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European Prevention of Alzheimer's Dementia Consortium

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**D8.4 Interim report on ethical and social
implications of biomarker disclosure:
approaches to disclosure in EPAD**

WP8 – Ethical, Legal and Social Implications

V2.0

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Responsible Author	Richard Milne		Email	Rjm231@cam.ac.uk
	Partner	UCAM	Phone	+44 (0)1223 761912

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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 Center (Spain)
 - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
 - **KI.** Karolinska Institutet (Sweden)
 - **VUmc.** Stichting VUmc (Netherlands)
 - **UCAM.** Masters and Scholars of the University of Cambridge (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)
 - **IQVIA.** IQVIA, Ltd (United Kingdom)
 - **AE.** Alzheimer Europe (Luxembourg)
 - **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)

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

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- **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 Limited (United Kingdom)
- **Amgen.** Amgen NV (Belgium)
- **Pfizer.** Pfizer Limited (United Kingdom)
- **UCB.** UCB Biopharma SPRL (Belgium)
- **ARIDHIA.** Aridhia Informatics Ltd (United Kingdom)
- **ROCHE.** F. Hoffmann - La Roche (Switzerland)
- **UKK.** University Hospital of Cologne (Germany)

- **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.


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Executive Summary

In the EPAD ethics guidance document (D8.1) we recommended against routinely returning CSF and PET amyloid information to asymptomatic research participants. However, this information will be communicated to some EPAD longitudinal cohort study (or LCS) participants as part of recruitment to the proof of concept (or PoC) platform. In D8.1 we also recommended that, should research participants explicitly request these data, they have a right to access data about themselves and the study should provide them with it.

This deliverable addresses these scenarios related to the communication of biomarker results within EPAD study, and the further situation in which treating clinicians may request EPAD data to inform clinical decisions. The deliverable identifies a number of different populations in EPAD, distinguished by their cognitive status, their route into the study and their existing knowledge of their biomarker status. The existence of these distinct populations has important implications for the approach adopted for recruitment into the PoC and for the communication of biomarker results.

We suggest considerations for best practice in PoC recruitment and biomarker disclosure for each of the EPAD populations. As the procedures for recruitment into the EPAD PoC platform are still under development, these should be considered as guidance, and can inform the development of the PoC protocol.

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1. Introduction


The aim of this deliverable is to detail the process for the communication of amyloid biomarkers to participants within the EPAD longitudinal cohort study, and map existing experience and expectations related to disclosure among EPAD centres.

Communication of biomarker information gathered during the EPAD Longitudinal Cohort Study (LCS) to research participants may occur in three scenarios:

- during recruitment to the Proof of Concept (PoC) trial platform, for which abnormal amyloid status is currently an inclusion criteria;
- if participants explicitly request their LCS results;
- if a participant’s treating clinician requests information about LCS results to inform care.

The deliverable builds on the work in D8.1 which identified disclosure as a key ethical issue associated with the EPAD project, and D8.3 which set out preferences of potential research participants related to disclosure. In D8.1 we recommended against routinely returning cerebrospinal fluid (CSF) and positron emission tomography (PET) derived amyloid information to research participants without cognitive impairment (including the ‘asymptomatic’ or ‘preclinical’ population), as the prognostic significance and clinical and personal utility of these biomarkers is currently unclear for this population. As a general rule, we suggested disclosure of AD biomarkers to healthy participants should be discouraged because of the biomarkers’ limited clinical validity and problematic personal utility. We considered two exceptions to this.

First, Article 8 of the CIOMS International Ethical Guidelines for Health-related Research Involving Humans states that participants should be informed about the reasons “for considering the individual suitable for the research”¹ as part of a responsible informed consent procedure. Transparent enrolment in Alzheimer’s Disease (AD) clinical trials, which entails disclosure of AD biomarker status when this was used as a basis for selection of participants,

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is thus broadly supported². Therefore, this information will be communicated as part of recruitment to the PoC platform.

Further, we recommended that, while disclosure should be discouraged, if LCS research participants explicitly request these data, the study should provide them with it, along with accompanying information and explanation to enable participants to make sense of its implications. This does not imply any judgement on the clinical or personal utility of the information, but rather reciprocates participants’ contribution to the study and is in line with the general right to access personal data acknowledged in the Charter of Fundamental Rights of the European Union.

This deliverable addresses these scenarios related to disclosure and forms the basis for best practice within the EPAD study.


2. Background

2.1. Existing practice in communicating amyloid biomarkers

To date, a small number of approaches to communicating biomarker results in AD have been published. The most detailed descriptions of disclosure processes are those which have been elaborated in clinical research settings, notably by Harkins *et al.* and Burns *et al.* for the communication of amyloid PET imaging to asymptomatic individuals^{3,4}, and by Lingler *et al.* for PET⁵ and CSF^{6,7} biomarkers in the case of mild cognitive impairment (MCI). Finally, the preferences of asymptomatic individuals and people with dementia related to the communication of biomarker-based risk have been studied in EPAD (D8.3; Milne *et al.* 2018).

2.2. Communicating amyloid biomarkers to asymptomatic individuals

The disclosure processes described by Harkins *et al.*³ for the communication of amyloid information to people without cognitive complaints is the most clearly elaborated and detailed approach published in the literature to date. It forms the basis for current practice in clinical

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trials in this population, including the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study⁸, which recruits cognitively healthy participants based on positive amyloid results on PET imaging.

The A4 approach provides a staged process for the disclosure of results and model language on describing the meaning of amyloid. Scan results are not shared with the participant's physicians nor entered into the medical record.

The Harkins *et al.* model is currently being adopted in practice within a number of 'preclinical' AD trials with asymptomatic populations and is similar in content to the approach described by Burns and colleagues⁴ in the context of the APEX clinical trial of exercise in AD prevention.

