# DEVELOPING A METHODOLOGICAL FRAMEWORK FOR TRIALS IN PRESYMPTOMATIC NEURODEGENERATIVE DISEASE: THE PRESYMPTOMATIC NEURODEGENERATION INITIATIVE (PRENI)

Report of a JPND Working Group on Longitudinal Cohorts

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JPND research

EU Joint Programme – Neurodegenerative Disease Research

*This document is the final report from one of ten working groups commissioned by the EU Joint Programme – Neurodegenerative Disease Research (JPND) in 2014 through a peer-reviewed call for proposals. The working groups were established to address methodological challenges preventing current population- and disease-based cohorts being further exploited for ND research. All ten reports are listed below and are available to download on the JPND website by clicking on the website link at the bottom of this page:*

- **HD-READy (High-Dimensional Research in Alzheimer's Disease)**
  *Coordinator: Professor M. Afran Ikram, Erasmus University Medical Centre, Rotterdam, Netherlands.*

- **Harmonization and innovation of cognitive, behavioural and functional assessment in neurodegenerative dementias**
  *Coordinator: Dr Alberto Costa, IRCCS Fondazione Santa Lucia, Rome, Italy.*

- **NETCALS (Network of Cohort Assessment in ALS)**
  *Coordinator: Professor Leonard van den Berg, University Medical Centre Utrecht, Utrecht, Netherlands*

- **21st Century EURODEM**
  *Coordinator: Professor Carol Brayne, University of Cambridge, Cambridge, UK*

- **Multi-centre cohort-studies in Lewy-body dementia: Challenges in harmonizing different clinical and biomarker protocols**
  *Coordinator: Professor Dag Aarsland, Stavanger University Hospital, Stavanger, Norway*

- **Developing a methodological framework for trials in presymptomatic neurodegenerative disease – the Presymtomatic Neurodegeneration Initiative (PreNI)**
  *Coordinator: Dr Jonathan Rohrer, University College London, London, UK*

- **BioLoC-PD: Harmonization of biomarker assessment in longitudinal cohort studies in Parkinson's disease**
  *Coordinator: Professor Daniela Berg, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, Tübingen, Germany*

- **Dementia Outcome Measures: charting new territory**
  *Coordinator: Professor Gail Mountain, University of Sheffield, Sheffield, UK*

- **Body fluid biobanking of longitudinal cohorts in neurodegenerative diseases**
  *Coordinator: Dr Charlotte Teunissen, VU University Medical Centre, Amsterdam, Netherlands*

- **Realising the potential of cohort studies to determine the vascular contribution to neurodegeneration**
  *Coordinator: Professor Joanna Wardlaw, University of Edinburgh, Edinburgh, UK*

**JPND Website link: http://www.neurodegenerationresearch.eu/initiatives/jpnd-alignment-actions/longitudinal-cohorts/**

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## Summary

This working group brought together experts in the field of presymptomatic neurodegenerative disease studies from across Europe, including experts in Alzheimer's disease, frontotemporal dementia, Huntington's disease, Parkinson's disease, prion disease, motor neuron disease and the spinocerebellar ataxias.

The key objectives were to discuss two key issues shared across neurodegenerative disease in performing presymptomatic clinical trials:

- *The design of presymptomatic clinical trials*
    - what is the optimal design, in the absence of symptoms?
    - what should the inclusion criteria be, beyond genetic risk?
    - how should biomarkers be used in trials?
- *Ethical issues in presymptomatic clinical trials*
    - how do we deal with presymptomatic prevention trials that require long term therapies with potential risks?
    - how should participants and their families be best supported in these trials?

The group met across two workshops with the initial workshop predominantly disease-based with experts from each disease group bringing their own perspective on these two issues within their own area. The second workshop provided a cross-cutting perspective across diseases of these two key themes, with the final outcome an initial methodological framework for performing presymptomatic trials in neurodegenerative diseases.

The outcome of the working group was to make a number of suggestions in order to improve planning for future trials including the use of adaptive or run-in trial designs, early assessment of feasibility of trial design, validation and harmonization of biomarkers, and appropriate consideration of ethical issues at an early stage in conjunction with trial design.

## Introduction

The field of genetic neurodegenerative disease has recently entered a new phase, with multicentre presymptomatic cohort studies now taking place in the majority of disorders. The goals of such studies are: to characterise the natural history of the disease from its earliest stages, to identify biomarkers of disease onset and progression, and to build large enough cohorts in relatively rare disorders that can form the basis of clinical trials. Accurate and detailed phenotyping furthers our understanding of disease mechanisms and in disorders with both sporadic and genetic forms, can allow translation of knowledge gained in a rare genetic disorder to the more common sporadic form (e.g. in Alzheimer's disease).

