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**European Prevention of Alzheimer's Dementia Consortium**

*Grant Agreement n°115736*

## **D8.5 Final report on ethical, legal and social implications and recommendations**

**WP8 – Ethical, Legal and Social Implications**

**V2.0**


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 EPAD - 115736	<b>D8.5 Final report on ethical, legal and social implications and recommendations</b>		
	<b>WP8. Ethical, Legal and Social Implications</b>	<b>Version:</b> v2.0 – Draft	
	<b>Author(s):</b> Milne, Brenman, Bunnik, Gregory, Saunders, Gove, Schermer, Smedinga, Richard	<b>Security:</b> [PU]	2/78

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<b>Description of the deliverable</b>	This deliverable reports on the work of WP8 (ELSI) within EPAD, including the findings of several ethics substudies, and provides recommendations for future ELSI work
<b>Key words</b>	Ethics, society, Alzheimer's disease, participation, PPI, disclosure, incidental findings

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*Confidential Information (please indicate here if any sections contain confidential information and should NOT be made publically available)*

<b>Relevant Section(s)</b>	6.1 – Report on the MCI Disclosure Study
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## DEFINITIONS

- 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)
  - **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)
  - **MSD.** Merck Sharp & Dohme (United States)

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- **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


The final WP8 deliverable revisits key areas discussed in the initial EPAD ethics deliverables, and presents the further development of recommendations and practice, and empirical research examining areas of specific concern. These include informed consent, the disclosure of dementia risk in clinical settings, the EPAD experience with the return of incidental findings and the experience of participants in the EPAD study:

**Informed consent:** We review the distinctive challenges in the informed consent process encountered at different stages of the EPAD study. In line with the staged consent model operating throughout the study, people cannot be considered to make an informed decision about taking part in the PoC platform without information on which interventions they may be assigned to. We therefore recommend that participants being asked to take part in platform trials should be provided with general information about the existence and contents of all arms including relevant information, with the aim of enabling them to understand the PoC platform as a whole. We provide a revised recommendation on what information needed to be provided to participants at different stages of the study.

**Participant Experience:** The SPEAR (Study of Participant Experience in Alzheimer’s disease Research) sub-study findings provide insight into motivations, expectations and experiences of research participation. They emphasise the importance of altruism as a motivation for participation, but also that motivations overlap, change over time and may differ as the study progresses and participants consider clinical trial participation. There was very little consensus about the value of the return of biomarker results, with some people keen to know as much as possible, and others actively preferred not to know results. However, during the course of the study, participants consistently found the promise that they would be told clinically relevant information (i.e. results you could “do something about”) as beneficial and desirable. We found discomfort and burden was almost always described in the context of positive interactions with the study team, indicating that caring practices and relations mediate ‘study burden’. A final set of questions on motivations explored potential *future* participation in an EPAD clinical trial. The findings suggest that the majority of EPAD LCS participants would be willing (and feel a sense of responsibility) to take part in a clinical trial, but that the timing, location and duration of such trials is critical.

**Incidental findings:** Incidental findings are findings pertaining to potentially serious medical conditions, that are clinically significant and actionable; in this case, they exclude findings related to dementia as this is the focus of the study. We set out the 8 recommendations, guided by principles of reciprocity and the careful handling of results, which we made in D8.1 before moving onto our recent empirical work. To evaluate policies and protocols for the handling of incidental findings within EPAD, we sent out a questionnaire per e-mail to TDC leads of all active TDCs. Here, we report on the detection of incidental findings, the management of incidental findings, and the communication of incidental findings. Policies and practices at local TDCs did not diverge significantly from recommendations for the handling of incidental findings presented in D8.1. The diversions noted were not deemed




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problematic, as they may have been more practical and feasible, seem to have sufficed, and are surely morally acceptable, as well.

**Participant representation:** In D8.3, we recommended the establishment of a research participant panel to incorporate the perspective of participants into the governance and running of the EPAD project. This recognised the importance of patient and public involvement (PPI) in health care research. We review the approach to setting up both the country level and project wide participant panels, the impact participant involvement has had on the project and how the model developed in EPAD could be used by other research fields. The EPAD participant panels have contributed in four main areas; study advocacy, review of study documentation, streamlining of study visits and input into overall EPAD study planning. We conclude that it is possible to set up and establish a successful network of participant panels across countries and languages to achieve meaningful involvement of participants as a stakeholders in the research process through a hybrid centralised-localised model.

**Return of results and risk disclosure:** The question of risk communication was identified in the EPAD Description of Work and has been a central concern of WP8 throughout the project. In addition to involvement in the development and refining of the disclosure protocol, empirical work has continued to explore the communication of dementia risk information in the clinic practice. This work is ongoing, albeit paused due to COVID-19 restrictions.

The report closes by reflecting on relevant learnings from the EPAD ELSI work for future IMI projects in Alzheimer's disease and other areas.


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## 1. Introduction

The EPAD project has, from the start, been a complex study combining elements of longitudinal research design and clinical trial practice, distributed across multiple European countries and delivered by a combination of partners from the public and private sector. As such, it has raised distinctive, novel and complex questions associated with research ethics, and with the social and clinical consequences of research into Alzheimer's disease prevention. The role of WP8 throughout the study has been to engage with these questions, working together with researchers, companies and participants to deliver a study which is innovative and world-leading in its approach to considering ethical dimensions of research practice.

The work of WP8 has been set out through a cumulative series of project deliverables. The ethical framework developed for the EPAD study in D8.1 and D8.2 focused on following the journey of research participants through the study. It provided recommendations on informed consent, the return of research results, study experience, and recruitment. In D8.3, we set out proposals for a research participant panel that would represent participants within study governance. Finally, in D8.4, we outlined a protocol for the disclosure of biomarker information to participants as part of recruitment to the EPAD PoC platform.

In this final report, we revisit the recommendations of these deliverables over the course of the participant journey. We report the further development of protocols during the course of the study, and empirical research into risk disclosure, study experience, and the return of incidental findings led by members of the WP8 team. Finally, we consider how the experience of the EPAD ELSI work package might contribute to refining the role of ELSI work within clinical research on Alzheimer's disease, and within IMI projects more broadly.

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## 2. Informed consent

### *2.1 Participant information related to randomisation within the EPAD PoC trial<sup>1</sup>*

The informed consent process for the EPAD study presents distinctive challenges at different stages. The first, discussed in detail in D8.1, was the need to ensure that potential participants were aware from the outset that they may become eligible to take part in a clinical trial, and that this may involve the communication of information relevant to their risk of developing dementia in the future. The second, discussed here, relates to the consent to join the PoC platform, prior to randomization to different trial appendices. Participants consenting to the EPAD PoC platform are randomly assigned to one of the different study arms concurrently running in the PoC trial to which they are eligible by application of high-level inclusion/exclusion criteria from the LCS database and a short baseline assessment post-master protocol PoC consent. Outstanding questions related to what information should be provided to participants on the different arms to which they could be randomised, at what point this information should be provided, and what course of action to take if a participant turns down the arm to which they are allocated.


The EPAD PoC platform is a single study with multiple arm, , each with a specific appendix. Before participants take part in the arm to which they have been assigned, they must be informed of all details related to that arm - as would be the case for any entry into a clinical trial. The other arms are not options that are open to participants, for which they need to consider the pros and cons of participating. While they may have been eligible for these arms, they are closed to them due to the first step of the randomisation process whereby they were not allocated to that arm of the trial. In discussions with researchers from across the study, particularly from WP2, it was argued that providing information on other arms risked introducing an element of choice between arms (for example, if participants would prefer to be randomized to an arm with a different mode of delivery), and that this would introduce a source of bias, jeopardising study integrity.

However, in line with the staged consent model operating throughout the study, people cannot be considered to make an informed decision about taking part in the PoC platform without information on interventions to which they may be assigned.

As such, we recommend that participants being asked to take part in platform trials should be provided with general information about the existence and contents of all arms including relevant information, with the aim of enabling them to understand the PoC platform as a whole. This would occur before

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<sup>1</sup> In addition to the authors listed for the deliverable, a number of former members of WP8 contributed to this discussion - Marianne Maman, Krista Tromp, Luc Truyen and Shirlene Badger.

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the first step of randomisation to the arm of the study where they may be eligible. These recommendations were discussed and agreed with representatives from WP2 and WP4 in 2016/17.

The recommended approach is that

1. The randomisation process and the lack of choice between study arms should be made clear at LCS recruitment, as a specific part of the study information. This should also make it clear that the arms within the PoC evolve over time, and that all interventions tested have been reviewed by an ethics board and have gone through a transparent review process conducted by the EPAD Clinical Compound Selection Committee.
2. Information on the different arms to which a participant is eligible to be randomised, including placebo, should be made available to participants at PoC recruitment. This will involve:
  - A table providing a summary of the core features of the intervention to be tested. This will include the mode of delivery, frequency of dosing and basic mechanism of action written for a public audience;
  - A statement that each intervention is associated with risks, burdens and potential benefits, and that these will be discussed in detail in the information for the arm to which they are ultimately randomised.

If a participant turns down the arm to which he/she has been randomised, to retain the integrity of the randomisation process, they will not be eligible immediately for another ongoing arm of the study. However, their continued participation in the LCS is valuable. Our preferred option is that the participant could continue to participate in the LCS, and become eligible to be re-randomised after six months, provided new assessment data is available and that they continue to meet eligibility criteria.

Taking into account this adaptation, a revised recommendation on what information needed to be provided to participants at different stages of the study was developed (see Table 1). This represents an iteration of the staged consent model described in D8.1.




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Table 1: Information provided to potential participants at different stages of the EPAD study, and the source of this information		
STAGE	Information provided	Information source
Consent to LCS	Provided with detailed information on LCS participation	LCS Participant Information Sheet
	Provided with overview information on EPAD structure	LCS PIS and How EPAD works leaflet /video
	Told that recruitment to a trial would involve disclosure of risk status and receive information on what this would mean	Amyloid leaflet, video, conversation with EPAD researcher
	Told that it may be some time before they hear about any opportunity for possible inclusion in a trial and that they may not meet appendix-specific inclusion/exclusion criteria	LCS PIS and How EPAD works leaflet/video
	Told that if they are contacted to take part in a trial they will be randomly allocated to a placebo or one of a number of investigational drugs/intervention arms currently recruiting through EPAD.	in <i>How EPAD works</i> leaflet/video
	Told that if they do not wish to participate in a specific arm they will continue to take part in the LCS and <i>may</i> become eligible for another arm in six months (provided new assessment data is available)	in <i>How EPAD works</i> leaflet/video
During LCS	Review information on amyloid, how EPAD works at regular intervals	Amyloid leaflet; How EPAD works
PoC first consent	Potential PoC participants receive amyloid status as part of contact to take part in PoC trial	In person, including review of amyloid information

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	Potential PoC participants receive specific information about extra testing required to establish eligibility to be assigned to an arm – this is however not ‘arm-specific’ information at this stage.	PoC PIS
	Potential PoC participants receive general information on the different investigational drugs/interventions and placebo to which one may be assigned	PoC PIS (will need frequent updating)
	Recap that if they do not want to take part in a specific arm, they will not be eligible to take part in another EPAD trial for six months (provided new assessment data available)	PoC PIS
PoC second consent	Receive specific detailed information on trial appendix including on risks, burden and potential benefits	Appendix PIS
	Recap that if they do not want to take part in a specific arm, they will not be eligible to take part in another EPAD trial for six months (provided new assessment data is available)	Appendix PIS

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### 3. Experience of EPAD participation<sup>2</sup>

In D8.1, the WP8 team pointed to the extent and intensity of tests and measurements deemed necessary to provide a sufficiently detailed picture of disease progression in contemporary Alzheimer's disease research. The EPAD LCS aims to generate a detailed picture of biological and cognitive change over time, which potentially represents a significant burden on participants, with further implications for recruitment and dropout. We recommended that work be undertaken to assess participants' experience of taking part in EPAD research, including dimensions of psychological, physical, and/or economic hardships associated with research.

This work has been carried out within the Study of Participant Experience of Alzheimer's Research (SPEAR) EPAD sub-study. This substudy aimed to better understand participation in Alzheimer's disease research, in order to improve study experience, informing future approaches to recruitment and retention and provide evidence for the assessment of ethical questions related to study participation. Both quantitative and qualitative arms of the study consider

- Motivations for taking part in EPAD and prior experience of research
- Experience and 'burden' of EPAD research tests and assessments
- Willingness or 'readiness' to take part in future clinical trials


In addition, the qualitative arm of the work further explored the role of care in the research context, building on prior work with longitudinal studies of ageing.<sup>1</sup> Ethical practice in biomedical research is closely connected to care, as it concerns "the whole situation" of research practice.<sup>2</sup> Importantly, it examined how questions of the burden and the value of research are influenced by the nature and degree of caring relations in the study.

#### *3.1 Methods and analysis*

The SPEAR study was a mixed-methods study of research participant experience. It involved a questionnaire survey, qualitative interview and observational data from EPAD centres in the UK. Recruitment focused on the UK for both methodological and pragmatic reasons, particularly the advantage of working within a comparatively uniform clinical research setting (albeit with some differences in the organization of both healthcare and research governance between England and Scotland), and in a single language. The design and implementation of the study was discussed with the EPAD participant panel in Scotland and feedback incorporated. The study received NHS Research Ethics approval (REC Reference 19/NW/0315).

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<sup>2</sup> This section written by Natassia Brenman (nkf23@medschl.cam.ac.uk) and Richard Milne (rjm231@cam.ac.uk)

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### 3.1.1 Questionnaire Survey

Survey design was informed by previous instruments.<sup>3-8</sup> Questions in Parts A and B were drawn from the short version of the Research Participant Perspectives Survey.<sup>6</sup> RPPS-S questions were supplemented by questions on AD-specific research procedures, namely cognitive testing, lumbar punctures and MRI scanning. A subset of questions examined attitudes towards future clinical trial participation informed by previous surveys examining Alzheimer’s disease clinical trial participation.<sup>9</sup>

Survey participants were contacted through the EPAD LCS after completion of at least one study visit. Links were generated and sent to each participant by the local study team.

The survey was structured in three stages which address the different study questions:

- Part A examines motivations to participate and continue to participate
- Part B examines participants’ experience of the study as a whole and of specific procedures
- Part C examines factors associated with the willingness to take part in future clinical trials

Study partners, who provide informant responses to neuropsychological testing in the studies, completed a short survey about their experience of participation. The survey text is included in Annex I.

Surveys were emailed or posted to all participants at EPAD centres in Edinburgh, Oxford, West London and Bristol, a total of 191 participants (October 2019). 101 completed participant questionnaires were returned (52.9%; 92/101 online, 9 by post), with 7 study partner questionnaires. Data was collected using Qualtrics survey software, and analysed using SPSS 25. Given the low number of study partner responses, we here concentrated on responses from EPAD participants only.


Of questionnaire respondents, 61% were female, 46.5% were over 70 and 71% educated to degree level or above. 84% of respondents had had EPAD visit within the last 6 months.

### 3.1.2 Qualitative study

Recruitment for interview and ethnographic observations took place over a period of 6 months at the same 4 sites (Edinburgh, Oxford, West London and Bristol). With their consent, “participant observation” was employed with participants, study partners, and the EPAD study team to observe practices of data collection and knowledge production. Observation of tests and assessments were carried out opportunistically at participating trial delivery centres subject to informed consent from participants who were comfortable having the research participant present during these sessions. Observational data has informed the findings in this report but will be reported in full in future publications.

25 semi-structured interviews were conducted with participants, sampled purposively to include current EPAD participants who had attended at least one study visit as a main participant (i.e. not study partner). We spoke to 9 men and 16 women, and this included both those with and without mild cognitive impairment (MCI). Reflecting the wider EPAD population, the majority of participants were cognitively healthy and did not have MCI. There was very little ethnic and cultural diversity in the



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sample, and the majority were of high socioeconomic status. However, recruitment was carried out in conversation with the EPAD study teams who indicated that the sample were generally typical of the cohort at large (at least in the UK). This informed us that it was appropriate to stop recruiting when data saturation was reached, despite the lack of socio-cultural and ethnic diversity. Interviews were either face-to-face (at clinical research facilities or home visit) or over the telephone (where participants were already familiar with the researcher from study visit observations). All lasted approximately 45 minutes.