1. Education in the form of an information brochure is provided in advance of the initial consent visit. This sets out the state of knowledge about amyloid imaging, the range of possible results and their implications.
2. The information in the brochure is then discussed in detail during the consent process, along with motivations to join the study.
3. Comprehension of the brochure is then assessed, and potential participants are screened for anxiety and depression to establish their suitability to receive amyloid biomarker results.
4. *PET imaging takes place at a separate visit.*
5. Disclosure occurs at a third visit. Prior to the disclosure of results taking place, study staff who are skilled in communicating and recognising distress again establish a participant's willingness to learn the results, their mood and whether they have had recent life stress.
6. Disclosure occurs using standardised language reflecting that in the information brochure, accompanied by written information and with a family member or friend present if desired. Comprehension of the results is then assessed.
7. Participants are followed-up by phone three days after disclosure to assess wellbeing, distress and the impact of disclosure, with a follow-up plan created based on responses. Participants are followed-up over the course of the trial.

(Adapted from Harkins *et al.* 2015)


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2.3. Communicating amyloid biomarkers to people with MCI

US and European consensus groups have suggested that the use of PET or CSF amyloid biomarkers is appropriate in the diagnostic evaluation of mild cognitive impairment^{6,9}. However, national guidelines on the use of biomarkers for the assessment of MCI vary¹⁰.

A number of groups have reported proposed models for communicating biomarkers to people with mild cognitive impairment. Witte *et al.*¹¹ describe a three-stage model of counselling, imaging and disclosure similar to the model described above, culminating in a discussion of the implications of a diagnosis and future treatment options. The counselling and decision making about the clinical use of biomarkers has also been approached as an example of shared decision making^{12,13}. Lingler and colleagues⁵ set out in detail a staged approach to the disclosure of amyloid status to people with mild cognitive impairment developed in consultation with experts in neurology, imaging, genetics and bioethics, and piloted with people with MCI and caregivers. Notably this did not include geriatricians or primary care physicians or other clinical disciplines involved in older people's care. It emphasises pre-disclosure counselling and post-disclosure assessments of comprehension and suggests the value of involving family or friends in the process as much as possible. Patient and caregiver comments also contribute important points on the content of information. They highlight the possible value of using brain images and the importance of clear graphics, a point increasingly recognised in the communication of genetic risk¹⁴. They also emphasise the importance of take home materials, and raise the question of whether and how test results are communicated to primary care providers.

The content of information provided to people with MCI has received recent attention from Grill *et al.*¹⁵ and Herukka *et al.*⁶. Herruka *et al.* provide recommendations concerning counselling before and after consent for lumbar punctures and the use of CSF biomarkers in the clinic. They suggest that before asking for consent for a lumbar puncture in a patient with MCI they should be informed that CSF biomarkers may identify the risk of symptom progression and confirm AD as the cause of the symptoms. They further propose quantifying approximate 3 year risks of progression to dementia with unknown, negative and positive biomarker status.

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However, given the absence of results on which to base anything with any certainty because of the inconsistency of results and variable quality^{16,17} of diagnostic accuracy studies, it is likely to be preferable to persist with a qualitative approach similar to that proposed by Grill *et al.* Grill *et al.* suggest standardised wording when PET imaging is used to support a diagnosis of MCI, which considers the risk of cognitive and functional decline and future planning. This wording emphasises the limitations of the available evidence on the prognostic or risk prediction value of biomarkers, stating that:


“Your scan results suggest that amyloid levels in your brain are elevated. Combined with the other tests we’ve done, it leads me to conclude that Alzheimer’s disease is the most likely cause of your cognitive changes, although other less likely causes remain a possibility. Although I can’t be absolutely certain and we don’t have the individual estimates for timing, people with results like yours are at increased risk for developing dementia over the next few years. Given all of this, I think we need to talk about making an overall plan to manage your condition.”

While this wording may not appropriately translate across national settings or between care sites, it provides a qualitative approach to the return of results which avoids prematurely stabilising uncertain clinical data and avoids communicating a sense of certainty about the clinical utility of these results for an individual.

3. Existing experience at EPAD centres

To inform the current work, 11 telephone interviews have been conducted with Trial Delivery Centre (TDC) leads and study clinicians at 7 EPAD TDCs. These interviews cover current practice at the TDC and expectations related to the disclosure process in EPAD.


The interviews show that Alzheimer’s disease biomarkers - primarily based on CSF - are widely used across the first wave EPAD TDCs. One Wave 1 TDC does not currently use either CSF or PET biomarkers in the clinic. In some centres, the use of biomarkers in the clinic dates back

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over 15 years. CSF markers are used primarily with patients who have mild cognitive impairment or suspected dementia and in the clinical assessment of people with subjective cognitive decline at two centres.

There is experience within EPAD from clinicians who are communicating results on amyloid biomarkers to people with mild cognitive impairment and AD dementia. However, there is less experience in communicating the results of biomarker testing to healthy, asymptomatic individuals within research settings. At least 3 centres have recent experience with conducting trials in this population. In France, there may be regulatory and ethics committee resistance to conducting trials with people without symptoms of cognitive impairment or disclosing biomarkers.

As further centres join EPAD, it is likely that experience with the clinical use of biomarkers will vary even more. However, there is little recent evidence about the use of biomarkers in the clinic. Among 37 research active memory centres surveyed by the European Alzheimer's Disease Consortium (EADC) in 2012, 11% described always using CSF biomarkers and a further 11% frequently in the aetiological diagnosis of mild cognitive impairment (Figure 1)¹⁸. 16% never used CSF biomarkers. At a national level, although 60% of Dutch centres surveyed through the EADC made use of biomarkers, in 5% of patients¹⁹. In France, a survey of 141 memory clinic physicians (61 neurologists, 65 geriatricians and 15 others) described CSF biomarker use primarily when there was atypical clinical presentation or diagnostic uncertainty, while 10.6% 'systematically' used CSF biomarkers for patients with MCI²⁰. However, there is less evidence about how such markers are used across age groups of people with dementia.

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	Never (0% of patients)	Rarely (<10% of patients)	Regularly (20-60% of patients)	Frequently (60-80% of patients)	Always (>80% of patients)	Centres using the biomarkers
 Medial Temporal Atrophy	0 (0%)	2 (6%)	7 (19%)	5 (13%)	23 (62%)	37 (100%)
 FDG PET	8 (22%)	18 (49%)	5 (13%)	3 (8%)	3 (8%)	29 (78%)
 CSF abeta/tau	6 (16%)	15 (40%)	8 (22%)	4 (11%)	4 (11%)	31 (84%)
 Amyloid PET	23 (62%)	8 (22%)	5 (13%)	1 (3%)	0 (0%)	14 (38%)

Figure 1: Reproduced from Bocchetta et al.


