing performance or prompt behaviour changes. It is unlikely that this bias will have any significant effect on the scientific validity of the cohort, although it should be controlled for where possible. However, within the context of the LCS, EPAD researchers may have the opportunity to observe whether changes in cognitive test scores occur following disclosure, particularly among participants randomised to placebo arms in the PoC.

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ANNEXES

Annex 1: Recommended informed consent forms


Annex 1.1 Recommended contents for EPAD LCS informed consent form

a. Necessary informed consents for EPAD-LCS (*research participant can only participate in EPAD LCS if he/she consents to these tasks*):

- I agree to my GP/treating physician/PI of PC being notified about my participation in this study
- I agree to the use of my data for the goals described in the information sheet
- I agree to the use of my data/samples to test for new biomarkers, that weren't mentioned in the information sheets, during EPAD, without further/separate consent being requested from me.
- I agree to the storage of my research data for 15 years after the completion of this study
- I agree to be contacted during my participation in EPAD LCS about the possibility to participate in a PoC drug trial. (you will only be contacted if you are eligible).
- I am aware that an invitation into such a PoC drug trial may be based on factors associated with Alzheimer's dementia risk and agree to possibly learning about carrying such factors.
- I want to participate in this study

b. Optional informed consents for EPAD LCS (*research participant can dissent to these tasks, without this affecting his/her participation in EPAD-LCS*):

- I agree to receive information about clinically relevant incidental findings not related to Alzheimer's disease.
- I agree to my GP/treating physician being contacted in relation to these clinically relevant incidental findings not related to Alzheimer's disease.
- I agree to the researchers contacting my GP and other relevant doctors I am seeing for further medical information if this is required.
- I agree to data collected from me during this study to be returned to *<the PI of the original PC>*
- I agree to the storage of my material for 15 years after the end completion of this study, so that it can be used for future research (you will be contacted at that time to consent for this)
- I agree to be re-contacted about future research with the same objective
- I agree to be re-contacted about future research with other objectives

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Annex 1.2 Recommended contents for EPAD PoC informed consent form

a. Necessary informed consents for PoC-trial (*research participant can only participate in PoC-trial if he/she consents to these tasks*):

- I agree to my GP/treating physician/PI of PC being notified about my participation in this study
- I agree to the use of my data for the goals described in the information sheet
- I agree to the storage of my research data for 15 years after the completion of this study
- I agree to be contacted after my participation in the trial about returning to the EPAD-LCS
- I want to participate in this study

b. Optional informed consents for EPAD LCS (*research participant can dissent to these tasks, without this affecting his/her participation in PoC-trial*):

- I agree to receive information about clinically relevant incidental findings not related to Alzheimer's disease.
- I agree to my GP/treating physician being contacted in relation to these clinically relevant incidental findings not related to Alzheimer's disease. I agree to the researchers contacting my GP and other relevant doctors I am seeing for further medical information if this is required
- I agree to data previously collected in the EPAD-LCS being exported and used in this study
- I agree to data collected from me during this study to be returned to the EPAD-LCS
- I agree to the storage of my material for 15 years after the end completion of this study, so that it can be used for future research (you will be contacted at that time to consent for this)
- I agree to be re-contacted about future research with the same objective
- I agree to be re-contacted about future research with other objectives

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Annex 2: Summary of evidence related to the effects of the disclosure of AD risk

The implications of disclosing information related to Alzheimer’s disease risk have been discussed in the clinical and scientific literature for two decades^{79,80}, primarily in terms of the communication of genetic susceptibility genotypes. This literature has identified a range of potential benefits and harms arising from disclosure.


Potential benefits of disclosure

After testing participants may be curious or may worry about their results. In this situation, disclosure can give relief from uncertainty⁸¹. Furthermore, disclosure of an increased risk of AD has been observed to encourage changes in health-related behaviour^{40,82}. Although this behaviour, such as increasing exercise, is not proven to prevent or delay the development of AD, it can be beneficial in preventing other diseases. In the USA, people who are at increased risk of developing AD have also been found to be more likely to increase long term care insurance than those who are at low risk^{83,84}. Although on a group or societal level, adverse selection can decrease insurance coverage and affordability of care, for people who are interested in predictive testing this is an important benefit of receiving results, together with other possibilities to plan for the future such as arranging care, preparing their family for their illness and making important life decisions^{85–88}. This suggests that the value of risk information or the lack thereof is not limited to clinical utility but involves personal utility as well.