Interviews were audio-recorded, transcribed and analysed on NVivo software using a combination of inductive and deductive thematic analysis.<sup>10</sup> All participants were assigned a pseudonym immediately after data collection, which we use in the reporting below.

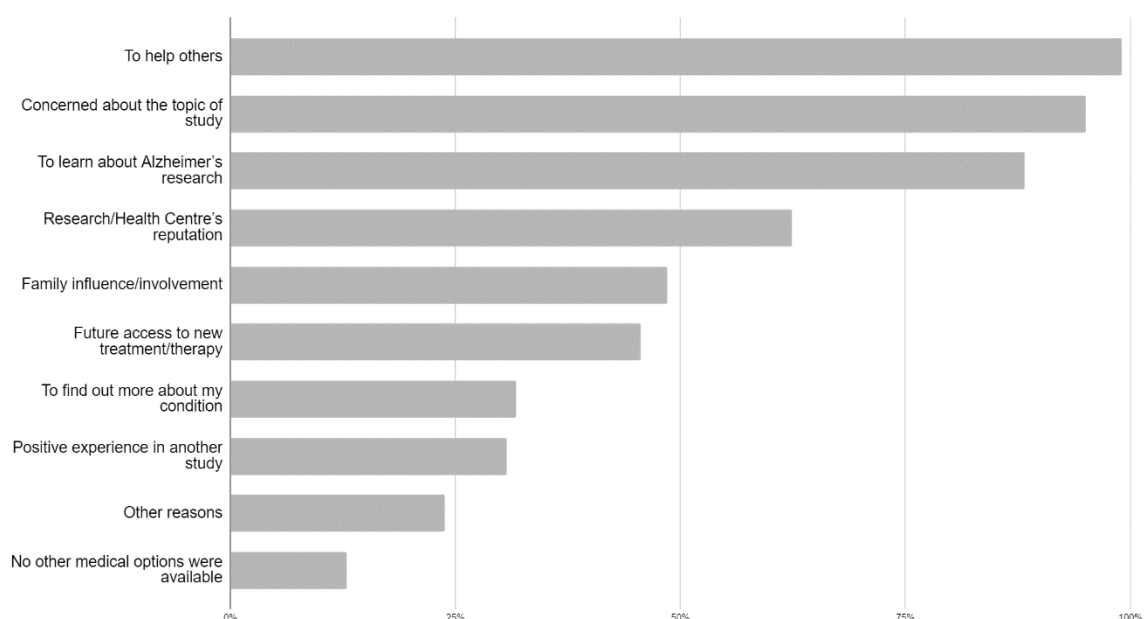
## 3.2 Findings

### 3.2.1 Motivations for initial and continued participation

The primary reason identified in the survey as very or somewhat important by respondents for joining the EPAD study was to help others (99%), echoing previous research that emphasizes the importance of altruism in study participation. However, respondents identified a range of other motivations as important, including the topic of research, and the opportunity for them to learn about Alzheimer's research (figure 1). While comparatively few respondents in this sample described taking part in order to find out about their condition (32.3%), this is still a considerable number given that the LCS is a cohort whose participants do not have symptomatic dementia, and, at the time of recruitment in mid-October 2019, 69% of the EPAD cohort (1068/1529) had a Clinical Dementia Rating (CDR) of 0.

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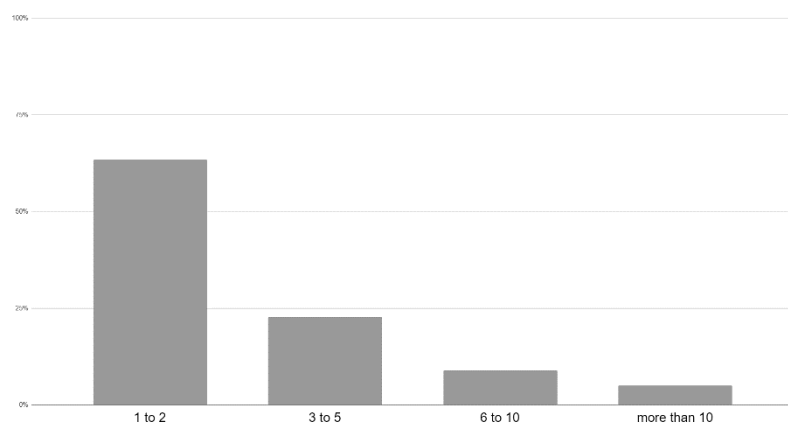
When you considered joining the EPAD study, how important were these reasons for you (somewhat/very important)? -




**FIGURE 1: MOTIVATIONS FOR JOINING THE EPAD STUDY**

Some participants had a long history of being involved with medical research, often becoming involved with EPAD via other studies. For the majority of participants, EPAD was either the first or second medical research study that they had taken part in. However, 36.3% of the sample had taken part in more than three studies in the past, while 7 participants were *currently* taking part in between 3 and 5 research projects.

How many medical research studies have you ever joined (i.e. studies that involve more than an online survey, including EPAD)?

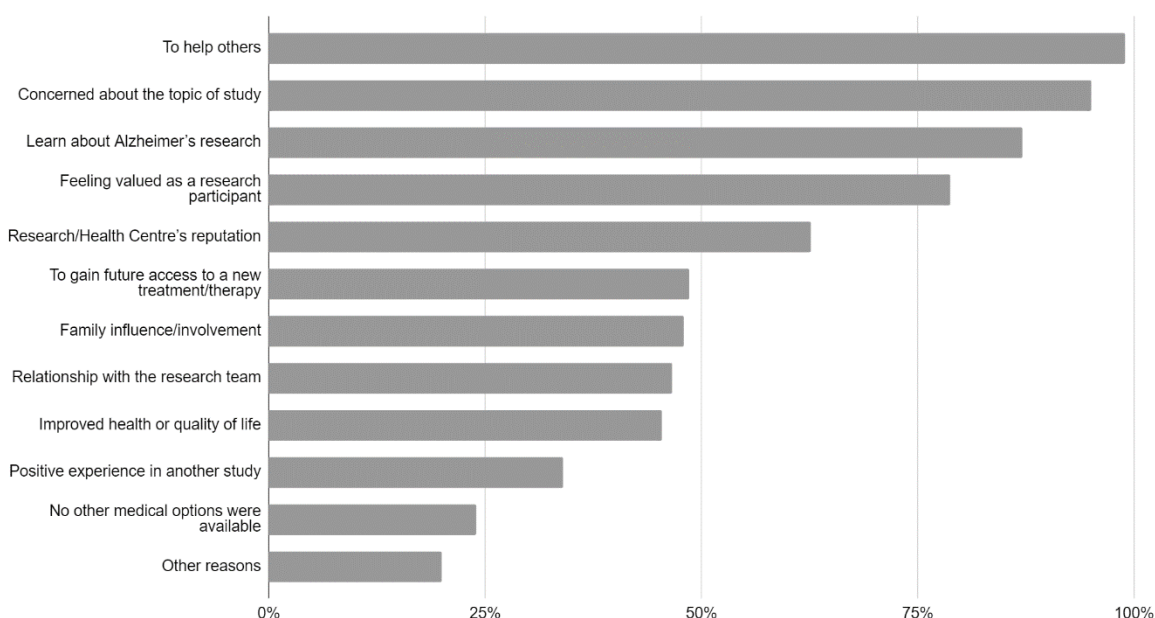


**FIGURE 2: PRIOR RESEARCH EXPERIENCES**

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Helping others was also the primary motivation selected by participants for continuing to participate in EPAD, with 99% again selecting it as somewhat or very important. Indeed, the three most significant motivations were unchanged from those associated with joining the study in the first place. However, participants did highlight the importance of feeling valued as research participants, something that has been a focus of significant activity in the EPAD study and which was seen as important by 79% of respondents, although a smaller percentage (47%) highlighted the importance of the relationship with the research team.

How important were these reasons for you in staying in the research study (somewhat/very important)?



**FIGURE 3: MOTIVATIONS FOR CONTINUING TO PARTICIPATE**

Reflecting the quantitative findings, participants in the in-depth interviews spoke about altruism or helping others (in society now or in future generations) as core motivation for participating in EPAD. However, motivations to participate and to continue participating were not static. We found that a key organising concept in how people talk about why they participate is time: how motivations for participation and expectations of future research emerge and change throughout the *research process* (i.e. before and during the LCS, and looking to future trial participation) and how they relate to participants' *lives and experiences of ageing* (i.e. life before EPAD, everyday experiences of ageing, and hopes for the future). This reflects the fact that EPAD is a longitudinal study and has a particular focus on cognitive and biological change over time, but it also speaks to participants' broader life experiences as ageing adults. Therefore, below, we outline a number of themes around motivations that relate to various past and present experiences. Then, in the next section, we outline themes relating to

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participants' expectations for *future* trial participation. In the final section, we discuss more general experiences of participating in EPAD.

The qualitative data indicated that some participants recognised themselves specifically as “the sort of person who volunteers” in biomedical research:

“I think the answer is once you're involved in one research project people then, somebody says, oh there's this other research project I think you'd be interested in and we already know you're the sort of person that volunteers.” (Denise<sup>3</sup>)

Previous demonstrations of willingness to participate was a major reason for being approached via registries and other channels they had consented to be contacted through. Several participants also incorporated other forms of medical donation into their narratives of how they got involved:

“I do things because I just don't know...I may help somebody. I may save a life. I mean, I've given blood, bone marrow, platelets, white cells and plasma... I may have made no difference; I may have made a lot of difference but that is to me satisfying” (Janet)

Participation as active ageing (keeping busy, staying useful)

Discussion of participants' motivations situated participation in the context of individuals' lives.

“In terms of the Alzheimer's study, I guess, yes, we all have a responsibility to try to ensure that, if not we, that others don't spend 10 or 20 years of their lives as cabbages. I mean, one of the things that makes life worth living is feeling useful, and if you can't give anything, if you can't be a part of society and react to it, then it would be pretty miserable”

These are the words of Marion, a sixty-eight-year-old woman who still worked full-time alongside participating in EPAD. For her, the imagined future of living passively “as a cabbage” is compared to her present possibility to be responsible and active in preventing this future, for herself and others. She goes on:

“I hope that my participation in the study is going to be useful...But as you get older, you are conscious that what you can give is decreasing” (Marion)


Losing the capacity to “give” in the future (due to cognitive decline or just ageing in general) creates an imperative to ‘act now’ in the present.

Several participants, like Malcolm below, located their research participation in a very particular moment in their working lives: the period of entering retirement.

“...to do something positive because there is this sense of ‘what's the point of retirement?’ Because it's very difficult when you stop full time work” (Malcolm)

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<sup>3</sup> As described above, all names are pseudonyms, not actual SPEAR participant names

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There were also several examples of people whose participation was a continuation, or slight adaptation of careers in research or medicine; a way of contributing, but now in a volunteer capacity.

The M.O.T – an ‘incidental benefit’

All participants had a clear understanding that they should not expect to be given feedback or test results on a routine basis, so knowing specific details about biomarkers or cognitive change was rarely cited as a motivation to participate. However, knowing that there had been *no change* to speak of (that they had not dipped below the threshold of cognitive decline) and the possibility of having *incidental findings* flagged up, did emerge as an attractive reason to continue participating. Because this benefit often became apparent during the research process, we refer to the health check as an ‘incidental benefit’ – comparable to the notion of ‘incidental findings’ in the study context

“That is a benefit that I wasn’t really expecting, so yes, it is useful” (Elizabeth)

This benefit was often described jokily as “the M.O.T” – referring to the regular check for roadworthiness that cars undergo in the UK. The M.O.T. was used by participants to refer to a functional check-up where you would be alerted to any (actionable) problems or given the ‘all-clear’ without needing to know the inner mechanics of what was going on:


“I looked on all these tests as getting a free MOT, they were checking everything and they found a couple of things, which as they said at the beginning, if you find anything, they report it to your GP - they don’t deal with it here”

The M.O.T was something that emerged during the research process and came to be seen as almost immediately useful. This is in contrast to biomarker/risk information, which was seen as a more uncertain benefit that may or may not become useful, depending on how successful treatment trials for early Alzheimer’s disease are in the future. As a result, there was a great deal of diversity in preferences for how much biomarker information participants wanted to be told. This ranged from participants saying:

“I certainly would like to know about all the changes... It's a bit like the house, if one of the tiles falls off, I'd like to know why it's falling off and I will do something about it” (Lindsay)

In contrast to others on the other end of the “spectrum” (as one participant called it):

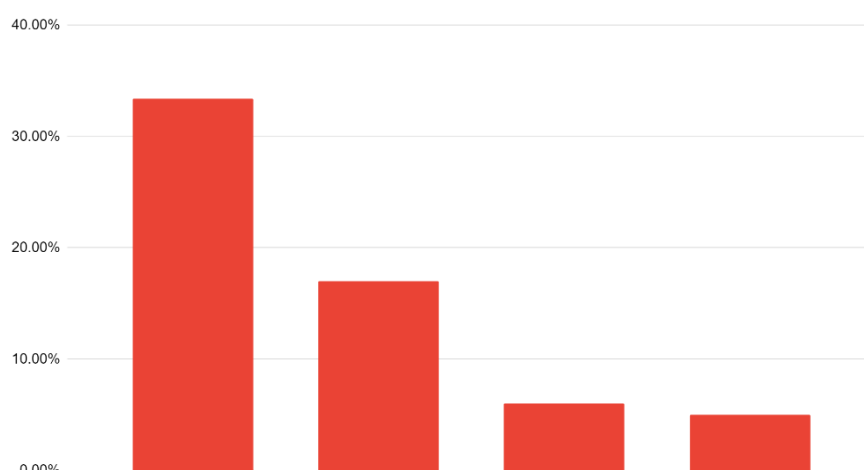
“I think I'd sooner not know quite honestly. Because, you know, I, you know, I don't want to start worrying unnecessarily about things,” (Bob).

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### 3.2.2 Experience

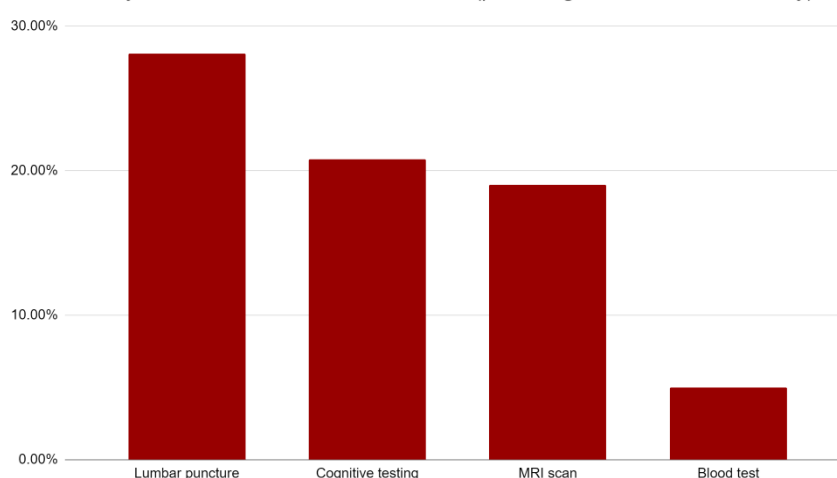
In the survey data exploring the experience of the study, the lumbar puncture was more likely to be reported to be somewhat or extremely physically (33.4% vs 17% for MRI, 6% blood test and 5% cognitive testing) and mentally (28.1% vs 20.8% for cognitive testing, 19% MRI and 5% blood test) uncomfortable. Further, 16.7% of participants reported feeling a moderate or lot of unexpected pain as a result of the lumbar puncture. However, only 7 participants would either probably or definitely not undergo one in the future.