In clinical practice in EPAD TDCs which use biomarkers, they are currently communicated face-to-face by clinicians as part of a comprehensive clinical assessment of cognitive problems, rather than in isolation. This clinical routine contrasts with the situation in clinical trial recruitment, in which biomarker information may be highlighted as a primary reason for eligibility, and consequently given greater emphasis.

The primary consequence of being identified as amyloid ‘positive’ at the TDCs is often an invitation to participate in Alzheimer’s disease research or clinical trials. People with MCI who are amyloid positive otherwise receive the same follow-up as those who are not. Nevertheless, there is also variation across the EPAD centres in terms of how amyloid biomarker findings are communicated. In three memory clinics attached to TDCs, patients are currently given binary results, told that they are either amyloid positive or negative. At another three, patients are given the value of their test results. Interviewees emphasised the importance of transparency about the limits of scientific and clinical knowledge related to the implications of biomarker findings

While standardised approaches have been suggested for the use of biomarkers, no EPAD centres have a current, formal protocol specifically for the communication of biomarkers in clinical contexts. Such protocols are under development at several centres. Once available, they may be useful for informing practice in the communication of biomarkers in populations who fulfil criteria for ‘prodromal AD’ within EPAD.

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At two centres, the decision whether to communicate amyloid biomarkers is complicated by the existence of a patient-accessible medical record. As biomarkers are assessed as part of the routine clinical work-up, this information is likely to become available to all patients and a range of medical practitioners, regardless of subsequent diagnosis.

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4. Disclosure and the EPAD study population

The EPAD cohort is heterogeneous, as it is drawn from clinical and research populations in different national contexts. People entering the LCS study will thus vary in the extent to which they have a clinically identified condition, and in the prior biomarker information they have received. This has implications for the approach adopted for recruitment into the PoC and for the communication of biomarker results.


In this section, we consider who is participating in EPAD and the pathways by which they enter and progress through the LCS to highlight differences in knowledge and expectations among participants.

4.1. Who is in EPAD?

The EPAD LCS is recruited to cover a spectrum of risk of developing Alzheimer’s disease dementia. However, this spectrum can also be broken down into distinct populations as they enter or transition from the LCS study to the PoC.

People currently enter the EPAD LCS study through two major pathways, either from a memory clinic register or from a volunteer cohort drawn from the general population. Each of these has distinct practices related to testing, disclosure and follow-up. These pathways are illustrated in the figure below.

In addition, it may be expected that, for the foreseeable future, trial appendices participating in the EPAD PoC platform will recruit either people with mild cognitive impairment (‘prodromal trials’) **or** people who are asymptomatic (‘preclinical AD trials’). The separation between these populations in the EPAD PoC will be made on the basis of the Clinical Dementia Rating (CDR) scale, with the former corresponding to a CDR of 0.5, the latter to CDR = 0.

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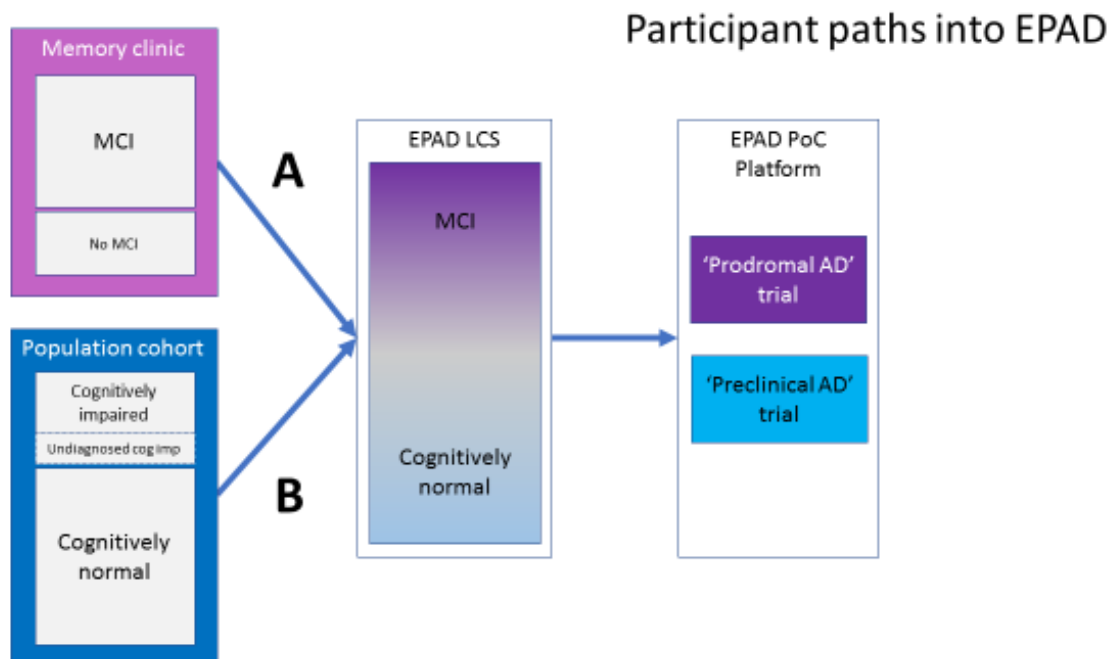



Figure 1: Participant Paths into EPAD

4.2. What do people already know?

The different routes of entry into EPAD mean that people may enter the LCS with different knowledge about their clinical and biological status in relation to Alzheimer’s disease. The different routes of entry and distribution of knowledge within the EPAD LCS mean that seven distinct groups can be identified in the EPAD LCS in terms of their previous knowledge about their clinical cognitive status and biomarker assessments (see figure 2); four via route A, three via route B³.

³ There may also be a very small sub-population in B1 and B3 of Route B participants who have received biomarker results, but this is likely to be very small. Group B2 may be similar to either A1 or A2.