Such studies are at different stages in different disorders, and there has been little overlap between the work occurring across the neurodegenerative diseases despite a number of shared aims. Furthermore, some cohorts are now at the stage of preparing for presymptomatic clinical trials of disease modifying therapy. These trials will evaluate disease modification during a phase in the disorder when standard clinical outcomes cannot be used and surrogate endpoints are likely to be necessary. Key issues of presymptomatic trials are:

- *The design of presymptomatic clinical trials*
    - what is the optimal design, in the absence of symptoms?
    - what should the inclusion criteria be, beyond genetic risk?
    - how should biomarkers be used in trials?
- *Ethical issues in presymptomatic clinical trials*
    - how do we deal with presymptomatic prevention trials that require long term therapies with potential risks?
    - how should participants and their families be best supported in these trials?

## Context

The factors described above are relatively specific to presymptomatic disease trials and the working group's aim was to identify solutions by bringing together experts across a number of different neurodegenerative diseases to provide a methodological framework for performing trials specifically within this group.

## Terminology

HD = Huntington's disease

AD = Alzheimer's disease

FTD = Frontotemporal dementia

PD = Parkinson's disease

MND = Motor neurone disease

SCA = Spinocerebellar ataxia

## Methods

Two workshops were held to discuss the key themes within presymptomatic neurodegenerative disease trials:

**Workshop 1: Discussion of individual disease perspectives and identification of cross-cutting themes*.*** The morning and early afternoon consisted of a series of talks about the current status in cohort studies and presymptomatic trials in different neurodegenerative diseases.

- How far has each disorder got? What has been learned so far?
- **AD** Martin Rossor
- **FTD** Jonathan Rohrer
- **HD** Sarah Tabrizi
- **MND** Kevin Talbot/Martin Turner
- **Prion disease** Simon Mead
- **PD** Thomas Gasser
- **SCAs** Thomas Klockgether.

The second half of the afternoon consisted of a discussion to identify the key cross-cutting themes.

**Workshop 2: Getting a consensus – have we found any solutions and where do we go from here?** The final workshop consisted of a series of interactive talks around the identified key themes:

- Design of presymptomatic trials: general principles
- Experience of presymptomatic trials in different diseases
- Developing a registry for neurodegenerative diseases
- Registries and recruitment to presymptomatic trials
- Controversial issues in presymptomatic trials
- Final discussion – what have we missed and what more information do we need?

Further discussion occurred via email in between and after the workshops including consensus decision of the final outcomes. We also performed an online survey to explore the anonymous views of the working group contributors on a number of controversial issues.

## AGREED GUIDELINES

### *A) Identification of key populations*

The following populations were identified by the group as the key populations important to consider in presymptomatic neurodegenerative diseases. The majority of these are familial cohorts with known (usually autosomal dominant) genetic mutations but the group recognized that in some disorders a presymptomatic period can be identified by carrying high-risk genetic risk factors and/or the presence of a particular biomarker.

**1) Alzheimer's disease (AD)**

a) Autosomal dominant AD

b) Down's syndrome associated AD

c) High risk for sporadic AD (genetic e.g. ApoE4 carriers)

d) High risk for sporadic AD (biomarker supported e.g. amyloid PET imaging positive)

**2) Frontotemporal dementia (FTD)**

a) Autosomal dominant FTD

**3) Motor neurone disease/amyotrophic lateral sclerosis (MND/ALS)**

a) Autosomal dominant MND/ALS

**4) Huntington's disease (HD)**

a) Autosomal dominant HD

**5) Prion disease**

a) Autosomal dominant prion disease

**6) Parkinson's disease**

a) Autosomal dominant PD

b) High risk for sporadic PD (biomarker supported e.g. presence of REM sleep behaviour disorder **or anosmia with DaTscan evidence of dopaminergic denervation)**

**7) Spinocerebellar ataxias**

**a)** Autosomal dominant SCA

***B) Identification of current status of presymptomatic studies in key populations***

The group identified whether there was a registry currently in place and whether there were either natural history and/or clinical trials currently occurring within the specific disorder.

**1) Alzheimer's disease (AD)**

a) Autosomal dominant AD

b) Down's syndrome associated AD

c) High risk for sporadic AD (genetic e.g. ApoE4 carriers)

d) High risk for sporadic AD (biomarker supported e.g. amyloid PET imaging positive)

Registry in place?

- As part of DIAN study (below)

Current natural history study?

- DIAN (autosomal dominant AD: http://www.dian-info.org)
- Alzheimer's Prevention Registry: http://www.endalznow.org/)

Current trials?

- DIAN-TU (autosomal dominant AD: http://dian-tu.wustl.edu/en/home/)
- API-ADAD (autosomal dominant AD)
- API-ApoE4 (homozygous E4 allele)
- TOMMORROW (ApoE and TOMM40 genotypes)
- A4 trial (positive amyloid PET scan)

**2) Frontotemporal dementia (FTD)**

a) Autosomal dominant FTD

Registry in place?

- No but planned as part of ARTFL study (below)

Current natural history study?