How physically uncomfortable was the assessment (percentage of somewhat/extremely)




**FIGURE 5: EXPERIENCES OF PHYSICAL DISCOMFORT ASSOCIATED WITH STUDY PROCEDURES**

How mentally uncomfortable was the assessment (percentage of somewhat/extremely)



**FIGURE 4: EXPERIENCES OF MENTAL DISCOMFORT ASSOCIATED WITH STUDY PROCEDURES**

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Experience of cognitive tests: “where the anxiety comes in”

Overall, the tiring and challenging nature of cognitive tests were stressed more than physical tests (except specific when specific challenges were faced). Despite the lack of feedback about cognitive test scores, participants felt they had an acute sense of how ‘well’ or ‘badly’ they were doing on each test, which could be encouraging or anxiety-provoking:

“with some of those tests, it’s really obvious that you can’t remember something. It’s like trying to remember the basic, who liked the food and their animal. I got to mine and I just said, I have no idea, I can’t remember and then the whole thing was lost and I felt...I felt a degree of failure and concern...” (Charlotte)

Many of the participants singled out the Four Mountains and Supermarket Trolley tasks as particularly hard-going:

“To be honest, it's like you go really brainy fog dead. With the mountains one they are so alike... Like the first couple is probably okay, but by the fourth one you kind of start to lose the will to live ... And I think that's where the anxiety comes in... And probably the same for the trolley because again it's 'cause it's so repetitive your mind can drift a bit, you know, particularly towards the end” (Alison)

An exception was when participants had professions or hobbies that required orientation skills, (for example hill-walkers), which made the 4 Mountains test in particular easier or more enjoyable.

Experience of Lumbar Puncture

Overall, people were surprised at how smoothly this went, with people with experience or contact with professionals who use LPs in clinical practice being particularly apprehensive:

“you should have seen my GP’s face when I told them I’d had a lumbar puncture for research... he’s, you know, super sensitive to the risks... Yes, I was a little bit [apprehensive], but the doctor who I think was a consultant was absolutely superb, and I barely felt anything at all and there certainly was no effect afterwards, I was okay.” (Audrey)


However, five participants we spoke to had adverse reactions to the LP: two of them less severe (mild headaches and feeling faint), and three severe headaches for about a week.

Experience of MRI

Participants had a wide range of experiences with the MRI, with most finding it went smoothly, or even finding it enjoyable (with two reports of participants hearing music in the noises!). Others who found it more challenging had various coping strategies, for example:

“The MRI scan actually I was surprised at myself - I hadn’t thought that I had any problem with confined spaces... I thought of my cat and my heartbeat went down and I started to get a grip on my breathing, and I calmed right down.” (Gordon)

Also, reflecting the theme that study burden is mediated by caring relations with researchers:

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“Going back to the MRI scan the radiologist was brilliant. He sat me up, he talked to me because he could see how anxious I was and I was anxious at the MRI scan even afterwards ... he talked to me and he probably gave me ten minutes he didn’t have and he was really helpful.”  
(Collin)

‘Burden’ is mediated by caring relations between researchers and participants

In the quantitative data, 7.9% of respondents described the study as ‘intense’, versus 41.6% who described the study as ‘simple’. While participants rarely described participation as burdensome overall, individual study visits (mainly the baseline) were intense and tiring:

“Some of the sessions are very long. Once you’ve been staring at a screen for so long, I mean, I can’t stare at screens for very long, your eyes start going and your brain starts.... I mean, ideally fresh air... does bring you back but maybe a bit more - sort of break it up a little bit”  
(Janet)

However, we found that discomfort and burden was almost always described in the context of interactions with researchers and study doctors and nurses. Generally, the researchers and research context went a long way in creating a sense of being cared for, which mediated these burdens:

“I think it’s just the general ambiance and the feeling that this team are very close to each other and very motivated by this potentially quite exciting research they’re on. So that’s reflected in the way that they take care of us when we’re there” (Audrey)

Crucially, difficult and uncomfortable experiences (with tests/technology) often ran in parallel to positive experiences with people delivering them.

Finally, there were examples of participants experiencing the testing and “checking over” involved in EPAD as care in itself:


“I quite enjoyed being examined by the doctor, actually, the reflexes ...I mean, it is quite nice knowing that you’ve been checked over even though obviously they might find something that perhaps you didn’t know about (and you perhaps didn’t want to know about) but, you know, so it’s nice ... I just like the attention.” (Clare)

This relates to the “M.O.T.” theme in the section above about motivations to continue participating.

### 3.2.3 Trial participation

A final set of questions on motivations explored potential *future* participation in an EPAD clinical trial. 61% of respondents stated that they would participate in a clinical trial at this time, with a further 37% stating that they would consider doing so in the future. One participant stated that they would never join a clinical trial. 13 participants had previously taken part in a clinical trial.

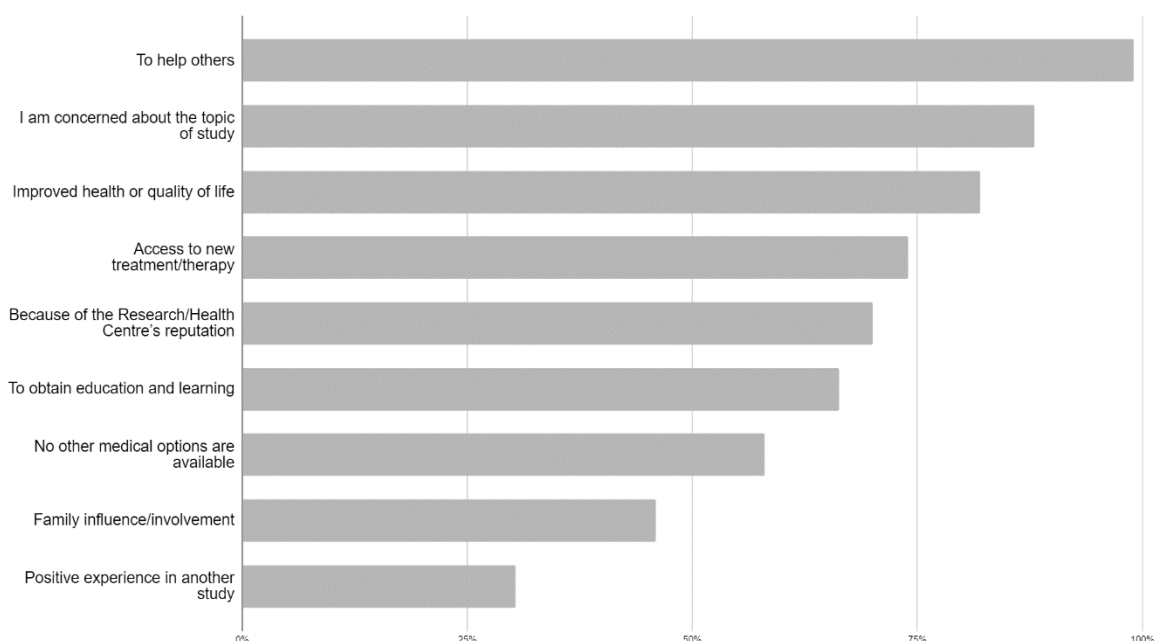


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## Motivations for participating in a clinical trial

Motivations for participating in a clinical trial were again similar, focused on the potential to help others and the importance of the object of study. However, when considering trials, a high proportion of participants emphasized the potential for improved health or quality of life (82.2%), or access to new treatments or therapies (74.2%). This difference in motivations re-emphasizes the importance of providing participants with clear information about future clinical trials, the randomization process and the uncertainties associated with trial outcomes, as discussed in section 2 above.

How important would these reasons be for you in joining a clinical trial of a new medicine (somewhat/very)? -



**FIGURE 6: POTENTIAL MOTIVATIONS FOR TRIAL PARTICIPATION**


A minority of qualitative interview participants had high hopes and expectations for the trial and cited this as one reason they were motivated to continue with the study:

NB: Did you think about [a drug trial] as something that you'd be open to?

Sarah: Yes, oh, I thought that was a positive. I mean, if it happened, I thought it was definitely a positive.

NB: And why is it positive?

Sarah: Because there might be...they might have got a treatment and... what's to lose, in effect, really. If you're in that situation, what's to lose?

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For Sarah, being “in that situation” refers to having early symptoms of dementia, emphasising the importance of a particular future in shaping motivations. Another participant, Christine, was keen to prepare for a future where she might develop dementia by doing everything she could to gain access to care and potential future treatments. Whilst she was no less aware than other participants that treatment benefits were unlikely, she was more motivated to access possible benefits of the trial:

“It’s almost a little...selfish is probably the wrong word. You know, I’m thinking about me going forward. Of course, you know, I’m more than happy to help anyone else, you know ... but, of course, I’m thinking about my future, and, you know, how I...how best I can be looked after or look after myself and be looked after perhaps at a stage when I would need, sort of, third party help... if I’m part of this exercise, this study, then going forward ... I’m hoping it just paves the way for perhaps future studies and help..” (Christine)

A key message from Christine and others with a family history of dementia and/or limited options for future care is that people’s experiences and expectations of ageing shape their motivations to participate in different ways.

Participants generally had a clear understanding that they were unlikely to gain treatment benefits from the study. However, not unlike the concept of ‘incidental benefits’ described above, participants did imagine futures in which a preventative treatment might be attractive:


“... I mean, I think if something like that happened and either of us had some symptoms and this was a possibility of counteracting those symptoms, then we would welcome that. But the purpose in jumping into the research was, in a way, much more altruistic, if you like, than personal gain, in that kind of way.” (Nigel)

The ways in which Nigel speaks about his motivations for participation and whom it might benefit reflects the shifting needs and interests at different moments in time. The initial motivation for “jumping in” was altruism, but in a certain imagined future, they might welcome this personal gain.

However, the majority of participants did not talk about gaining access to potential treatments as a primary motivation for participating. By far the most common expectation and attitude towards the trial was a sense of having made a commitment and having a responsibility to continue participating in the trial phase of the study, with a pharmaceutical intervention drug:

“I just think there’s a possibility that there’d be some information that being in one or other groups would be...we would feel would give us an unacceptable risk. So, you know, it would depend on the details but otherwise I’d sort of feel morally obliged to continue.” (Ross)

This participant was describing the kinds of caveats he and his wife (who was also an EPAD participant, and part of the joint interview) anticipated they might have to agreeing to participate in the trial, but ultimately he was expressing a sense of responsibility to take part, even if there were some “acceptable” risks.

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From the way that others described the initial consent procedure, most participants were clear that could easily opt out of the trial, but maintained a sense that this be a deviation from what they had initially signed up for:

“I think it said very clearly when I read through all the documentation before I agreed to do the study that they didn’t want people who would be unwilling to go on a drugs trial so I felt committed then that I would go on a drugs trial if I was asked to.” (Claire)

Overall, participants tended to be willing to take part in the trial, even though they understood that there was only a small possibility that the intervention would be successful. However, a (relatively small) number of participants did have serious misgivings about taking part in a drug trial. We found a range of tentative attitudes towards the prospect of being contacted to take part in a clinical trial. From “not wanting anything to hurt” to knowing quite simply that “I don’t want a drug,” some participants were far from certain that going into a clinical trial was the best thing for them.


“I’ll try dietary, herbal, other things that could do it or even exercise rather than go for drugs every time because so many drugs have side-effects and the long-term knowledge of them is not always as good as it ought to be. I’ve watched drug things on television where they’ve gone wrong. I mean, that is...that was disgusting what happened. I mean, it’s happened throughout history but people don’t understand...if you understand enough about it, what do they say, what is the prime thing, do no harm.” (Janet)

#### Effect of trial type

The extract from the qualitative interview with Janet highlights the potential impact of study type on the willingness of EPAD participants to take part in clinical trials.

In the survey data, respondents were less likely to say that they would take part in a study that involved an infusion (65.4%) than any of a pill (84.1%), lifestyle change (83%) or nutritional supplement or dietary change (91.1%). Respondents were positive about taking part in a trial that involved cognitive testing (97% likely/extremely likely), MRI (96%), blood tests (98%) or PET scans (89%). However, they were less likely to take part in trials involving lumbar punctures (78.8%) or bringing a study partner (74.2%).

Changes in the logistics and commitment associated with a clinical trial also had an effect on people’s willingness to take part. For example, 88.1% of participants said that they would be likely or extremely likely to take part in a trial that involved monthly study visits, compared to 54.1% for weekly visits and only 17.4% for daily visits. Travel also had a significant effect – 93.8% of respondents said that they would travel less than 1 hour, compared to 26.3% for travel over 2 hours. The effect of study length was less pronounced – 89.8% responded that they would be likely or extremely likely to take part in a trial that lasted 12 months, compared to 71% for a trial that lasted 4 years.

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### 3.3 Discussion and conclusions:


The SPEAR findings provide insight into motivations, expectations and experiences of research participation. They emphasise the importance of altruism as a motivation for participation, but also that motivations overlap, change over time and may differ as participants consider clinical trial participation.

In the qualitative interviews, initial motivations to participate were often linked to prior experience of research: being “the sort of person who volunteers”. This suggests that decisions are part of a much longer process of becoming engaged in research and available for recruitment, and may reflect the influence of recruitment through the EPAD Register. However, these data also suggest that the “sort of person” who participates is also highly educated, often has a professional background in science and medicine, and feels a responsibility to “stay useful” in retirement. The fact that everyone we spoke to was white and almost everyone English or Scottish reflects the literature on the lack of representation of ethnic minorities in dementia research<sup>11</sup> and health related research more generally<sup>12</sup>. These findings shed some light on how this is perpetuated by the way recruitment processes are aligned with the lives of certain groups.

There was very little consensus about the value of the return of biomarker results, with some people keen to know as much as possible, and others happy not to know results. Reflecting previous work within WP8<sup>13</sup>, the degree to which people could “do something” with the information shaped participants’ responses about biomarker results. However, participants consistently described the return of incidental findings and clinically relevant information about cognitive decline (i.e. results you could “do something about”) as beneficial and desirable. It is important to note, however, that this was based on people’s *expectation* of value more than *experiences* of receiving such information.

Overall, both quantitative and qualitative data emphasise that participants’ experiences of the EPAD LCS were positive, despite the intensity and discomfort of some tests. The qualitative data in particular suggest the importance to this of the interactions and relations with researchers and staff throughout the study process.

Finally, the findings suggest that the majority of EPAD LCS participants would be willing to take part in a clinical trial, but that the timing, location and duration of such trials is critical.

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## 4. Evaluation of incidental findings protocols in EPAD<sup>4</sup>

In the course of conducting research, researchers may come across findings that are of potential health or reproductive relevance for individual research participants, but are beyond the aims of the study – so-called incidental findings.<sup>14</sup> Incidental findings are findings pertaining to potentially serious medical conditions, that are clinically significant and actionable. As they are not within the aims of the study, incidental findings are not actively looked for; rather, they are stumbled upon by researchers.

Within the EPAD-LCS, this definition of incidental findings excludes findings related to dementia, Alzheimer's disease, or risk factors associated with Alzheimer's disease, as these are variables of interest which are within the aims of the study. It also excludes other findings that are actively looked for as part of the study protocol.

In D8.1 we presented guidance for the detection, management and communication of incidental findings in the EPAD-LCS. This section presents the results of an evaluation of policies or protocols for the handling of incidental findings within the EPAD LCS.


### 4.1 Recommendations on incidental findings

EPAD places high demands on research participants, in terms of time investment, invasive and uncomfortable procedures, long-term commitment, disclosure (or not) of risk status for Alzheimer's disease, and uncertainty regarding future drug trial participation. The principle of reciprocity requires a careful handling of incidental findings on the part of EPAD. Our recommendations were the following:

- Given the unclear clinical significance and utility of many incidental findings and the risks and burdens associated with their feedback, as a general rule, in research settings, incidental findings should not (or need not) be actively looked for.<sup>15</sup>(2) However, **clinically actionable incidental findings should be reported to research participants**, as doing so may help protect research participants against avoidable harms.
- In imaging studies, it is currently best practice to review research scans for clinically relevant findings.<sup>16,17</sup> All (diagnostic-grade) research scans in EPAD should be **screened for abnormalities** by trained researchers. When abnormalities are flagged during routine review, expert radiologists should be consulted to confirm the finding prior to feedback decision-making.
- EPAD TDCs are recommended to identify possible incidental findings for all tests and examinations to be conducted as part of the EPAD LCS. Thus, the TDC may decide in advance which (types of) incidental findings should be communicated with research participants and their general practitioners, and establish a **pre-determined list of findings (not) to report**.