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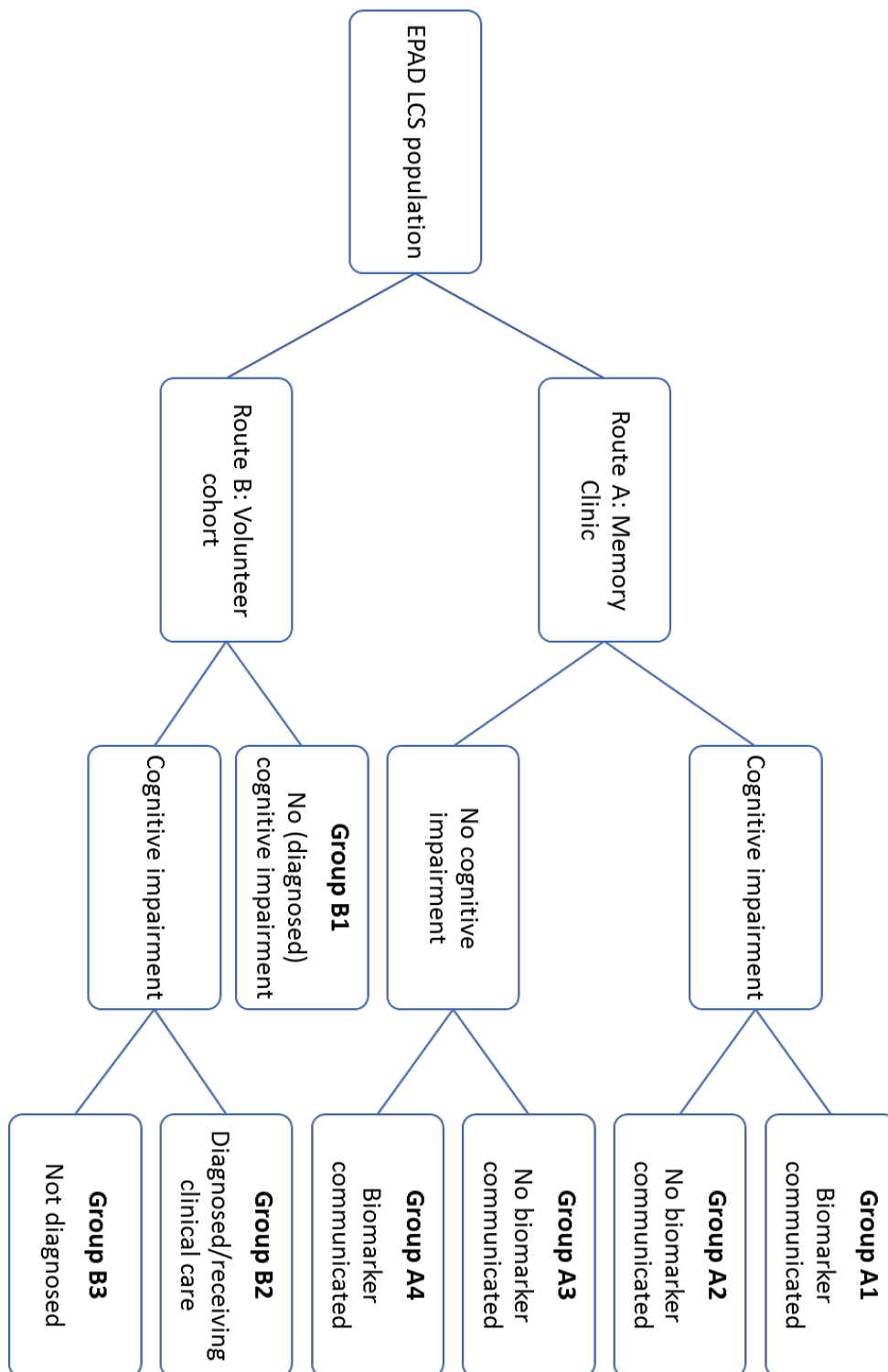



Figure 2: EPAD study populations

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4.3. Route A: Recruitment through memory clinics


People entering the EPAD LCS from memory clinics (Route A) are **more likely to be in receipt of a clinical label of MCI or subjective cognitive decline**. A subgroup will have been identified in clinic as having no impairment or subjective cognitive decline, but will have been invited to take part in the EPAD cohort. People entering EPAD through Route A are also **more likely to have received the results of biomarker examinations**⁴. Four groups can be identified.

4.3.1. Group A1

LCS participants in this group are recruited from TDC memory clinics (Route A). A substantial proportion of EPAD participants recruited into the LCS from Wave 1 memory clinic populations will fall into this group, and will have been informed of their biomarker status. **PoC recruitment from this group thus does not involve telling participants anything they do not already know**. As one interviewee suggested, amyloid disclosure may thus “not be an issue for centres with established routines”. There is little reason or possibility for EPAD to intervene in practice at these centres. However, EPAD should check that participants are aware of these results.

EPAD should also be aware of the possibility that LCS test results will differ from those communicated in the clinic, either because of a change in amyloid levels over time for those close to the cut-off, lack of reliability in the test across time, or because of differences between local clinical and centralised EPAD cut-offs on CSF. **This fact argues for clarity in conveying what being amyloid ‘positive’ or ‘negative’ means as this status may change between the clinical testing and the cohort testing.**

⁴ Based on interviews with TDC leads and clinicians conducted Oct-Dec 2017

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4.3.2. Group A2

Some participants recruited via route A will come from centres where biomarkers are not currently used routinely. This group may well expand as new centres join EPAD, especially in the UK where CSF/PET Amyloid biomarker testing is not routine. There is a need for best practice protocols for assessment and follow-up, not least because of the potential prognostic value of biomarkers in this group. If EPAD results are requested by treating clinicians, they should be returned, along with information about their implications (see below).


4.3.3. Group A3

This group includes those who have presented at a memory clinic, and have been found to have no cognitive impairment. Biomarkers have not been communicated in the clinical assessment. This group has similarities with group B1 below, in that they have no objective cognitive impairment. However, having attended a clinic in the absence of cognitive impairment, they are likely to be more worried about their memory and cognitive decline.