Potential for harm

Disclosure of AD risk has been considered potentially harmful because of a lack of therapeutic and preventative options. Although this is still an important reason for people not to want presymptomatic or susceptibility testing for AD, the view on disclosure has changed as research has suggested that the potential for psychological harm due to genetic risk disclosure is limited^{85,87,89–91}. In addition, family risk and family relationships were not perceived differently by participants following genetic risk disclosure⁹².

Although the disclosure of genetic risk seems to have few harmful consequences, there are potentially negative implications. First, informing people that they are APOE ε4 positive seems to have a negative effect on subjective and objective memory functioning³⁹. Second, probabilistic results such as those provided by biomarkers are difficult to communicate effectively and complicated to interpret on an individual level^{93,94}. People find it hard to understand probabilistic information and in research into the perceived potential impact of AD risk some people report that an increased risk of AD would inform life decisions such as spending all their money or committing suicide^{95–97}. There also evidence that the disclosure of risk status is experienced as a diagnosis⁹⁸. Consequently, there is the potential that people become ‘patients-in-waiting’, neither healthy nor ill,

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but living in anticipation of disease⁹⁹. Planning one's life in the expectation of a disease that one may or may not get can be considered harmful. Third, one of the most important reasons people do not want to undergo predictive testing for AD is fear for loss of insurance and employment discrimination^{85,87,100,101}. In the existing work, including the REVEAL study, disclosed results were confidential. It is thus not clear to what extent this would be a problem in the future if risk status is disclosed outside research or if results are not confidential. However, biomarkers such as amyloid are not covered by existing genetic non-discrimination laws¹⁰⁰.


The effects of disclosure on family members and professional caregivers have not been investigated in detail. However, upsetting loved ones and concern about children's risk are among the most important concerns about predictive genetic testing, suggesting that this effect might be considerable^{85,87}.

Finally, the approach to the disclosure of risk results has an important effect on the burden laid on professional caregivers. In the REVEAL II study, individuals who received their APOE genotype in a condensed protocol without a face to face pre-disclosure session were significantly more likely to discuss their results with a healthcare professional than those who received their results in an extended protocol¹⁰².


Gaps in the evidence

A number of dimensions are known to affect understandings of AD risk, including age, gender, level of education and familial experiences of Alzheimer's disease and the extent to which this creates an existing perception of being 'at risk'^{41,89,92,103}. However, there is a particular need to examine differences among two groups. Firstly, there may be potential differences in the communication of results depending on the position of the participant on the AD risk 'spectrum', from cognitively normal with biomarker changes through to MCI-AD. For patients with MCI, being at increased risk of developing AD may be less unexpected than for healthy individuals, but results such as amyloid positivity are more predictive of progression to AD than in the latter group²⁸ and might therefore have a greater impact. Secondly, the existing evidence is limited in its geographical scope. As such, it inevitably reflects US attitudes towards health risks, Alzheimer's disease, healthcare and clinical research. Importantly, research by Alzheimer Europe¹⁰⁴ along with a small body of comparative work^{86,105,106} suggests that attitudes to AD risk vary significantly between and potentially within countries, including between the USA and Europe.

Finally, existing research has concentrated on the disclosure of genetic-based risk information and has examined disclosure approaches based around the model of counselling for genotype disclosure. This reflects the prominence of APOE genotype in thinking about AD risk, and concerns around the implications of the disclosure of this status, particularly considered against the example of the disclosure of highly penetrant mutations such as those for Huntington's or in the case of autosomal


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dominant AD^{95,107}. While genetic counselling approaches are undoubtedly an excellent starting point for the disclosure of risk information, important questions remain about its broader applicability¹⁰⁷. In particular, there is a need to explore whether such trait information, which may make only an incremental contribution to individuals' knowledge of their future health in the context of well understood family histories⁹², differs from state information, such as the results of PET imaging or CSF sampling⁹⁴.


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