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<sup>4</sup> This section led and written by Eline Bunnik, [e.bunnik@erasmusmc.nl](mailto:e.bunnik@erasmusmc.nl) with additional findings from the SPEAR sub-study

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- EPAD should consider setting up **multidisciplinary expert panels** at the TDCs, which will be tasked with decision-making regarding the communication of incidental findings that have not been anticipated (i.e. included on the pre-determined list of findings (not) to report).
- 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’.
- EPAD TDCs should make arrangements with local hospitals or medical centres about referrals for **clinical follow-up** of potentially serious incidental findings, to help ensure timely diagnosis and high-quality clinical management.
- EPAD should offer a **qualified opt-out option** to participants. As part of the informed consent process, participants may indicate that they do not wish to know about incidental findings. In principle, EPAD-researchers will 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 (duty of rescue).
- As part of the informed consent process, research participants may indicate whether or not they would like EPAD to report incidental findings to their **general practitioners**.

TDC leads were responsible for setting up policies or protocols for the handling of incidental findings at their TDCs in line with this guidance offered in D8.1 as well as with local laws, regulations and professional guidelines.


## 4.2 Questionnaire

To evaluate policies and protocols for the handling of incidental findings within EPAD, we sent out a questionnaire per e-mail to TDC leads of all active TDCs in May 2019. The questionnaire can be found in Annex II. In October 2019, we sent out the questionnaire per e-mail again.

### 4.2.1 Development of questionnaire

In the EPAD LCS, various types of data are routinely collected: “clinical, cognitive, functional and biomarker (including imaging) measurements” (D4.13). For a full list of data collected within the LCS, see Annex III. Based on this list of data collected within the LCS, we expected that incidental findings could technically be detected during the following types of tests and examinations:

- Vital signs
- Physical examination
- Blood sampling
- CSF sampling
- Saliva sampling
- Urine sampling
- MRI

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In the questionnaire, we asked for numbers and examples of incidental findings detected during these tests and examinations. Also, we asked questions about protocols and pathways for the detection, management, and communication of incidental findings. Finally, we asked whether TDC researchers monitored the impact of feedback of incidental findings on research participants, and we asked for their valuation of that impact. The questionnaire consisted of 12 questions. It was reviewed by and discussed within WP8 before it was sent out to TDC lead of all active TDCs. In the email, we also asked for patient information sheets and blank informed consent forms.

#### 4.2.2 Response

After the first mailing, 7/30 approached TDCs sent their responses. After the second mailing, we received responses from 3 additional TDCs. We received 10 responses in total. The mailings were conducted in May 2019 and October 2019. We take 1 September 2019 as a benchmark. The 10 TDCs who responded had +/- 700 participants enrolled (SEEPAD Graphs; <https://lcsgraphs.pr-epad.org/>) on 1 September 2019. At that time, there were 30 TDCs active, and a total of slightly over 1500 participants enrolled. We did not receive responses from a few large TDCs. We received patient information sheets and informed consent forms from 6 TDCs.

### 4.3 Results

The results section is subdivided in three parts: the detection of incidental findings, the management of incidental findings, and the communication of incidental findings.

#### 4.3.1 Detection of incidental findings

Incidental findings may theoretically be detected during the following tests and examinations:

##### Vital signs

In 3 TDCs, no incidental findings were detected during vital signs examinations. In 3 TDCs “many” (or “multiple”) findings were detected, notably hypertension and bradycardia. In the remaining TDCs, this had happened either once or occasionally. The numbers of findings detected were not related to the number of participants included. In some relatively large TDCs (e.g. number of active participants > 150), no findings had been detected during vital signs examinations.


##### Physical examination

Most respondents did not mention any incidental findings detected during physical examinations, whereas others reported “multiple” or even “many (too many to list)”. Findings included abnormalities detected on ECG and abnormal neurological signs. The TDC that mentioned “many” findings gave the following examples: bruising, joint deformity, varicose veins, moles, surgery scars, and cysts.

##### Blood sampling

Most TDCs reported one or more incidental findings detected in blood. Examples included high cholesterol, low haemoglobin count (HB), raised white cell count (WCC), abnormal red blood cell count (RBC), abnormalities in factor V, altered renal function, altered thyroid function, altered liver function.



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Some TDCs mentioned that blood samples are not analysed locally, and researchers were not aware of the central results.

### Urine sampling

Only 2 TDCs reported incidental findings detected in urine. These included presence of protein, leukocytes, or blood in the sample. In one TDC, this had happened in one research participant, and in the other TDC, this had happened in 3 participants (in a total of +/- 40 participants enrolled). Some TDCs mentioned that urine samples are not analysed locally, and researchers were not aware of the central results.

### Saliva sampling

Saliva samples are analysed centrally, not (also) locally; the TDC is not made aware of the results of this test.

### CSF sampling

CSF samples are analysed centrally, not (also) locally; the TDC is not made aware of the results of this test.

### Cognitive testing


One TDC reported 10 findings detected through cognitive testing. Other TDCs reported either 1 finding or no findings. These typically pertained to unusually low scores on cognitive tests (CDR, RBANS, GDS, STAI, SNAC), suggestive of a cognitive disorder. In some research participants, Mild Cognitive Impairment (MCI) was thus 'diagnosed' or found to have progressed, which was "unexpected" for the research participant.

### MRI

In 7 out of 10 TDCs, incidental findings were detected through MRI of the brain. In total, the number of findings was > 50 in (around) 700 participants. In the three largest TDCs which responded (with > 90 participants enrolled), the number of findings were 5 and "many" and "around 30", respectively. In one TDC with over 60 participants enrolled, the number of findings was 10. In the remaining TDCs, there were 1 or 3 or "multiple" cases, or the number was not offered. The following examples were given:

- White matter damage, meningioma (5)
- Imaging abnormal findings (i.e: possible microadenoma, possible cerebral amyloidosis) (3)
- Vascular changes have been common, including lacunar infarcts, one calcified meningioma, one aneurysm (10)
- Cysts, aneurysms (many)
- Enlarged perivascular space in the left globus pallidus (1)
- Aneurysm, cysts (multiple)
- Cavernous angioma (1)
- Ophthalmic aneurysm, severe spinal stenosis, small vessel disease



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- Meningioma or cavernoma or cystis formation discovery, vascular cerebral incident discovery, vascular lesions, thalamic lacuna, microbleeds (around 30)

#### 4.3.2 Management of incidental findings

At the various TDCs, different policies and protocols may be in place for the handling of incidental findings detected in the course of research.

##### Existing protocols

Six TDCs have no formal policy or existing institutional protocol for the handling of incidental findings. One respondent mentions that “the local imaging centre” has a policy that is used also for EPAD. One respondent refers to GCP guidelines. One respondent refers to the in- and exclusion criteria of the EPAD LCS, “clinical judgment” and to a national policy, in which the involvement of a multidisciplinary team is recommended. One respondent described their local policy as follows: “any findings, abnormal test values, which are clinically significant or otherwise, must be reported to the study doctor for assessment and/or the PI for appropriate action determined by the finding.”

##### Checking for incidental findings

All TDCs reported that available results (e.g. vital signs, physical examination, cognitive test and MRI) are routinely checked for incidental findings. In some TDCs, research personnel are instructed to watch out for incidental findings. One TCS lead reports: “All physicians and research assistants involved in data collection-and analysis are instructed to be aware of incidental findings.” Another reports: “They are asked to look for and report any significantly abnormal findings to the PI and can discuss these if they are unsure if they are significant or not.” And another reports: “We are aware that we need to look for incidental findings.”


In other TDCs, personnel do not seem to be instructed to watch out for incidental findings: “In our site the doctors or other personnel involved in the study EPAD LCS neither actively searching neither avoiding the detection of incidental findings.” Another TDC lead writes that the instructions are as follows: “Utilising clinical judgement effectively.....”

##### Recording

Most TDCs record incidental findings both locally and in Case Report Form (CRF) of EPAD. Local records are referred to as source documents or source worksheets. Two TDCs mention only local recording of incidental findings. Some TDC leads explain that incidental findings that are not clinically significant will not be recorded on the CFR but will be recorded locally.

##### Confirmation

In most TDCs, the PI is alerted if the finding is deemed “clinically significant/requires input/participant discontinued”. Findings are usually confirmed by a clinician (or “doctor” or “responsible medic”) of the study team. One respondent indicated that findings are *not* confirmed, and one respondent did not answer the question.

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Three TDCs mentioned the involvement of (external) others for confirmation of incidental findings. This may apply to findings detected through imaging: “If the finding is related to MRI imaging, we required a confirmation of the finding to the neuroradiologist who performed the exam.” Another TDC lead writes that in rare cases, (“e.g. ophthalmic aneurysm”) neurosurgeons are consulted. One TDC lead refers participants to “the community mental health team” for re-testing when “any results are significant (unusually low RBANS/MMSE/CDR) for age).”

### Multidisciplinary teams

Responses are variable. In most TDCs, multidisciplinary teams have not been established (specifically) to discuss the management of incidental findings. The study doctor will usually decide whether or not to report the incidental finding. Respondents explain that the study doctor may consult with a neuroradiologist, a neurologist, or the study coordinator or PI. The research team may be involved, “if needed” or “if required”, and in some TDCs, the research team consists of personnel with various disciplinary backgrounds, including neuropsychologists, neurologists, radiologists, and/or physicians. One TDC lead writes that there is no involvement of a multidisciplinary team. Another has not answered the question.

#### 4.3.3 Communication of incidental findings


When the incidental finding is confirmed and discussed and deemed clinically relevant, it may need to be reported to the research participant. In most TDCs, the research participant is informed about the finding by the study doctor or PI.

### How and by whom is the finding communicated?

The study doctor or PI informs the research participant “preferably by face-to-face meeting”. Some TDCs distinguish between urgent and non-urgent or major and minor findings: “urgent matters are communicated face-to-face during a consultation with a neurologist”, whereas “non urgent matters are communicated by phone, email or letter”. The study doctor need not always be involved in communication with research participants. One TDC lead explains that for findings like elevated blood pressure, the participant is informed by “the sub-coordinator who was taking the vital signs” after checking with the study doctor. One TDC states that all findings are communicated “by phone”.

### Informing the general practitioner

Almost all TDCs will inform the general practitioner. Some respondents qualify this policy, explaining that only in case “abnormal (blood or urine) values (...) are likely to affect the management or care of participant” will they be reported to the general practitioner. The general practitioner is usually informed by (report) letter. One TDC reports that the general practitioner is also informed by phone. One TDC qualifies the policy stating that the general practitioner will only be informed “as long as the participant is happy for this”. Not all TDCs allow research participants to opt out of letting their general practitioners know about incidental findings.

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## Opt-out

Six of our respondents do not offer an opt-out; prospective participants are informed, as part of the informed consent process, that they will receive information about clinically relevant incidental findings. If they do not consent to receiving information about incidental findings, they cannot take part in the EPAD LCS. Three TDCs do offer an opt-out. One informed consent form reads, for instance: "I agree to receive information about clinically relevant findings not related to Alzheimer's disease." The participant may indicate yes or no, and indicating no does not compromise enrolment. Two TDCs that do offer an opt-out, noted that none of the participants have disagreed with learning about incidental findings. One TDC noted that they changed the informed consent forms and now offer an opt-out.

## Referral

Some TDCs refer research participants in whom incidental findings have been detected to their general practitioners for follow-up. For instance, for repeat of abnormal blood tests or for 'rechecking' of blood pressure, research participants will usually be referred to their general practitioners. Some TDCs refer participants to general practitioners also for "clinical follow-up of MRI and ECG findings".


Two TDCs refer directly to medical specialists, such as neurologists, "because of incidental findings on the MRI scan (white matter hyperintensities, meningioma)". Participants have been referred to specialists in cardiology and onco-geriatrics. One TDC will arrange an "appointment at clinic" for the research participant.

## Follow-up

We asked whether the research team monitors the implications of the feedback of the incidental findings for research participants. We received variable responses. Some TDCs state that there is no monitoring of the participant following feedback of the incidental finding. Two respondents indicate that there is follow-up: "during follow-up visits, the study doctor will check with the participant whether the incidental finding, such as high blood pressure, has been addressed by the volunteer." And: "We then follow up with the participant to see if any new medications have been commenced and whether they have been referred for any further investigations." Two other respondents mention that they have requested feedback from the participants in whom incidental findings had been detected. Reactions were positive. Participants "welcomed the close monitoring and detecting abnormal values which might have been overlooked or not detected."

## 4.4 Discussion

Only one third of TDCs provided information on incidental findings and their procedures. Although policies and practices for the handling of incidental findings differed across TDCs, there were similarities on key aspects, for instance: if individual research results or images were available to researchers, they were routinely checked for abnormalities by trained staff. Abnormalities flagged or

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detected in the course of research that were deemed of clinical relevance to the research participant, were reported to research participants. In case of clinically relevant incidental findings, EPAD LCS participants have been referred for clinical follow-up. All TDCs had been confronted with incidental findings.


Incidental findings were detected in vital signs, physical examination, cognitive testing and/or imaging. Blood, saliva, urine and cerebrospinal fluid samples were analysed centrally, and in some TDCs, individual research results and information on any abnormalities detected in these samples, were not available to researchers. Many incidental findings resulted from cognitive testing. Strictly speaking, however, findings such as unusually low scores on cognitive tests are not incidental findings, as they fall within the aims of EPAD. The same applies to some of the findings (e.g. white matter lesions, amyloidosis) detected through imaging of the brain.

The frequency with which findings were detected differed across TDCs, also when corrected for the number of research participants enrolled. In one TDC, for instance, over 50 incidental findings were detected in slightly over 60 enrolled participants, whereas in another TDC, which had over 150 participants enrolled, hardly any findings were detected, except during imaging. These differences in frequency may result largely from differences in definition and/or understanding of the concept 'incidental finding'. To some respondents, for instance, findings such as bruising or varicose veins during physical examinations are included in their concept of incidental findings, whereas for others, such findings may not. The frequency may also be affected by the instruction given to researchers regarding whether to look or not to look for incidental findings. In some TDCs, researchers were instructed to watch out for abnormalities, whereas in others, researchers were told neither to watch out nor to try to avoid incidental findings.

## 4.5 Qualitative findings

In the SPEAR sub-study, the topic of incidental findings was discussed during interviews with EPAD participants in the UK. As described in section 3, an important narrative from participants was that the health check (or "MOT") aspect of EPAD emerged as a real benefit as they moved through the study - though not usually an initial motivation for taking part. But crucially this benefit seemed to be more the *possibility* of problems being flagged than examples of actual individual research results or incidental findings.

To the EPAD participants interviewed in the SPEAR study, the receiving of information about incidental findings that were indicative of abnormalities of limited or moderate severity and were actionable, was largely experienced as a benefit. Participants mentioned examples such as vitamin deficiencies, high cholesterol, high blood pressure, and thyroid abnormalities. Some participants sought clinical follow-up of incidental findings through their GPs, while others did not. Some participants who did consult their GPs, were told that the finding could not be confirmed.

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However, participants were less positive about the receiving of information about abnormalities of unclear clinical significance, such as those detected on MRI of the brain. A few participants had found out things they would rather not have known. Two of these cases likely pertained to white matter damage. To EPAD participants, this came across as quite ominous, and little advice was offered on what could be done. An example can be seen in the interview excerpt below:

R: The study doctor at the time did ring me up with the MRI because they found these white spots, which he reassured me about is slightly more for my age, but he thought it might have been because I'm diabetic maybe before I was diagnosed and before I was getting treatment. I think that's...I think, presumably, they will keep me up to date on that...to see if there's any deterioration at the next time I have an MRI.