4.3.4. Group A4

Participants in this group are those who have been seen at a memory clinic, and found to have no objective cognitive impairment but to have abnormal amyloid biomarkers. The clinical use of biomarkers with this group is not common, and should not be encouraged, given the lack of evidence. Again, this group may be more likely to be worried about their memory and cognitive decline.

As with Group A1 therefore, this population will arrive at the EPAD LCS with existing knowledge of their biomarker status, and this should be recognised in the communication process. However, it is important that the TDC reconfirms what information people have received and what they have understood, and that the uncertainties associated with the predictive value of amyloid biomarkers are re-iterated.

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4.4. Route B: Recruitment through volunteer cohorts

Route B represents recruitment from volunteer cohorts. Given that most studies from which EPAD recruits through Route B (including the PREVENT Dementia, ALFA and Generation Scotland cohorts) recruit from the general population and do not routinely return research results to participants, this group is:

- **Less likely to have received the results of biomarker examinations (even when such examinations are done as part of the parent cohort protocols).**
- **Less likely to have cognitive problems and be in receipt of a clinical label of MCI or subjective cognitive decline.**

Nevertheless, some participants from population cohorts may well be receiving primary or secondary care for mild cognitive impairment or, in some cases, subjective cognitive decline. There will also be a group of people entering EPAD through this route **who meet EPAD's criteria for cognitive impairment but have not sought clinical care.**


Three groups can be identified as:

4.4.1. Group B1

This group is the second major population in the LCS and will form the majority of the population recruited from non-clinical settings. They do not have objective cognitive impairment and have not previously been informed about their biomarker status.

4.4.2. Group B2

In addition to those people recruited from Route A, it can be expected that some EPAD participants with cognitive impairment will be recruited from general population cohorts. Some may already be receiving treatment or care at memory clinics or in primary care settings which are not connected to the TDC.

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4.4.3. Group B3

Participants in this group are also recruited from population cohorts. However, this group are those who may have previously undetected or undiagnosed cognitive impairment. For this group, taking part in EPAD may thus result in the disclosure of both a cognitive problem and biomarkers associated with it.


5. Suggestions for best practice for communicating amyloid biomarkers during PoC recruitment

The diversity of the population has implications for the proposed process for disclosing biomarkers. Here, we propose suggestions for best practice to inform the disclosure of amyloid biomarkers to EPAD participants with and without cognitive impairment as part of PoC recruitment. In the following section, we discuss the communication of results on participant or physician request.

The implementation of these recommendations will be shaped by the overall process for recruitment to the EPAD PoC study. This process is under development by EPAD WP4 and the detail is beyond the scope of this document. The recommendations made here should be discussed and developed further in that process, and ideally piloted in EPAD populations with and without cognitive impairment prior to implementation to ensure best practice.

5.1. Overall practice recommendations


Specific suggestions for best practice in EPAD are divided according to the two populations likely to be recruited for clinical trials through EPAD – those with objective cognitive impairment and those without, as defined by the CDR. However, a number of overall recommendations can be suggested, covering both biomarker disclosure and the PoC consent process:

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- EPAD TDCs should check consent regularly, and confirm that participants are aware that participating in the study may mean being invited to a clinical trial and that this would involve learning results from EPAD biomarker assessments.
- All those responsible for taking consent and involved in the necessary disclosure if approached about the PoC study at each site should be experienced clinicians. Ideally, each EPAD participant should have a designated study clinician who is responsible for communication about the LCS, PoC and biomarker results.
- All those involved in disclosing biomarker results should receive training on the consent and disclosure process, and on recognising and dealing with distress caused. WP4 should incorporate this training into PoC platform development.
- The communication of biomarker results should be supported by information and education about the meaning of these results. This should be provided at consent for the EPAD LCS, and reiterated during the disclosure discussion.
- Information should be transparent about the uncertainties associated with the prognostic and predictive value of amyloid biomarkers in both MCI and asymptomatic populations. It should take as a starting point the amyloid information developed in collaboration with Work Packages (WPs) 1, 4 and 6 (see appendix).
- The impact of disclosure should be followed up and those at risk of harm identified – for example through follow up phone calls at 3 weeks and 6 months.
- TDCs should have a protocol in place for dealing with anxiety and distress if it arises.

These considerations should be addressed within the development of the protocol for the EPAD PoC platform. This protocol should also consider that:

- Participants should only be invited to join the PoC platform should take place only once trial appendices are available for which they are eligible.
- Recruitment to the EPAD PoC platform should explain the adaptive trial and the randomisation process. It should describe the process of random allocation between trial arms, and then within each trial ‘appendix’ to either active drug or placebo.

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- The PoC protocol should provide outline information on the trials for which they may be eligible (mode of administration, frequency of visits), emphasise that each study will have specific risks and that it will involve further information and request for informed consent.

5.2. Communicating biomarker results to EPAD participants with no objective cognitive impairment

The disclosure process involves a minimum of three stages: a discussion prior to LCS recruitment of the meaning and possible implications of learning amyloid biomarker results in the future; the information to be provided at PoC recruitment, and follow-up of the impact on participants.

At LCS consent


- Participants are asked to provide informed consent to potentially learning their amyloid status in the future.
- They should be informed that being recontacted for trials is likely to mean that they are “amyloid positive”. However, they should also be informed that not being contacted does not mean they are “amyloid negative”, nor does it necessarily mean they have a lower risk of dementia.
- Prior to consenting, participants should be provided with the EPAD amyloid video and information sheet (Appendix 1), and the consenting clinician should reiterate that:
 - o An ‘amyloid positive’ result does not mean you now have Alzheimer’s disease dementia or that you will ever get Alzheimer’s disease dementia.
 - o Studies suggest that elevated levels of amyloid may increase your risk of developing Alzheimer’s disease dementia in your lifetime.
 - o However, while we think having abnormal levels of amyloid means higher risk of developing dementia, we do not yet know what that means, and many people in their 80s and 90s have high levels of amyloid in their brain, but no dementia.