I: Yes. Did you...so, yes, tell me about that - when they called you up and you found out about that - Were you, kind of, pleased that they'd rang and explained it? how did that go?


R: I think I really...because I can't do anything about it, I think I'd rather not know...not have known... Because what can I do about it? They'll...they said, it's fine, you don't have to do anything about it. No need to worry really, so I think I would rather not have known, but, I suppose, really, they felt they had to let me know.

## 4.6 Evaluation

Policies and practices at local TDCs did not diverge significantly from recommendations for the handling of incidental findings presented in D8.1. All responding TDCs supported the policy that clinically relevant incidental findings should be reported to research participants. The results of the questionnaire did reflect different local experiences with incidental findings, which can be used by TDCs to refine their own policies and practices in the future.


There were a few divergences, which need not, however, be problematic. We recommended, for instance, the establishment of pre-determined lists of findings to report and not to report, given that findings can be anticipated, and that decisions regarding clinical significance had best be made based on expert assessment of available evidence rather than on an *ad hoc* basis. Working with lists is currently a best practice for large-scale studies involving human participants. TDCs did not do this, and referred to clinical judgment instead. Also, we recommended the setting up of a multidisciplinary team to discuss incidental findings. Most responding TDCs did not do so. Minor findings were handled by the study doctor or PI, while for major findings, in some TDCs, specialists were consulted for confirmation or (multidisciplinary) team discussions were held. These solutions may have been more practical and feasible, seem to have sufficed, and are surely morally acceptable, as well.

We recommended TDCs to allow research participants to opt out of receiving information on incidental findings, with an appeal to participants' right not to know, which is generally acknowledged for the clinical setting. Most TDCs did not. In TDCs that did allow for an opt-out, participants have not refused or withheld consent for the receiving of information on incidental findings. In some TDCs, the informed consent process allowed participants to withhold consent to contact the general practitioner in case

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of incidental findings, but again, in most TDCs, this is not optional. Here, too, there is no international research-ethics consensus on whether or not such opt-out options should be offered. Both policies are acceptable.

In D8.1, we recommended monitoring the effects of feedback of incidental findings on research participants. As it is not yet entirely clear whether feedback benefits or harms participants, we felt that a large-scale study such as EPAD should contribute to our general understanding of the consequences of informing research participants about incidental findings, also to see whether our policies and practices are ethically responsible. While this has not been done in any systematic manner, the topic of incidental findings was discussed in the SPEAR study (section 4) and in the participant panels (section 6). The findings from the SPEAR sub-study suggest that EPAD participants value feedback of actionable findings regarding not-so-severe conditions, such as hypertension or vitamin deficiencies. At some TDCs, the study team monitors what happens to participants after feedback of incidental findings; for instance, the study doctor may inquire about clinical follow-up. Overall, participants seem to have responded positively to the handling of incidental findings by TDCs.

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## 5. Report on the EPAD Participant Panel<sup>5</sup>

In D8.3, we recommended the establishment of a research participant panel to incorporate the perspective of participants into the governance and running of the EPAD project. This recognised the importance of patient and public involvement (PPI) in health care research. It built on learning from previous approaches to PPPI work, work with research participants and patient groups, and the success of PPPI input within the PREVENT Dementia project, a parent cohort for EPAD.<sup>18</sup> It was agreed participant input should be incorporated throughout the study, including but not limited to study design, understanding the research experience, input on communications and future planning.

In this section we review the approach to setting up both the country level and project wide participant panels, the impact participant involvement has had on the project and how the model developed in EPAD could be used by other research fields. We draw on our experience of being involved in designing, setting up and participating in the panels, including the perspective of research participant panelists across the study. It is based on reports from study staff at each centre with a currently operating panel, study documents related to the panel developed by the EPAD ethics workgroup, and feedback from panelists in each local participant panel.<sup>19</sup>


### 5.1 How do the panels work

Key features of the EPAD participants' panel developed in D8.3 included a proposal for a nested panel structure, in which multiple panels function locally and independently. Figure 1 shows how this model works in practice. Individual members or small teams of members of local panels then form a single study wide panel. This central panel meets once a year, alongside the General Assembly of the project. Local meetings are chaired by participants rather than staff. The central panel meeting is chaired by the EPAD Ethics group and is closed to other members of the consortium unless specifically invited by the panel members. In D8.3, we proposed a three tier structure, in which a representative from the central panel would attend regular EPAD leadership meetings. However, following discussion of this proposal with panel members, it was felt that two levels of operation were more effective, with frequent meetings with local study teams complemented by the annual meeting of the central group.

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<sup>5</sup>This section draws on input from the centres running participant panels, reported by Gregory S, Bunnick EM, Callado AB, Carrie I, Boer CD, Duffus J, Fauria K, Forster S, Gove D, Knezevic I, Pennetier D, Saunders S, Sparks S, Rice J, Ritchie CW, Milne R (2020). "Involving Research Participants in a Pan-European Research Initiative: The EPAD Participant Panel Experience," pre-print at <https://doi.org/10.21203/rs.3.rs-23355/v1>.



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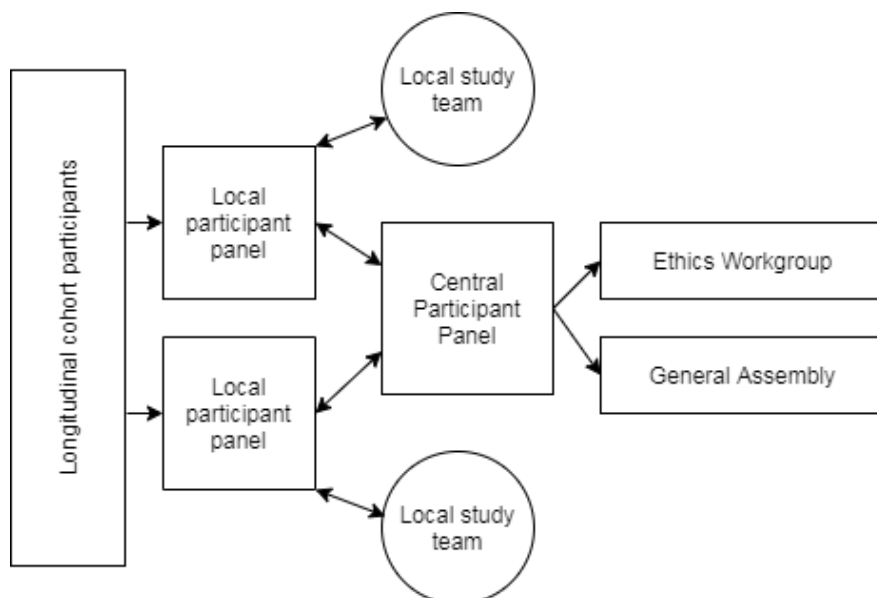


Figure 5.1: Overview of local and central participant panel set-up within the EPAD LCS study structure

### 5.1.1 Central panel

The central panel meeting has two main goals – to co-ordinate activities across the local panels, and to provide for direct participant input into the development of the study. Participation in the General Assembly has also provided the opportunity for participants to learn about the progress of the study and to provide feedback, through both plenary meetings and closed meetings chaired by the EPAD ethics workgroup. Two meetings of the central panel have taken place, in 2018 and 2019, with six and ten members respectively. In addition, one participant representative attended the 2017 project General Assembly.

### 5.1.2. Local panels

Each country was given a mandate to establish participant involvement on either a research centre or country level in the form of a panel. While the common language spoken at the central panel is English, requiring a certain level of ability to speak English, the local panels facilitate multi-lingual involvement with participants. A terms of reference document was created as a guide for research teams, but these terms were adapted to meet local requirements and based on discussions with local panel members.


#### Scotland

In Scotland a centralised country wide panel included members from all four recruiting centres (NHS Lothian, Grampian, Greater Glasgow & Clyde and Tayside). The choice to form one country wide panel was advocated for by the participant members and worked well in a small country.

#### England: Oxford, West London and Bristol

England similarly established a panel to represent participants from multiple centres. The panel ran from Oxford, England and involved participants from three centres (Oxford, West London and Bristol).



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The Netherlands: Amsterdam

The panel in the Netherlands is housed at the VuMC (Vrije Universiteit Medical Centre). There is only one centre in the Netherlands and therefore this panel operated both as the country and centre wide panel.

France: Toulouse

France currently has one panel in operation, based and run from the Toulouse centre. Due to the size of France and the distances between centres it was not feasible to have a country level representation, and centres are encouraged to set up their own panels.

Spain: Barcelona


Spain's panel was in Barcelona, the first EPAD centre to open in Spain.

### 5.1.3 Establishing the panels

The Scottish and Barcelona based panels were established in early 2017, and the newest panels, England and Toulouse, established in 2019. All panels met at least twice.

Panels employed a variety of recruitment methods, with equal levels of success, during the initial set-up period. Three panels (Scotland, England and Toulouse) contacted all local participants via letter or email to explain that a participant panel was being established and asking for interested participants to contact the coordinating centres to receive more information. In Amsterdam the panel was first introduced during an annual meeting for participants, to which all EPAD participants were invited, and the panel opportunity was followed up during the dissemination of minutes from this meeting. In order to maximise the engagement of the participants and the output of the panel, the team in Barcelona established a list of criteria for the selection of the potential panel members such as: proximity to the centre, sex, age, English language level, motivation. These were participants who had previously expressed interest in being more involved in the study and each participant was contacted by phone to assess interest in joining the panel. Most panels enrolled people on a first come first served basis, with the exception of Toulouse which enrolled based on longevity in the EPAD study. A waiting list operated at the Scottish, English, Toulouse and Barcelona panels due to levels of demand. New recruits were informed about the participant panel using flyers in Scotland and via email in Barcelona, while Amsterdam elected to maintain a static panel as the participants involved had the most experience of the EPAD study and were motivated to remain in the panel. Scotland was a unique example in this group as it was initially established as an Edinburgh based panel and expanded on the advice of the panel members to include participants from all Scottish centres.

The initial meetings of each panel involved similar agendas set by EPAD staff, with setting the scene and explaining the purpose of the panel, establishing rules of engagement around confidentiality and terms of reference for the panel, and nominating a participant as chair of the panel. At the Barcelona and Toulouse panels, a vice-chair was also selected to support with the leadership of the panel.

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#### 5.1.4 Logistics of running the panel

The panels were all set up to run twice a year, with ad-hoc contact in between for matters arising that are time sensitive. The Barcelona panel met up to 4 times a year on the request of the participant panel members. Numbers of panel members ranged from 7 in Amsterdam to 12 in the Scottish panel, with the group size aimed to be large enough to capture a diversity of experience and opinions, while remaining small enough to allow everyone time to meaningfully contribute to the meetings. EPAD study staff attended every panel meeting to organise the logistics of the meeting, provide study updates and answer specific questions from the panel, facilitate discussions if required and to minute the meetings. On the invitation of panel members, the Chief Investigator or Principal Investigator also attends in most centres. Panels meet at locations convenient for participants, travel expenses are provided alongside refreshments.

#### 5.1.5 Content of panel discussions


The content of panel discussions was led by structured agendas developed by the panel chair and members with the support of EPAD study staff. The Scotland panel has standing items discussed at every meeting which include dementia moments (recent news stories about brain health and dementia), an update on the study progress to date (both internationally and for Scotland) and the proof of concept trials. Other topics discussed in the panels include sustainability and longevity of the project, communicating about EPAD, feedback on study visits (including experiences, practicalities and logistical aspects), reviewing documentation and discussing personal views on receiving desirability of receiving feedback through the EPAD study on risk factors for dementia.

### 5.5 Results

The EPAD participant panels have contributed in four main areas; study advocacy, review of study documentation, streamlining of study visits and input into overall EPAD study planning.

#### 5.5.1 Study advocacy

Panel members attended a variety of events to speak about their involvement with EPAD and contribute to meetings based on their experiences both as participants and as panel members. These include the IMI Stakeholder Forum 2017 where a participant represented the EPAD study on a panel discussion on PPI, National Research Scotland (NRS) annual meeting in Perth 2018 where two panelists co-authored a poster about the panel, the EUPATI (European Patients Academy) 2018 meeting where two panelists spoke about their involvement in EPAD, and co-hosting a webinar to discuss the set up and running of a participant panel to support other centres considering hosting a panel. The Scottish and English panels contributed to the annual EPAD conferences held in these countries. The Barcelona panel was credited by centre staff with raising the profile of Alzheimer's disease research in the Catalonia region through their outreach activities.

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### 5.5.2 Review of study documentation

Review of study documentation was an important role played by the panels, helping to ensure any information provided to participants is understandable and appropriate for use. The participants provided valuable feedback for the on-going development and updating of the EPAD website. Suggestions from the panel have led to rewording of study documents, improving readability and adapting images used in videos. Staff developing documents have commented on the impressive feedback received from the panel, noting the benefit of receiving both positive and constructive criticism to improve the documentation. Multiple panels have also been asked to discuss protocol amendments and consulted for advice on implementation, particularly when changes had the potential to have a significant impact on study participants. By discussing with the panel and adapting to the panelists' feedback, the centre staff felt confident in the protocol amendment roll-out across the centre.

The Barcelona centre developed videos with the panel focusing on the mandatory lumbar puncture procedure in the study protocol. Participants are able to watch these videos prior to the procedure as a communication mechanism to support both with the learning about the procedure. An additional benefit reported by some participants was a reduction in pre-procedural nerves. Also, animated videos are supplied by the central EPAD team to introduce participants to both the project and provide information about the amyloid protein that is associated with Alzheimer's disease. Many centres had not worked with digital information in studies prior to EPAD and were hesitant to implement this in an older aged participant group. However based on positive feedback from panel members, staff felt able to confidently introduce this information to participants and were reassured of the importance of offering information in a multitude of formats.


In Amsterdam, the panel initially fed back that they often did not know whom they were seeing during their visit, as the complex procedures require a large number of staff to successfully deliver the study. Following this the team are introducing a 'study card' to better explain the logistics of the visit and the roles of the EPAD team members involved, with the panel members collaborating on the wording and presentation of this card. This simple communication tool ensures that participants have the knowledge they want and need about their study visit, improving their overall experience at the centre.

### 5.5.3 Streamlining of visits at trial centres

At each panel meeting participants are invited to provide feedback on any study activities they have recently completed with the aim of maintaining a high level of positive study experience for the participant group. Changes have ranged from small changes such as improved signage to clearly signpost participants to one of the Scottish centres, through to changes in communication methods.

## 5.6 Participant panel perspective

The Scottish and BBRC participant panels were asked by a fellow panel member to reflect on their experiences of the panel and provide feedback for use in evaluating the panel.

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Prior to joining the panel, members had few expectations of what joining might mean, and there was some doubt about how much *‘influence the participants would have on the day-to-day workings of EPAD’*. People did anticipate that the meetings would be forums to *‘provide (sic) feedback on our EPAD experiences’* and *‘the chance to get to know other participants and to share experiences with them’*. Participants thought the panel would offer an avenue for collaboration and to spread the word about both EPAD and Alzheimer’s disease. Panel members were often motivated to join the panel by their personal experiences of living with parents with dementia.


Considering the set-up of the meetings, panel members felt there was a *‘nice balance’* of a structured approach that remained *‘flexible as the agenda is set by the participants in conjunction with EPAD staff’*. Members appreciated the attendance of staff members who are *‘aware of the items on the agenda...and know the outcome of each discussion’*. They report the meetings as *‘inclusive’*, with a pleasant working atmosphere, and the Scottish group in particular note that *‘the fact that [the Principal Investigator] takes the time to come to meetings is hugely empowering’*. These experiences demonstrate the importance of providing resources to PPI groups to ensure efficient operation and maintaining an informal and flexible meeting style to encourage all participants to voice their experiences and opinions.

In some centres participants advocated for more regular meetings. This led to conflicts between the ambitions of the panel and desire for increased regularity of meetings, against the limits of resources the research team have to allocate. The Barcelona team were able to support an increase in regularity of meetings, while other centres currently maintain a six-monthly schedule.

Panel members reflected staff views that their input had helped to improve the participant experience by providing *‘a forum for participants to have their concerns voiced and attended to’* which has made the yearly visits to study centres *‘as comfortable as possible’*.

Importantly the panel members were key decisions makers in *‘the decision to have a Scottish panel rather than a participant panel for each Scottish trial delivery centre’*. By combining the collective experiences from these centres it is likely the panel has been able to have a bigger impact than that of four individual panels. The panel felt that they solidified the role of participants as stakeholders in EPAD, by *‘reinforcing (sic) their importance in the scheme of things’* and demonstrating the *‘humanity of EPAD’*. Panel members reported attending numerous events but by meeting other panel member groups from across Europe at the EPAD General Assembly, the groups *‘had found a voice’*. One panel has the slogan *‘we want to be part of the solution’* and this ethos is clearly reflected in many of the EPAD participant panels.

Areas for future development were identified by the panel and focused on the importance of communication and representation of all Scottish EPAD participants. Discussions dedicated time to considering various ways to ensure *‘everyone’s voices [are] heard by the research team’*.

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## 5.7 Discussion

The EPAD participant panel was beneficial to the set-up, running and future of the EPAD project, providing participants a role as stakeholders in the research. A key feature of the participant panels was their aim to be participant-centred and, where possible, participant-led. They aimed to create spaces for participant involvement and to establish the remit and scope of this involvement through ongoing dialogue between researchers and participants.

The panels were established using overarching terms of reference that mandated meetings that were participant-led and held at least twice a year. Each centre developed and adapted the set-up in line with the needs and ideas of the local panel members. However, the panels have many similarities, with meetings chaired by a participant member and EPAD staff in attendance to organise and minute meetings. Differences arise in how regularly panels meet and how panels communicate between face to face meetings.

### 5.7.1 Strengths


Benefits of PPI involvement in the EPAD study were reported by both panel members and researchers. Participant panel members felt they have a voice as part of the research team by being involved in PPI activities, and that being part of this is an empowering experience. Panel members reflected that they had been able to influence EPAD to make study visits as comfortable for fellow participants as possible, felt they had advocated successfully for the study in public facing forums, and had importantly introduced a reminder of the human aspect of EPAD.

Researchers attributed the panel with making changes to how centres run parts of the study visit, supporting centres with changes to documentation and providing confidence in using information tools, advocacy work on behalf of the study and contributing to strategic decisions at a project level.

### 5.7.2 Challenges

Challenges at the central panel level included the time commitment of participants and resourcing of travel for non-research staff to attend meetings that are held across Europe, the need to develop glossaries of the acronyms and jargon associated with a large research study, and the challenge of explicitly incorporating a participant role into pre-defined governance structures. The first benefited from the allocation of a specific budget for participant involvement at the outset of the project, and a glossary has been developed with input from participants. The question of formal governance involvement was discussed with the central participant panel and participants were invited to attend meetings of the study's governance committees. This invitation has been declined with participants stating that involvement in the General Assembly, alongside the EPAD research community, and directly with study leads through the local panels, provided a sufficient level of input into decision-making.

The participant-led nature of the panels also raises challenges. For example, both researchers and panel members found occasional conflicts between the ambitions of the panel and the realities of what the research staff can deliver. During meetings each panel encouraged open and transparent dialogue,

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listening to all feedback and discussing what can and cannot be acted on with reasons discussed for actions that cannot be delivered. As the panels were established over time conflicts tended to decrease, with the group learning how to best work together to achieve the best outcomes for the study.


Particular challenges related to the area of research and the scope of the study. The first was the recruitment of a group of participants across the diagnostic spectrum involved in the cohort study. The aim is to capture a variety of voices to represent the spectrum of experiences in the EPAD study. However, the panel members at all centres are for the most part representative of healthy volunteers rather than participants with mild cognitive impairment. One of the contributors to this imbalance is that the original participant recruitment to the study was biased towards healthy volunteers and as such when the panels were established the majority of participants invited to join were cognitively healthy. Staff involved in supporting the panels also reported concerns about burdening patient participants, participant confidence in attending an unfamiliar environment and logistics of attending for someone who may prefer to have a study partner with them. As such there is a group of participants in the EPAD LCS cohort who were not well represented in the panel memberships.

The final notable challenge was the pan-European context and the variety of languages spoken by participants. Although local panels operated in each country's native language, the central panel was conducted in English and thus did require participants to speak English. Non-UK panels have thus had to ensure that at least some participants have a level of English sufficient to enable the panel to be involved in central study discussions. However, the EPAD panel structure has allowed for local panels to be more inclusive and less likely to be biased to a sub-set of participants likely to have a higher level of education.

## 5.8 Lessons Learned

It is possible to set up and establish a successful network of participant panels across countries and languages to achieve meaningful involvement of participants as a stakeholders in the research process through a hybrid centralised-localised model as presented in figure 5.1. Ensuring some shared terms of reference across the local panels is important to manage the involvement process and feed into the central panel. Having flexibility within these terms of reference allows the panel to adapt to the local needs and wishes of panel members. Staff members attending the panels was deemed important in all centres, with staff taking responsibility for organising the logistics of the meetings as well as taking notes and taking action on change where relevant. Communication methods vary across the panels with the importance placed both on what is preferred by panel members and possible under local governance. Successes included the development of appropriate communication tools, representation at meetings and input into the planning of the EPAD project. Challenges include taking time to establish what is possible to change while hearing feedback from panel members and ensuring that researchers take active measures to ensure that people with cognitive impairment are able to access and engage with the panels.



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## 6. Return of results and risk disclosure

EPAD participants become eligible to take part in clinical trials conducted through the PoC platform in part because of their biomarker status. Contacting participants to invite them to the PoC platform involves communicating this biomarker status. Consequently, the question of risk communication was identified in the EPAD Description of Work and has been a central concern of WP8 throughout the project. It is discussed in deliverables 8.1, 8.3 and 8.4, which describe the need for a clear disclosure process, explored the potential impact of learning Alzheimer's dementia risk information, and set out a draft disclosure protocol, drawing on the prior clinical and research experience of EPAD centres, published and unpublished materials from prior clinical trials and consultation with potential EPAD participants and the European Working Group of People with Dementia (EWGPWD).

Since the completion of D8.4, the disclosure protocol has been finalised with the PoC team and prepared for piloting, and discussed with the study as a whole at the 2019 General Assembly. Further feedback was received from EFPIA partners. However, because no trial has been run through EPAD, further work will be needed to pilot and refine the protocol, and finalise educational materials for study clinicians.

In addition to involvement in the development and refining of the disclosure protocol, empirical work has continued to explore the communication of dementia risk information in the clinic. This study looks at the shorter and long-term impact of risk disclosure in memory clinics. The study recruited its first participant in June 2018 and with a temporary halt due to the COVID-19 pandemic, the last follow up visits are now expected to finish by April 2021. We recognised the study will over run the EPAD funding period but considered a longitudinal study design essential to gathering evidence for long-term impacts of receiving risk information about Alzheimer's disease. As such, the data completion and therefore results are not complete by the time of submission of the deliverable 8.5, but we report the background to the study, the study design and the current status of study visits and descriptive characteristics of the sample.


### *6.1 Mild Cognitive Impairment Disclosure study update<sup>6</sup>*

#### ***Adjustment to test, risk and diagnostic disclosures in people with mild cognitive impairment: an observational cohort study***

This project aims to explore the short and long-term impact of disclosing diagnostic test results currently available in clinical practice. The term Mild Cognitive Impairment (MCI) is used in both research and clinical practice despite overwhelming evidence regarding its limited value. There is considerable uncertainty over the prognosis of MCI as there is evidence that the cognitive impairment may well remain stable or improve over time. While the future may be informed by empirical evidence

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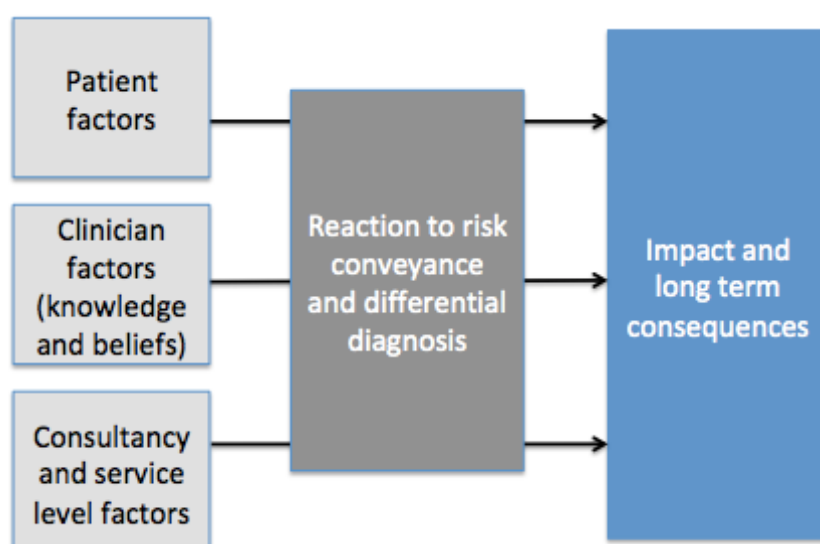
<sup>6</sup> This section written by Stina Saunders [stina.saunders@ed.ac.uk](mailto:stina.saunders@ed.ac.uk)

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from large, well phenotyped, longitudinal cohort studies, the clinical context of the *here and now* is the focus of this project, led by Stina Saunders at the University of Edinburgh. The current prognostic uncertainty of MCI leads us to question which methods should be employed to identify individuals at high risk of conversion to dementia which would allow us to ultimately intervene in the disease process.


As we have described in previous deliverables D8.1, D8.3, and D8.4 there is a lack of empirical data to help predict response to conveyance of test results. To date, no research has examined how patient factors (e.g. personality type, coping styles) and clinician factors (communication style, consultations process) predict cognitive and other clinical outcomes in the setting of a cognitive disorders service.

The study looks at the risk disclosure process as a potential moderator that impacts cognitive performance and subsequent adjustment to illness. There is a pervasive assumption that in dementia, early detection and diagnosis is beneficial by allowing planning, control and access to interventions. An understanding of the effect of different adjustment styles to risk disclosure should ideally contribute towards the discussion of the individual's risk of developing dementia in the future. Accordingly, we do not yet understand how to communicate the uncertain risk of dementia in MCI in a way that conveys this uncertain risk information without leading potentially to adjustment issues. The uncertainty with regards to the true accuracy of biomarkers and clinical assessments in people with MCI creates an intricate dynamic between attitudes of the patient to complex clinical tests, practitioner knowledge and beliefs and the underlying accuracy of the test itself (Figure 2).



**Figure 2.** The process of risk disclosure accounting for patient, clinician and consultancy factors, followed by the individual's interpretation of risk and subsequent impact on clinical outcomes



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### 6.1.1 MCI Disclosure Study objectives

1. To undertake an observational cohort study investigating the impact of test, risk and diagnostic disclosures during the course of the consultation process, focusing on changes in cognition, anxiety, psychological well-being and adjustment to illness.
2. To relate patient, clinician and service-level factors to subsequent cognitive and functional outcomes
3. To involve a subset of participants in a qualitative study to understand the experience of being referred to a memory assessment service and during the consultation process receiving information about test results
4. To explore clinician's views on the concept of MCI and conveying risk information around neurodegenerative disease

### 6.1.2 Methods

#### Design

This is an observational longitudinal mixed methods study. Individuals referred to a range of local memory assessment services in South East Scotland were recruited into the study. Baseline assessments (Visit 1) were undertaken after the patient had been referred to the study but before the consultation process at the memory assessment service. The study follow-up visits are currently on-going and undertaken after the consultation process is completed. During the first follow up visit (Visit 2), study participants are asked about their overall experience of being told about their memory problems – this is a screening question which has created a subset of 12 participants who are taking part in the qualitative part of the study.


Follow-up assessments (Visit 2; Visit 3; Visit 4) with are tethered to the date the disclosure process is completed and conducted over the next 18 months.

#### Outcome measures

#### Completed at every follow-up visit

##### Patient factor:

1. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998). RBANS is a battery of tests for neuropsychological testing with a predominant **memory** loading
2. State-Trait Anxiety Inventory (STAI) (Julian, 2011). STAI is a self-report instrument that delineates between state (current feeling) anxiety and trait (usual disposition) **anxiety**.
3. Psychological General Well-being index (PGWBI) (Dupuy, 1977) measures self-perceived **psychological well-being** or distress, focusing on affective or emotional states. It is a 22-item health related quality of life measure.
4. Perceived Deficits Questionnaire (PDQ)(Sullivan M, 1990). The PDQ is a self-report instrument for subjective reports on four major cognitive domains i.e. attention; retrospective memory; prospective memory; planning & organisation. The PDQ has 20 items.

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5. Psychosocial Adjustment to Illness Scale (PAIS) (Derogatis). PAIS is a semi-structured interview designed to assess the quality of a patient's **psychosocial adjustment** to a current medical illness. There are 46 items.
6. The COPE Inventory (Carver et al., 1989) is a multidimensional **coping inventory** to assess the different ways in which people respond to stress. Consists of five domains: problem-focused coping; emotion-focused coping; focus on and venting of emotions, behavioral disengagement, and mental disengagement.
7. Pittsburgh **sleep quality index** (PSQI) (Buysse et al., 1989). PSQI is a self-rated questionnaire, which assesses sleep quality and disturbances over a 1-month time interval.

*From June 2020 onwards after the temporary halt due to the global COVID-19 pandemic:*

8. *COVID Impact Assessment*

### Completed at baseline only

1. Sociodemographic variables
2. HEXACO Personality Inventory (Lee & Ashton, 2004), a measure to assess **personality**. The model describes six domains of personality focusing on five domains: neuroticism, agreeableness, conscientiousness, extraversion; openness and honesty-humility.

### Clinician factors:


- Clinician descriptive characteristics
- Knowledge and beliefs around MCI. Qualitative interview guide for assessing clinicians' views on MCI disclosure

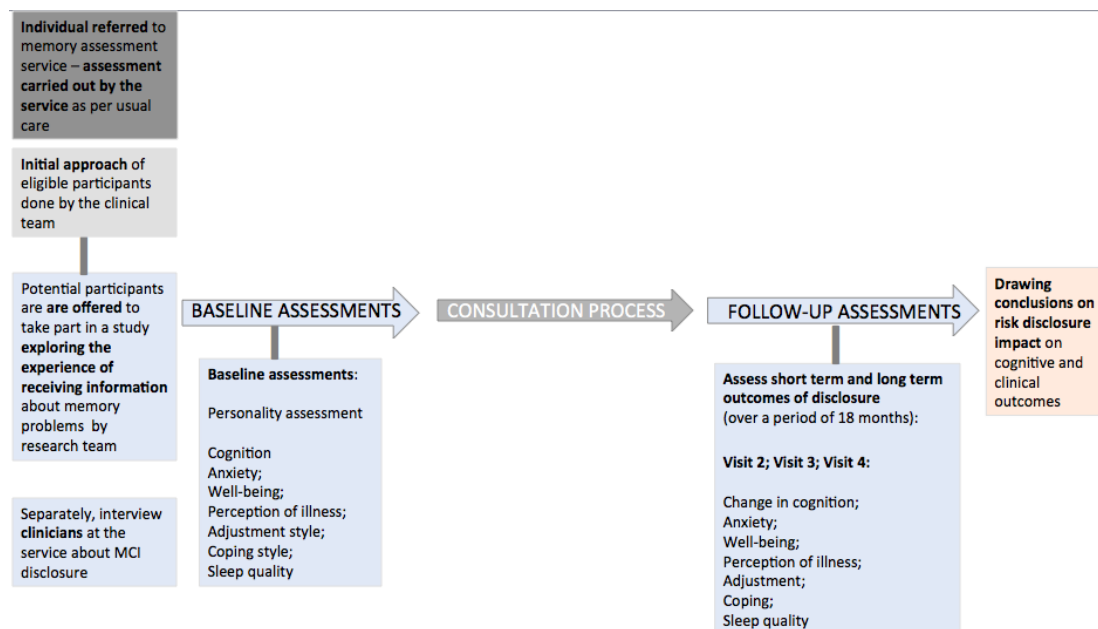
### Consultancy and service level factors:

- Record the number of consultations the participants has at the service during the consultation process
- Document the nature of the visit

**The quantitative** part of the study measures study participants' individual characteristics at baseline in order to determine predictors for better adjustment to risk disclosure and then review the impact at short and long term post disclosure. A full list of study assessments is provided in Annex IV.