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- The EPAD study doctor should discuss the possible implications of learning amyloid status. This includes discussing how learning this result can change how people feel about themselves and their future, and how others interact with them. This may include:
 - o You may have a different sense of how much time remains. Some people, after they learn their result shows elevated amyloid, feel the same while others feel they have less time left.
 - o You should think about how others may react to learning your result, such as family, friends and co-workers.
- The clinician should then answer questions regarding the study and amyloid and ask open questions on LCS information consent and amyloid. On the study, these may include: “Can you tell me in your own words what we just talked about?”; “From your understanding, what is EPAD trying to achieve?”; “How do you think participation in the EPAD trial would impact you?”. On amyloid, they may include: “Suppose your result showed ‘elevated amyloid,’ what would you do? How would you feel?” and “Suppose your result showed ‘not elevated amyloid,’ what would you do? How would you feel?”

Introducing the PoC and Eligibility

- Prior to discussing the PoC, the study doctor should assess the participant’s mood, anxiety, stress, based on their clinical impression and EPAD assessments of anxiety and depression, particularly signs that feature a worry about Alzheimer’s disease.
- The participant should be informed that because of their cognitive status and biomarker results, they may be eligible to take part in the EPAD PoC trial.
- Study doctor should then communicate LCS results
 - o Re-iterate that ‘abnormal’ amyloid is not predictive of future dementia, nor does ‘normal’ amyloid exclude it and that significant uncertainty surrounds what it actually does mean – and the outcome of EPAD will help work this out.
 - o Amyloid status should be discussed in terms of the threshold (positive/negative).

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- However, the study doctor should be prepared to provide numerical values, discuss how these relate to the cut-off, and explain that the cut-off is an artefact of the clinical trial recruitment process. The study doctor should expect that some subjects will want to equate their risk of developing Alzheimer’s disease dementia with their numerical standardized uptake value ratio (SUVR). Education prior to the disclosure should reinforce that data are not available to link a particular SUVR value to a risk score, as is the case in other medical diseases such as hypertension where a blood pressure value is associated with risk of cardiovascular event.
- Question-back approach should be used to assess comprehension, i.e., “Can you tell me back in your own words what we’ve talked about?”
- The disclosure process should take as much or as little time as the participant wants.

Follow-up

- A contact number for the study doctor should be provided.
- Participants should be followed-up by phone by either the study doctor or a member of TDC staff familiar to the participant 3 days after the conversation, and again six weeks after, and at their next study visit.
- Emotional wellbeing should be assessed. In general, this means asking about overall mood, anxiety about Alzheimer’s disease, and worries about cognitive health. Each TDC should have a protocol in place for dealing with distress, ensuring the availability of a counsellor or clinician as required.


5.3. Communicating biomarker results to EPAD participants with objective cognitive impairment (CDR=0.5)

- Participants are asked to provide informed consent to potentially learning their amyloid status in the future.
- The study should encourage the person to have someone accompany them to education and disclosure visits. This person should be someone they trust and who would help them

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in the event of a medical problem. In the case of persons with MCI or AD dementia this may be a person who is their “caregiver”. However, many people with MCI or mild dementia may be living independently. The advantage of having the person at the visit includes a common understanding of the meaning of the results.

- The TDC should confirm with the participant whether and what they have already been told about their cognitive status and biomarker results and what the latter means.
- Participants should be provided with information about the meaning of amyloid biomarkers in MCI which reflects the current state of scientific evidence and uncertainties about its prognostic value.
- The EPAD study doctor should discuss the possible implications of learning information about amyloid status. This includes discussing how learning this result can change how people feel about themselves and their future, and how others interact with them. This may include:
 - o You may have a different sense of how much time remains. Some people, after they learn their result shows elevated amyloid, feel the same while others feel they have less time left.
 - o You should think about how others may react to learning your result, such as family, friends and co-workers.
- The clinician should consider the message to a person who has MCI or AD dementia whose amyloid result is not consistent with “elevated” or “positive” amyloid.
- The clinician should then answer questions on the study and amyloid and ask open questions on LCS information, consent and amyloid. On the study, these may include: “Can you tell me in your own words what we just talked about?”; “From your understanding, what is EPAD trying to achieve?”; “How do you think participation in the EPAD trial would impact you?”. On amyloid, they may include: “Suppose your result showed ‘elevated amyloid,’ what would you do? How would you feel?” and “Suppose your result showed ‘not elevated amyloid,’ what would you do? How would you feel?”


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At PoC Recruitment

- The participant should be informed that because of their cognitive status and biomarker results, they may be eligible to take part in the EPAD PoC trial.
- The implications of being “amyloid positive” should be re-iterated. Recommended wording for introducing amyloid biomarkers in this population has been proposed by Grill *et al.* (see 2.3 above). Given the heterogeneity of the current evidence about the ability of amyloid biomarkers to predict progression from MCI to AD dementia, such qualitative descriptions of uncertainty is likely to be preferable at this time to providing numerical estimates or tools like pictographs. However, this wording may need to be revised for European populations.
- An important exception relates to *participants with undiagnosed cognitive impairment*. If participants are not currently seeking care for cognitive complaints, the study doctor should discuss cognitive problems with the participant and decide whether to refer back, adopting a shared decision-making approach to consider possible treatment options, implications of diagnosis (and possibly biomarkers) on medical records for employment, insurance, driving. In cases where previously undiagnosed cognitive impairment results in a clinical referral, the PoC should not be discussed until the implications for care have been established.

Follow-up

- A contact number for the study doctor should be provided.
- Participants should be followed-up by phone by either the study doctor or a member of TDC staff familiar to the participant 3 days after the conversation, again after six weeks and at their next study visit.
- Emotional well-being should be assessed. In general, this means asking about overall mood, anxiety about Alzheimer’s disease, and worries about cognitive health. Each TDC should have a protocol in place for dealing with distress, ensuring the availability of a counsellor or clinician as required.

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6. Suggestions for best practice in communicating biomarkers on participant or physician request


6.1. Communicating biomarker results to EPAD participants with no objective cognitive impairment on participant request

The results of EPAD biomarker tests are *research* results and are not clinically relevant in people without cognitive impairment.

- EPAD participants should not be encouraged to request their biomarker information and the default remains non-disclosure, as explained in the informed consent form.
- If they express an interest, the EPAD study doctor should discuss the participant's motivation for knowing and expectations of the utility of the information, and the possible implications of learning it. Implications include:
 - o You may have a different sense of how much time remains. Some people, after they learn their result shows elevated amyloid, feel the same while others feel they have less time left.
 - o You should think about how others may react to learning your result, such as family, friends and co-workers.
- Useful questions to assess motivation is to ask the person “Suppose your result showed ‘elevated amyloid,’ what would you do? How would you feel?” and “Suppose your result showed ‘not elevated amyloid,’ what would you do? How would you feel?”.
- The study doctor should assess the person's overall mood and well-being with attention to signs of anxiety and depression, particularly signs that feature a worry about Alzheimer's disease. Clear plans should be in place for dealing with anxiety and depression.
- The education should include discussing how learning this result can change how people feel about themselves and their future, and how others interact with them.

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- The study doctor should encourage the person to have someone accompany them to the education and disclosure visit. This person should be someone they trust and who would help them in the event of a medical problem. The advantage of having the person at the visit includes a common understanding of the meaning of the results.
- If an EPAD participant wishes to learn their biomarker information, this should be communicated to them.
- The clinician should re-iterate the EPAD amyloid information and the message that:
 - o The results do not suggest that the participant has any cognitive problems as they are a biological measurement, not a cognitive one
 - o An ‘elevated amyloid’ result means that amyloid plaques are present in your brain but does not mean you now have Alzheimer’s disease dementia or that you will ever get Alzheimer’s disease dementia.
 - o Studies suggest that elevated levels of amyloid may increase your risk of developing Alzheimer’s disease dementia in your lifetime.
- Participants should have time to ask questions, and confirm their interest in knowing the information.
- Study doctor should then communicate LCS results
 - o Re-iterate that ‘abnormal’ amyloid is not predictive of future dementia, nor does ‘normal’ amyloid exclude it and that significant uncertainty surrounds what it actually does mean – and the outcome of EPAD will help work this out.
 - o Amyloid status should be discussed in terms of the threshold (positive/negative).
 - o However, the study doctor should be prepared to provide numerical values, discuss how these relate to the cut-off, and explain that the cut-off is an artefact of the clinical trial recruitment process. The study doctor should expect that some subjects will want to equate their risk of developing Alzheimer’s disease dementia with their numerical SUVR. Education prior to the disclosure should reinforce that data are not available to link a particular SUVR value to a risk score on an

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individual basis, in contrast to other medical diseases such as hypertension where a blood pressure value can be associated with a range of risks of cardiovascular event with some certainty about magnitude and time.

- Question-back approach should be used to assess comprehension, i.e., “Can you tell me back in your own words what we’ve talked about?”
- The disclosure process should take as much or as little time as the participant wants


Follow-up

- A contact number for the study doctor should be provided.
- Participants should be followed-up by phone by either the study doctor or a member of TDC staff familiar to the participant 3 days after the conversation, and again after six weeks and at their next study visit.
- Emotional well-being should be assessed. In general, this means asking about overall mood, anxiety about Alzheimer’s disease, and worries about cognitive health. Each TDC should have a protocol in place for dealing with distress, ensuring a counsellor or clinician is available as required.

6.2. Communicating biomarker results to EPAD participants with objective cognitive impairment on participant request


Participants with cognitive impairment may wish to know biomarker results. However, again it is necessary to emphasise that the results of EPAD biomarker tests are *research* results, and that participants should not expect diagnostic information from the study.

- If they express an interest, the EPAD study doctor should emphasise that the default remains non-disclosure, as explained in the informed consent form.
- They should ascertain a participant’s motivation for knowing and expectations of the utility of the information, and the possible implications of learning it. Useful questions to assess motivation are to ask the person “Suppose your result showed ‘elevated amyloid,’

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what would you do? How would you feel?” and “Suppose your result showed ‘not elevated amyloid,’ what would you do? How would you feel?” Implications include:

- You may have a different sense of how much time remains. Some people, after they learn their result shows elevated amyloid, feel the same while others feel they have less time left.
 - You should think about how others may react to learning your result, such as family, friends and co-workers.
- The clinician should consider the message to a person who has MCI or AD dementia whose amyloid result is not consistent with “elevated” or “positive” amyloid.
 - The study doctor should encourage the person to have someone accompany them to these education and disclosure visits. This person should be someone they trust and who would help them in the event of a medical problem. In the case of persons with MCI or AD dementia this may be a person who is their “caregiver”. However, many people with MCI or mild dementia may be living independently. The advantage of having the person at the visit includes a common understanding of the meaning of the results.
 - If an EPAD participant wishes to learn their biomarker information, this should be communicated to them.
 - Participants should be provided verbal and written information on the meaning and implications of biomarker results. Recommended wording for clinical use is proposed by Grill *et al.* (see 2.3 above). Given the heterogeneity of the current evidence about the ability of amyloid biomarkers to predict progression from MCI to AD dementia, this qualitative description of uncertainty is likely preferable at this time to providing numerical estimates or tools like pictographs. However, as discussed above, this wording may need revising for European populations.


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6.3. Communicating biomarker results to EPAD participants with objective cognitive impairment on physician request

The clinical utility of amyloid information, in the sense of improving health outcomes, remains uncertain.¹⁰ In many countries the use of CSF or PET in routine clinical practice. In the Netherlands a recent addendum to the dementia guideline, specifically about MCI, recommends against routine use of CSF or PET in daily practice due to the uncertain value of these tests. In the UK 2018 NICE guidelines recommend the use of CSF analyses for the assessment of dementia *only if it would help to diagnose a dementia subtype and knowing more about the dementia subtype would change management*. It is not yet clear what, if any, benefit accrues to patients from the use of biomarkers in the clinic. It may increase physicians' diagnostic confidence, but it is not known whether there are beneficial effects on patient outcomes, nor do we know whether this confidence is correct with respect to disease progression or developing of clinical dementia.

However, for participants with cognitive impairment treating clinicians may wish to request results from EPAD investigations if they think this can support patient management.