In **the qualitative** part of the study, interviews are carried out with a subset of 12 participants to talk about their experience of receiving information about their memory problems. The qualitative part of the current study uses longitudinal interviews (Calman et al., 2013) to capture how the experience of risk disclosure is perceived over time. See *Figure 4* Measuring the impact of disclosure of MCI.

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**Figure 4** Measuring the impact of disclosure of mild cognitive impairment

#### Follow-up visit windows June 2018 – June 2020

Visit type	Time point	Visit window
<b>Baseline</b>	Before consultation	Any time after initial assessment at the service but before the consultation process
<b>CONSULTATION PROCESS</b>		
<b>Visit 2</b>	1–3 months after the consultation process	+/- 1 week
<b>Visit 3</b>	4 months after Visit 2	+/- 2 week
<b>Visit 4</b>	18 months after the consultation process	+/- 1 month

#### Follow-up visit windows June 2020 – April 2021 (amended due to the COVID-19 pandemic)

Visit type	Time point	Visit window
<b>Baseline</b>	Before consultation	Any time after initial assessment at the service but before the consultation process

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CONSULTATION PROCESS		
<b>Visit 2</b>	1–3 months after <b>the consultation process</b>	+/- 1 week
<b>Visit 3</b>	4 months after <b>Visit 2</b>	+/- 3 months
<b>Visit 4</b>	18 months after <b>the consultation process</b>	+/- 9 months

### 6.1.3 Recruitment

Participant recruitment started in June 2018 and the last participant was recruited July 2019. Follow-up assessments are currently on-going and will be finished by April 2021.

#### Inclusion criteria

- Referred to one of the memory assessment services enlisted as research sites in this study
- Suspected of having problems not consistent with dementia
- Over 60 years old
- Have the capacity to consent

#### Exclusion criteria

- Suspected of having dementia by the initial assessment at the service
- Not able to speak English
- Individuals who have not provided consent


### 6.1.4 Results

Participants were recruited across five memory clinics in South East Scotland. 180 individuals were referred to the MCI Disclosure study. Of the individuals referred, 63 were recruited to the MCI Disclosure study. 12 participants are taking part in a qualitative part of the study. All participants were asked to rate their experience of being informed of their memory problems at the first follow up visit and the first four individuals to rate their experience as *poor*, *average* or *good* proceeded in the qualitative study which meant they were asked to expand on their experience using a semi-structured interview.

All clinicians who disclose test results at the participating memory clinics are also interviewed.

Completed visits and still to do follow-up visits at the time of submission of deliverable 8.5

Completed	Still to do	Dropped out by this visit
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Baseline visit	63	0	0
Visit 2	49	7	7
Visit 3	25	30	8
Visit 4	3	51	9
<i>Total visits done</i>	140		
<i>Total visits still to do</i>	88		
<i>Total visits at start of study</i>	252		

*Break down of follow-up visits at the time of submission of deliverable 8.5*

#### **Quantitative data:**


Follow-up assessments (Visit 2; Visit 3; Visit 4) with the study participants are tethered to the date the disclosure process is completed and conducted over the next 18 months during which participant and clinician factors will be used to assess the impact of disclosure on the outcomes specified earlier. Descriptive statistics are produced to better understand the characteristics of the samples collected. Variables from the outcome measures will be employed in longitudinal data analysis methodologies (such as random effects models) to estimate rates of decline and risk factors will be considered to generate information about differences between individuals in adjustment to the MCI disclosure. If heterogeneity in the sample exists latent class-modelling approaches will be employed to identify participants with distinct trajectories of change.

Initially, the independent effect of disclosure type (poor; average; very good) will be evaluated in models adjusted for sociodemographic factors (age, sex and education). In a second step, depending on data, 2-way interaction terms will be added to the model to examine whether the impact of disclosure type on level and rate of cognitive change varies by personality type. A final model will be constructed to test whether these associations are modified by the rest of the variables collected.

This analysis is not completed by the time of submission of deliverable 8.5 but will be finalised once the follow-up visits are completed and disseminated in peer-reviewed journals and presented and scientific conferences.

#### **Qualitative data:**


The qualitative aspect of the study consists of interviews with participants and interviews with clinicians. The 12 patients in the qualitative part of the study are interviewed at every follow up assessment (Visit 2; Visit 3; Visit 4) creating a longitudinal set of qualitative data. The study uses longitudinal qualitative interviews (LQI) and so the topic guide is designed to change over time. LQI has been chosen as this method is useful for studying how people experience, interpret and respond to change (Murray et al., 2009). The current study aims to link the patients' experience of the disclosure to outcome measures. The analysis method for the interviews will be Interpretative Phenomenological

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Analysis (IPA) (Moustakas, 1994). IPA is a method that studies a specific pre-defined phenomenon, in this case the experience of being disclosed MCI, and the interpretation of this experience.

For the clinicians' interviews, these will be one-off interviews and thematic analysis will be used to elicit key themes and subthemes.

As well as the main part of the MCI Disclosure study, the analysis of the interviews is not completed as the visits are still on-going at the time of submission of deliverable 8.5. The analysis will be finalised once the follow-up visits are completed and disseminated in peer-reviewed journals and presented and scientific conferences.

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## 7. Recommendations for future ELSI work in IMI or other public-private partnerships

The EPAD project committed in study planning to establishing a workgroup on ethical, legal and social implications that would run throughout the duration of the study. WP8 was tasked with monitoring and addressing ELSI as they arose within the EPAD project on the one hand, and with conducting ethical research on relevant aspects of the EPAD project on the other hand.

In this section, we reflect on the effectiveness of the ELSI role in EPAD, the benefit to the study, and the value of the collaboration for the development of work on the ethical and social implications of contemporary developments in Alzheimer's disease research, clinical trials and biomedicine. In line with the larger programme of our work, however, we do not reflect on the legal situation – a limitation we return to below.

### The role of WP8


Local study teams were responsible for adherence to local and national regulatory requirements and for the obtaining of research ethics review committee approval. These regulatory aspects of the project were thus beyond the purview of the WP8 team.

The WP8 team was led by researchers from neurology, public health and industry and consisted of team members of various disciplinary backgrounds, including social scientists, ethicists, philosophers and experts working in patient advocacy, from various member countries. It has also included, at various times, two senior representatives from the pharmaceutical industry. One senior researcher had a fulltime appointment for the duration of the project and was fully dedicated to the work to be performed within WP8. In addition, an Ethics Advisory Board was established as a first task of the workpackage to contribute independent advice to the WP8 team on complex ethical issues arising within the project.

### 7.1 Reflections on the role of WP8

Firstly, we feel that the existence of a dedicated workpackage for ethical legal and social issues (ELSI) (WP8) has been beneficial, both for the conduct of the ELSI work and for the EPAD project as a whole. The existence of ELSI as a clear area of expertise and responsibility acknowledges the importance of ethical, legal and social considerations to a major project like EPAD. The multidisciplinary nature of the group has enabled EPAD to include different perspectives, bodies of evidence, values and priorities in planning and decision making. The independent status of the ELSI group within EPAD has enabled our work to contribute to the development of a positive agonistic dialectic through which the consortium's work on topics related to risk disclosure, recruitment from parent cohorts, and the informed consent process has developed.

The efforts of study leads and the project management team in providing dedicated plenary time and break-out sessions for the ELSI work has ensured that these considerations remained highly visible to

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the wider EPAD research community, and have allowed a continuity of ELSI discussions through the project, again, particularly around risk disclosure and informed consent. This was facilitated by the engagement of the project leadership with the ELSI workpackage, and the continuing contribution of the overall study leads, cohort and PoC teams, and other workpackages to WP8 meetings, particularly at the General Assembly.

Indeed, we feel that our work has benefited significantly from broad engagement within the consortium as a whole, from representatives across workpackages, and from both public and private sector partners. This has led to lively discussions on ELSI topics and avoided the ethics team operating in isolation of the rest of the project. Again, this has been facilitated by the inclusion of WP8 within study leadership groups including the Steering Committee (initially) and later the CDEx, as was as the Data Oversight body.

Further, the inclusion of a distinct domain of ELSI work enabled the development of original and independent empirical and conceptual research on ethical and social issues in the area of Alzheimer's disease research. This empirical work has been closely bound to the specifics of the main study and represents part of the overall contribution of the study to research in Alzheimer's disease, as well as providing an interface with parallel and relevant discussions in bioethics and the social sciences. However, ELSI work can contribute to identifying gaps and guiding best practice related to novel study designs and/or controversial research areas and, as the work on incidental findings presented above shows, capture and reflect on differences in practice/understandings across local sites, in order to make overall judgements about the effectiveness of ethical recommendations.


This work also contributes to a better understanding the context within which the EPAD project operates, and its potential value and consequences for wider society and clinical practice. The independent work conducted by the ELSI group has resulted in a series of scientific papers both specifically related to the Alzheimer's disease prevention context and platform trial design, papers for researchers in ethics and the social sciences and more generally oriented papers which can be relevant for research in neurodegenerative diseases in general. This corpus of work has contributed to the inclusion of EPAD work in international guidance and collaborations, including the US-based Advisory Group on Risk Evidence Education for Dementia (AGREED) group (Rosen et al. 2020, AAIC poster).

Finally, the work of the ELSI group throughout EPAD has been supported by the involvement of an independent international Ethics Advisory Board, initially with three members, and latterly with two. The accumulated expertise in medical ethics, philosophy, clinical trials and risk disclosure of our ethics advisory group (Marianne Boenink, Xavier Carne and Jason Karlawish) has been helpful at times of particular complexity or in resolving disagreement.

## 7.2 Challenges

Here, we would like to highlight three particular challenges associated with ELSI work in the context of projects such as EPAD.



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First, the unique value of the ELSI research agenda is necessarily tied to the overall project, and relies on it to be fulfilled. In addition to creating potential conflicts of interest, it also means that planned research activities may not be possible. For example, one planned piece of work planned by the ELSI group was to undertake a qualitative study of the impact of learning biomarker-based risk information. However, as no participants within the LCS received this information as part of trial, this work was not possible as originally planned (although as described above and in D8.3, work on disclosure has been undertaken).

Second, although the ELSI group have been effectively included in senior study governance bodies, there remain limited opportunities for an ELSI group or ethics advisors within IMI or similar projects, to make substantive interventions into research practice. While this has not been an issue faced in practice in the EPAD study, it is a topic for future consideration.


Finally, and as mentioned above, although the workpackage is nominally ‘ELSI’, the focus of the work set out in the study description and that carried out, has been primarily on the ‘Ethics’ and ‘Society’ aspects of this. In part, this reflects the existence of significant legal expertise throughout the project, particularly related to regulatory aspects of the study.

### 7.3 Recommendations

In a commentary on ‘responsible innovation’, Balmer and colleagues suggest five ‘rules of thumb’ for ELSI collaborations:<sup>20</sup> a commitment to working together which is practically rooted; a search for a mutually productive collaborative relationship for ELSI work, rather than that of an external critic; encouraging and engaging partners in reflections on collaborative relationships; transparency about which goals are not shared by all partners; and, critically, neighbourliness - a disposition towards collaboration and a style of engagement that emphasises the need to remain close and to work together in the face of open differences and contestation. These heuristics, and the values that underpin them, capture much of the work that we have undertaken in EPAD, and our experience of interacting with the project as a whole.

To build on, and capture our experience within EPAD, we tentatively suggest a series of recommendations for the future development of ELSI work within IMI-funded project.


1. A dedicated workpackage or task on ethics with independence to operate within the study should be created. It should also be recognized, however, that the mandate of this group relates to the wider social and ethical context of the project.
2. Relatedly, it is important that study leads and researchers recognize the distinction between obtaining regulatory approvals and developing a broadly ethical and socially responsible programme of work. To ensure this, the ELSI team should not have the final responsibility for drafting and submitting the paperwork to have studies approved by local ethical committees.
3. The ELSI team should be multidisciplinary, reflecting the range of perspectives within the study as a whole, as well as societal stakeholders.

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4. Consideration should also be given to questions of diversity and inclusion in the incorporation of public and patient perspectives within studies.
5. Strong support from the project leadership is critical for the success of the ELSI role, accompanied with visibility within the project and interaction at GAs.
6. ELSI researchers, as well as those from the wider consortium, should attempt to engage constructively and collaboratively in a 'neighbourly' way
7. To ensure the visibility and continuity of the ELSI perspective, there is value in funding a full-time research post for the duration of the study


## 8. Conclusions

The ELSI workpackage has been involved in the planning, development, and conduct of the EPAD study from its earliest stages. Throughout this time, our aim has been to identify and address practical ethical challenges associated with the study, including conducting empirical research to inform our practice. Our approach has been structured along the 'participant journey' through the EPAD study – a lens that has allowed us to engage with the complexities and challenges of a complex multinational collaboration between the public and private sectors. In this final report, our aim has been to collate much of the work across this journey that has taken place over the recent years of the EPAD study, and, in closing, to reflect on what has been learned through this process, and to share our recommendations for the future establishment of similar groups.


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## PUBLIC SUMMARY<sup>7</sup>

This report presents the final work of the EPAD ethical, legal and social implications workgroup. It presents recommendations that have been developed and refined during the course of the study, including the process of recruiting participants from the longitudinal cohort study to the clinical trial. In addition, the report presents the findings of research conducted by the workgroup into participants' experience of taking part in EPAD and how the EPAD participants' panel has worked across the different centres. Finally, it presents work examining how EPAD researchers have dealt with 'incidental findings' of research, and ongoing research into the communication of dementia risk information.

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<sup>7</sup> This summary will be published on the EPAD website in case the Executive Summary cannot be published. In case the Executive Summary can be made publically available, you can simply copy/paste for the Public Summary.

It will be accessible at: <http://ep-ad.org/publications/?mdocs-cat=mdocs-cat-1>

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## ANNEXES

### *Annex I: SPEAR study questionnaire survey*

#### **Study of Participant Experience of Alzheimer's disease Research (SPEAR)**

#### **RESEARCH PARTICIPANT QUESTIONS – TO BE COMPLETED BY PARTICIPANTS ONLY (NOT STUDY PARTNERS)**

##### **Background**

How many medical research studies have you ever joined (i.e. studies that involve more than an online survey, including EPAD)?

1 to 2                      3 to 5                      6 to 10                      more than 10

How many medical research studies are you currently taking part in?

1 to 2 / 3 to 5 / 6 to 10 / more than 10

How long ago was your last EPAD study visit?

within the last month / 2-4 months / 5-6 months / longer than 6 months

Below is a list of possible reasons for joining a research study. When you considered joining the EPAD study, how important were these reasons for you? (Very important / Somewhat Important / Not very important/ Not at all important)


To find out more about my condition
Be cause no other medical options were available
To gain future access to new treatment/therapy
To help others
Because of the Research/Health Centre's reputation
Because I am concerned about the topic of study
To learn about Alzheimer's and dementia research
Because of a positive experience in another study
Because of family influence/involvement
Other reasons

Did you ever consider leaving the study?

No / Yes briefly / Yes, a great deal / Yes, I am leaving the study

If you have considered leaving the study, have you felt pressure from the Research Team to stay?