- In such cases, it is paramount that the primary purpose of EPAD data collection remains scientific research rather than clinical care, and that this distinction remains clear at all times to both participants and clinicians.
- The EPAD study leadership team should underline that the state of the available evidence related to the clinical utility of CSF biomarkers is such that the routine clinical use of EPAD data are currently not recommended.^{10,16}
- Clinicians requesting EPAD biomarker results should be discouraged, and if insistent ensure that they are aware of the current state of evidence and its limitations related to the diagnostic use of CSF biomarkers before they receive this information.
- If results are returned in this way, it is important that a consistent approach is used across EPAD and that this approach is approved by central (Edinburgh) and local research

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governance and ethics review boards. Clinicians should complete a request for EPAD information.


7. Conclusions

Selecting people on the basis of their biomarker profile, that of potentially increased risk raises profound ethical issues. The communication of biomarker results to participants is one of the primary challenges facing the EPAD project. This deliverable has shown that the process for communication should reflect the different populations within EPAD, and the different routes by which people enter the study. Consequently, we have suggested considerations for approaching the communication of biomarker results within EPAD. These should be considered in the development of the final protocol for recruitment to the EPAD PoC.

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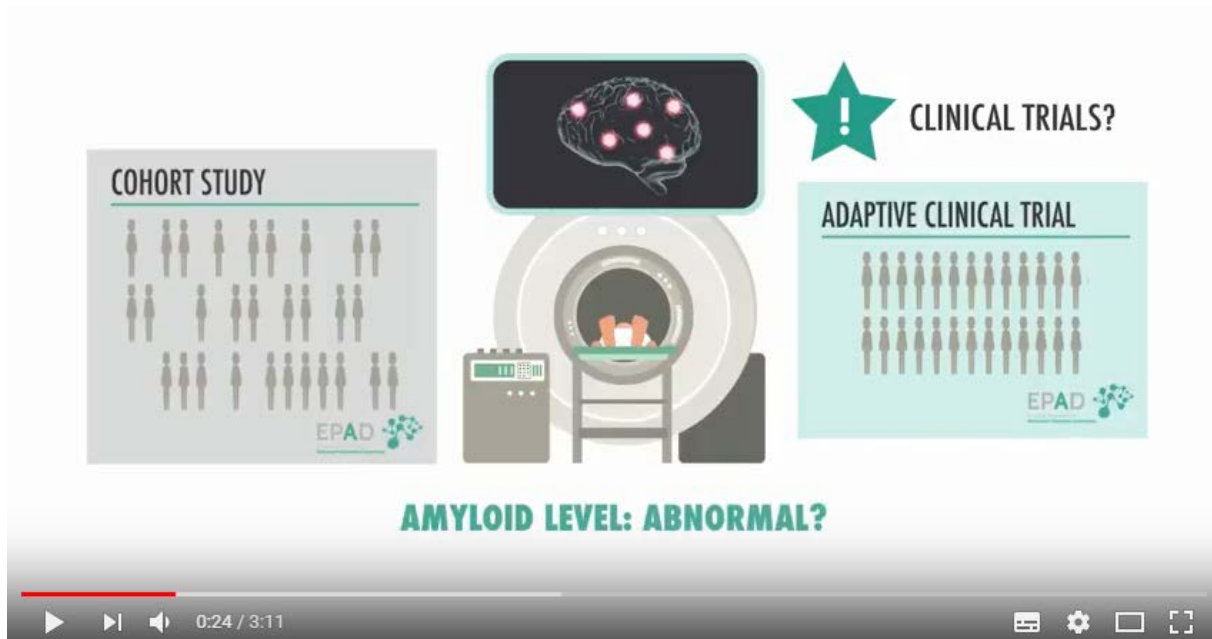
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Appendix 1: EPAD Information on the implications of being amyloid positive for someone without cognitive impairment

The information sheet overleaf and video at

<https://www.youtube.com/watch?v=GiRFlmzz2Ng> (available in multiple EPAD languages)

are provided to potential participants at LCS recruitment, and should be revisited at subsequent study visits.



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LEARNING YOUR AMYLOID STATUS

Before you join EPAD, you should be aware that during the project you will be tested for risk factors for Alzheimer’s disease. In the future, you may be invited to take part in a clinical trial on the basis of your profile for these markers; one of which is particular patterns of a protein called amyloid. If you have such patterns, it may mean you have a higher risk of developing Alzheimer's dementia in later life.

Before you decide whether or not to join EPAD, we’d like to explain what we currently understand about amyloid and how it relates to dementia.

What is Amyloid?


In the brain small, perfectly normal amyloid proteins are produced. However, as we age, they can join together to form plaques. These plaques are an important characteristic of the disease, alongside others such as tangles of another protein called tau.

The type of amyloid protein that is associated with Alzheimer’s disease is called amyloid beta. Amyloid beta protein has a role in normal brain function. Its levels can be measured in the spinal fluid using a lumbar puncture, or by using a “positron emission tomography” (PET) brain scan.

Much research suggests that amyloid plaques are an early sign of damage, including to nerve cells, but scientists are still researching this. Plaques can start to form as early as 20 to 30 years before any dementia symptoms appear. We are trying to find out why this happens and how this is related to possible later dementia. Importantly, most people in their 80’s and 90’s have amyloid plaques in their brains and many show no dementia symptoms.

What does it mean to have abnormal amyloid levels?

If your amyloid beta level is abnormal, then you may have an increased risk of developing dementia in the future. However, this is not a certainty. Amyloid levels are just one of many potential factors that determine a person’s risk of developing Alzheimer’s dementia. Not everyone with amyloid plaques develops Alzheimer’s dementia, in the same way that not


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everyone with high blood pressure develops heart disease. What’s more, amyloid levels can vary over time. You should also know that your amyloid levels tell you nothing about your risk of developing other, non-Alzheimer forms of dementia.

SUMMARY

If you decide to participate in EPAD, then you may at some point learn about your amyloid status. An abnormal level indicates an increased *risk* of developing Alzheimer’s dementia, but does not mean that you will definitely do so. Amyloid levels are just one of many potential factors that determine a person’s risk of developing Alzheimer’s dementia.

Please think about this before you decide to join EPAD. If you have any questions, please don’t hesitate to contact us.

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