Never / Sometimes / Usually / Always / Have not considered leaving the study

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Below is a list of possible reasons for leaving a research study. How important would these reasons be for you in considering leaving the study? (Very important / Somewhat Important / Not very important/ Not at all important)


Pain or discomfort related to participation
Worried about risks of treatment
Side effects that occurred during the study
Invasion of privacy
Too much time spent waiting around
Time commitment required
Travel time required
Family/work issues unrelated to the study
Interactions with research team
Not getting test results
Undue pressure to stay in study
Unexpected tests and procedures that occurred during the study
Transportation/parking
Other reasons

Below is a list of possible reasons for staying in a research study. How important were these reasons for you in staying in the research study? (Very important / Somewhat Important / Not very important/ Not at all important)

Because no other medical options were available
To gain future access to a new treatment/therapy
To help others
Because of the Research/Health Centre's reputation
Because I am concerned about the topic of study
To learn about Alzheimer's and dementia research
Because of a positive experience in another study
Because of family influence/involvement
Because of my relationship with the research team
Feeling valued as a research participant
Improved health or quality of life
Other reasons

Did the Informed consent form prepare you for what to expect during the study?

No      Yes, somewhat      Yes, mostly      Yes, completely

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Did the information and discussions you had before participating in the research study prepare you for your experience in the study?

No      Yes, somewhat      Yes, mostly      Yes, completely

Did the research team members listen carefully to you?

Never	Sometimes	Usually	Always
-------	-----------	---------	--------

Did the research team members treat you with courtesy and respect?

Never	Sometimes	Usually	Always
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During your discussion about the study, did you feel pressure from the research staff to join the study?

Never	Sometimes	Usually	Always
-------	-----------	---------	--------

Do you feel you were a valued partner in the research process?

Never	Sometimes	Usually	Always
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How much does the study demand of you? (Pick the answer that most closely describes your experience)

Simple (for example: a few visits or simple tests or surveys)

Moderate (for example: multiple visits or a short inpatient stay; only a few procedures, not risky or intense)

Intense (for example: long or multiple inpatient stays or many visits; procedure(s) that are intense, risky, or complex)

I had a good experience of taking part in the research study

Strongly disagree / Disagree / Neither agree nor disagree / Agree / Strongly agree


Would you recommend joining the research study to your family and friends?

Definitely no / Probably no / Probably yes / Definitely yes

Is there anything else you would like to share about your experience in the study?

[open]



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## The study experience

In the following questions, you'll be asked about your experience of specific tests and assessments which you have undergone in the EPAD. Which (if any) of these tests had you previously had before taking part in EPAD?

<input type="checkbox"/>	cognitive testing
<input type="checkbox"/>	lumbar puncture
<input type="checkbox"/>	blood test
<input type="checkbox"/>	MRI scan
<input type="checkbox"/>	None of the above

How *physically* uncomfortable was the EPAD **cognitive testing**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
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How *mentally* uncomfortable was the EPAD **cognitive testing**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
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Did you experience any pain or discomfort that you did not expect as a result of the EPAD **cognitive testing**?


No	Yes, a little	Yes, a moderate amount	Yes, a lot
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Would you be willing to have **cognitive testing** in the future?

Definitely yes	Probably yes	Probably not	Definitely not
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How *physically* uncomfortable was the EPAD **lumbar puncture**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
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How mentally uncomfortable was the EPAD **lumbar puncture**?


Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
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Did you experience any pain or discomfort that you did not expect as a result of the EPAD **lumbar puncture**?

No	Yes, a little	Yes, a moderate amount	Yes, a lot
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Would you be willing to have a **lumbar puncture** in the future?

Definitely yes	Probably yes	Probably not	Definitely not
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How physically uncomfortable was the EPAD **blood test**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
-----------------------	----------------------	---------------------------------------	------------------------	-------------------------

How mentally uncomfortable was the EPAD **blood test**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
-----------------------	----------------------	---------------------------------------	------------------------	-------------------------

Did you experience any pain or discomfort that you did not expect as a result of the EPAD **blood test**?

No	Yes, a little	Yes, a moderate amount	Yes, a lot
----	---------------	------------------------	------------

Would you be willing to have a **blood test** in the future?


Definitely yes	Probably yes	Probably not	Definitely not
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How physically uncomfortable was the EPAD **MRI scan**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
-----------------------	----------------------	---------------------------------------	------------------------	-------------------------

How mentally uncomfortable was the EPAD **MRI scan**?

Extremely comfortable	Somewhat comfortable	Neither comfortable nor uncomfortable	Somewhat uncomfortable	Extremely uncomfortable
-----------------------	----------------------	---------------------------------------	------------------------	-------------------------

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Did you experience any pain or discomfort that you did not expect as a result of the EPAD **MRI scan**?

No	Yes, a little	Yes, a moderate amount	Yes, a lot
----	---------------	------------------------	------------

Would you be willing to have an MRI scan in the future?

Definitely yes	Probably yes	Probably not	Definitely not
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### Clinical Trials

Have you previously been involved a clinical trial of a new medicine

Yes / No

Which of the following applies to you?

I would participate in a clinical trial of a new medicine at this time.

I would not participate in a clinical trial of a new medicine at this time but would consider doing so in the future.


I would never participate in a clinical trial of a new medicine

Below is a list of possible reasons for joining a clinical trial of a new medicine. How important would these reasons be for you?

Very important / Somewhat important / Not very important / Not important at all

Below is a list of possible reasons for joining a clinical trial of a new medicine. How important would these reasons be for you? (Very important / Somewhat important/ Not very important / Not at all important)

To gain access to new treatment/therapy
Improved health or quality of life
To help others
Because no other medical options are available
Because of the Research/Health Centre's reputation
Because I am concerned about the topic of study
To obtain education and learning
Because of a positive experience in another study
Because of family influence/involvement

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How likely would you be to participate in a clinical trial of a new medicine which required (Extremely likely/ Likely / Unlikely / Extremely unlikely):

Daily study visits
Weekly study visits
Monthly study visits

How likely would you be to participate in a clinical trial of a new medicine which lasted (Extremely likely/ Likely / Unlikely / Extremely unlikely):

12 months
2 years
4 years


How likely would you be to participate in a clinical trial of a new medicine which required you to travel (Extremely likely/ Likely / Unlikely / Extremely unlikely):

30min – 1 hour each way
1 hour –2 hours each way
More than 2 hours each way

How likely would you be to participate in a clinical trial of a new medicine which involved: (Extremely likely/ Likely / Unlikely / Extremely unlikely):

A life style change like diet or exercise?
A vitamin or dietary supplement?
An experimental medication in the form of a pill?
An experimental medication that was infused into the blood stream?

How likely would you be to participate in a clinical trial of a new medicine that required (Extremely likely/ Likely / Unlikely / Extremely unlikely):

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Magnetic resonance imaging (MRI) scans
Positron emission tomography (PET) scans (PET scans take pictures of the brain using radiation)?
Lumbar punctures?
Blood tests?
Cognitive testing?
Bringing a study partner to every visit?

I would be more likely to participate in a clinical trial of an experimental medication if I knew that I had a ... (Strongly disagree/ Disagree / Neither agree nor disagree/ Agree/Strongly agree)

50% chance of getting the actual medication and not placebo
75% chance of getting the actual medication and not placebo
Higher chance of getting the placebo and not actual medication

### About you

Age

50-60 / 60-70 / 70+

Gender

Male / Female

Marital status


Married / Widowed / Divorced / Separated / Never married

Employment status

Employed, working 1-39 hours per week / Employed, working 40 or more hours per week / Not employed, looking for work / Not employed, NOT looking for work / Retired / Disabled, not able to work

Education level

Degree or equivalent / A Level or equivalent / GCSEs or equivalent / Other qualifications / No qualification / Don't know

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### PART 3: STUDY PARTNER QUESTIONS – TO BE COMPLETED BY STUDY PARTNERS ONLY

What is your relationship with the research participant?

Spouse/Partner / Friend / Sibling / Child / Grandchild / Other

How long have you known the research participant

<5yrs / 6-10 yrs / 11-20 yrs / >21yrs

Below is a list of possible reasons for joining a research study. When you were asked to become a study partner, how important were these reasons for you? (Very important / Somewhat important / Not very important/ Not at all important)

Because my partner/friend/family member encouraged me
To find out more about my or my partners condition
To help my partner gain access to new treatment/therapy
To help others
Because of the Research/Health Centre's reputation
Because I am concerned about the topic of study
To learn about Alzheimer's and dementia research
Because of a positive experience in another study
Other reasons

Did the Informed consent form prepare you for what to expect during the study?

No / Yes, somewhat / Yes, mostly / Yes, completely

Did the information and discussions you had before participating in the research study prepare you for your experience in the study?


No / Yes, somewhat / Yes, mostly / Yes, completely

Did the research team members listen carefully to you?

Never	Sometimes	Usually	Always
-------	-----------	---------	--------

Did the research team members treat you with courtesy and respect?

Never	Sometimes	Usually	Always
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During your discussion about the study, did you feel pressure from the research staff to join the study?

Never	Sometimes	Usually	Always
-------	-----------	---------	--------

Do you feel you were a valued partner in the research process?

Never	Sometimes	Usually	Always
-------	-----------	---------	--------

How much did the study demand of you?


- Simple (for example: a few visits or simple tests or surveys)
- Moderate (for example: multiple visits or a short inpatient stay; only a few procedures, not risky or intense)
- Intense (for example: long or multiple inpatient stays or many visits; procedure(s) that are intense, risky, or complex)

I had a good experience of taking part in the research study.

Strongly agree / Somewhat agree / Neither agree nor disagree / Somewhat disagree / Strongly disagree

Is there anything else you would like to share about your experience in the study




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## *Annex II: Incidental findings questionnaire*

For the purpose of this questionnaire, incidental findings are defined as findings that are detected during the course of research, but are beyond the scope of the study, and that may be of potential health or reproductive importance to the research participant. Incidental findings include findings that are clinically relevant or actionable, and exclude findings that pertain to Alzheimer's disease. Incidental findings are reported to either the research participant or a primary care physician or treating physician, or considered to require referral.

### **Detection**

1. Have incidental findings been detected at the TDC during the conduct of the following tests or examinations? (please tell us for each test/examination conducted during study visits at the EPAD TDC: yes/no (or Y/N), how many, and what kinds).
2. Are all test results routinely checked for abnormalities? .....3
3. Are those involved in data collection or analysis instructed to look for or rather to avoid incidental findings (e.g. by limiting the number of tests/examinations, by choosing targeted testing modalities, by not-following-up of slightly abnormal test results)? .....


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Tests/examinations	Yes/no	Number	What kinds?
Vital signs			
Physical examination			
Blood sampling			
CSF sampling			
Saliva sampling			
Urine sampling			
Cognitive testing			
MRI			

## Management

4. Please explain what happens at the TDC when an incidental finding is detected (multiple answers possible):

- The finding is recorded in the Case Report Form (CRF)
- The findings is recorded locally at the TDC
- The Principal Investigator is alerted
- The finding is confirmed by a clinician of the study team
- The finding is confirmed by a clinician outside of the study team (e.g. in a nearby hospital)
- The finding is discussed with a multidisciplinary team within the TDC

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- The finding is reported to the research participant directly
- The finding is reported to the GP/treating physician of the research participant
- The research participant is referred for clinical follow-up
- Something else (also) happens, namely: .....

5. Has the TDC established a (multidisciplinary) team to discuss the management of incidental findings? If yes, which disciplines are represented? .....

6. Does the TDC have a pre-determined list of potential incidental findings that do or do not warrant reporting? If yes, has the TDC used existing lists? If yes, which ones? .....

7. Does the TDC have a pre-existing local protocol for the handling of incidental findings?....

If yes, is this protocol used for EPAD?.....

If yes, in what respects does it diverge from EPAD policy? .....

### Communication

8. Is an opt-out option offered to patients (i.e. can they participate in the LCS *without* consenting to the receiving of information about incidental findings?).....

If no, was the lack of an opt-out option ever a reason for a prospective research participant to decide *not* to take part in EPAD?.....

If yes, have participants made use of the opt-out option?..... If yes, for what reasons?....

9. By whom is the information about the incidental finding communicated (e.g. by LCS researcher (and what degree and/or position does this person hold), LCS PI, hospital-based clinician, through the general practitioner?) .....

10. How is the information about the incidental finding communicated? (e.g. by letter, phone, email, face-to-face meeting?)

### Follow-up

11. Have LCS participants been referred to primary care physicians or medical specialists because of incidental findings? If yes, for which types of findings?


.....

12. Has the TDC monitored the clinical or other consequences of feedback of (or referral because of) incidental findings for LCS-participants? If yes, what were these (positive and negative) consequences?

Thank you for completing this questionnaire.


Please return it to the ethics team at EPAD at e.bunnik@erasmusmc.nl.

Please attach your patient information sheet and informed consent form to the email.

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### *Annex III. Data collected within EPAD LCS (D4.13)*

File Name	Description of Contents
AE_GL_900	Adverse Events
AE_GL_900YN	Adverse Events Summary
BLOOD	Blood sampling
BLOOD1	Blood sampling (Amendment 28FEB2017)
CM_GL_900	Concomitant Therapy
CM_GL_900YN	Concomitant Therapy Summary
COENE	Cognitive and Clinical outcomes
COENE2	Cognitive and Clinical outcomes (Visit 2)
CSF	CSF sampling
CSF1	CSF Sampling (Amendment 28FEB2017)
DDPP	Dementia diagnosed by the participant's physician
DM_GL_900	Socio-demographics
DM_GL_901	Subject
DSALIVA	Drooling Saliva sampling
DSALIVA1	Drooling Saliva sampling (Amendment 28FEB2017)
DS_GL_900	Trial Disposition
ICF	EPAD LCS Informed Consent Form for Research Participants
IE_GL_900	Eligibility/Exclusion Criteria Not Met
LCS	HATICE Questionnaire
LIFE	Lifestyle factors (Other)
MHFAM	Family History of AD/Dementia
MH_GL_900	General Medical History
MRI1	MRI (Amendment 28FEB2017)
MRI_SCR	MRI
PE_GL_901	Physical Examination
POC	PoC trial participation
REICF	EPAD LCS Re-Informed Consent Form for Research Participants and Study Partner
RETEST	Biological sample retest
SALIVA	Cortisol Saliva sampling
SALIVA1	Cortisol Saliva sampling (Amendment 28FEB2017)
SNAC	SNAC Questionnaire
STUPART	Study partner change-Informed Consent
SV_GL_900	Date of Visit
SV_GL_901	Date of Visit (Screening / Baseline)
URINE	Urine sampling
URINE1	Urine sampling (Amendment 28FEB2017)
VS_GL_901	Vital Signs (Screening)
VS_GL_902	Vital Signs (Other Visits)
MEDAVANTE	Virgil tablet cognitive data set


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IXICO	MRI data set
ROCHE	CSF biomarker results data set
APOE	APOE results data set
iPAD	iPAD cognitive data set (4MT, SMT, Dot counting, Flanker, Favourites)

## Annex IV: MCI Disclosure Study study assessments

### Study assessments

Time point	Name of measure	Duration of assessment
Baseline	1. Sociodemographic data  2. RBANS 3. STAI 4. PGWBI 5. NEO Personality 6. PDQ 7. PAIS 8. COPE Inventory 9. PSQI	1. 10 min  2. 20 min 3. 10 min 4. 30 min 5. 20 min 6. 10 min 7. 10 min 8. 5 min 9. 5 min = 2h
Baseline	<i>Subset of participants</i> Interview	30min
Visit 2	1. RBANS 2. STAI 3. PGWBI 4. PDQ 5. PAIS 6. COPE Inventory 7. PSQI	1. 20 min 2. 10 min 3. 30 min 4. 10 min 5. 10 min 6. 5 min 7. 5 min = 1h 40min
Visit 2	<i>Subset of participants</i> Interview	30min
Visit 3	1. RBANS 2. STAI 3. PGWBI 4. PDQ 5. PAIS 6. COPE Inventory 7. PSQI	1. 20 min 2. 10 min 3. 30 min 4. 10 min 5. 10 min 6. 5 min 7. 5 min = 1h 40min
Visit 3	<i>Subset of participants</i> Interview	30min

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Visit 4	1. RBANS 2. STAI 3. PGWBI 4. PDQ 5. PAIS 6. COPE Inventory 7. PSQI	1. 20 min 2. 10 min 3. 30 min 4. 10 min 5. 10 min 6. 5 min 7. 5 min = 1h 40 min
Visit 4	<i>Subset of participants</i> Interview	30min
n/a	Interview with clinicians	30min