- GENFI (www.genfi.org.uk)
- ARTFL (https://www.rarediseasesnetwork.org/cms/ARTFL)
- LEFFTDS (https://www.nia.nih.gov/alzheimers/clinical-trials/longitudinal-evaluation-familial-frontotemporal-dementia-lefftds)

Current trials?

- FORUM HDAC inhibitor study (includes presymptomatic and symptomatic progranulin carriers: http://www.forumpharma.com/content/innovation-pipeline/hdac-program)

**3) Motor neurone disease/amyotrophic lateral sclerosis (MND/ALS)**

a) Autosomal dominant MND/ALS

Registry in place?

- Local European registries in place (UK registry in set up)

Current natural history study?

- Euro-MOTOR study (http://www.euromotorproject.eu)

Current trials?

- No

**4) Huntington's disease (HD)**

**a) Autosomal dominant HD**

Registry in place?

- Enroll-HD [combination of COHORT (Co-operative Huntington Observational Research Trial) and European HD Registry] (https://www.enroll-hd.org)

Current natural history study?

- PREDICT-HD (https://www.predict-hd.net)

Current trials?

- Legato-HD
- ISIS Pharmaceuticals/Roche HTT Gene Silencing
- Pfizer Phosphodiesterase 10A inhibitor

**5) Prion disease**

a) Autosomal dominant prion disease

Registry in place?

- UK MRC prion cohort (see below)
- Local European registries

Current natural history study?

- UK MRC prion cohort study (UCL)
- FFI study (INCB – Tagliavini)

Current trials?

- No

**6) Parkinson's disease**

a) Autosomal dominant PD

b) High risk for sporadic PD (biomarker supported e.g. presence of REM sleep behaviour disorder or anosmia with DaTscan evidence of dopaminergic denervation)

Registry in place?

- No

Current natural history study?

- Proband Study (www.proband.org.uk)
- TREND (http://www.trend-studie.de/: enriched population at-risk for PD)
- PRIPS (population based)
- RBD study group
- MiGAP (http://www.jung-und-parkinson.de/2015/04/09/migap-studie/)
- MJFF LRRK2-cohort study (https://www.michaeljfox.org/page.html?lrrk2-cohort-consortium)
- PREDICT-PD
- OPDC (RBD cohort ~60 subjects)

Current trials?

- No

**7) Spinocerebellar ataxias**

a) Autosomal dominant SCA

Registry in place?

- EuroSCA - European Spinocerebellar Ataxia Registry (http://www.ataxia-study-group.net/html/studies/eurosca)

Current natural history study?

- RISCA (http://www.ataxia-study-group.net/html/studies/risca/)

Current trials?

- No

***Controversial issues in presymptomatic trials***

There are a number of controversial issues in presymptomatic trials that remain unresolved. We asked the expert contributors to the working group using an online anonymous survey their view on these issues. The results with 25 contributors were as follows:

*1) Do you feel that a disease-modifying therapy is more likely to be effective in presymptomatic individuals, symptomatic individuals or equally in both?*

- In presymptomatic individuals 84%
- In symptomatic individuals 0%
- Equally in both 16%

*2) Do you feel that a disease-modifying therapy is more likely to be shown to be effective in a trial of presymptomatic individuals, a trial of symptomatic individuals or equally likely in both?*

- A trial of presymptomatic individuals 48%
- A trial of symptomatic individuals 32%
- Equally likely in both 20%

*3) If a treatment is shown to be effective presymptomatically does a further trial need to be done in symptomatic individuals?*

- Yes 72%
- No 28%

*4) Should a disease modifying therapy that is biologically active and has significant side effects be trialled in symptomatic individuals first before presymptomatic individuals?*

- Yes 80%
- No 20%

*5) Should we only include presymptomatic individuals who are aware of their genetic status in disease modifying trials (and exclude those who are not)?*

- Yes 40%
- No 60%

*6) Would you be willing to go to a Phase 3 trial in presymptomatic subjects based on imaging or biomarker changes only?*

- Yes 83.3%
- No 16.7%

*7) In order to be approved, a disease modifying therapy needs to show a functional outcome or delay in onset (rather than just a biomarker/imaging change)?*

- True 79.2%
- No 20.8%

*8) Would only imaging or biomarker changes be enough to permit use of a disease modifying therapy with the caveat of phase 4 monitoring?*

- True 52%
- No 48%

| ***Key guidelines*** |
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| A. The group recognized the need for further research into the natural history of the preclinical period of neurodegenerative disease, noting that this period may last from birth through to symptom onset. |
| B. The group supported the collaboration of expert research centres on multicentre observational natural history studies of the preclinical period of neurodegenerative disease. |
| C. Regarding the initial questions set out for the group the key suggestions of the working group were as follows: |
| *1) The design of presymptomatic clinical trials* |
| a) Optimal trial design |
| The group noted that using measures such as time to symptoms (e.g. time to 'dementia') or other symptomatic clinical or functional outcome measures would result in lengthy clinical trials. The group supported the need for shorter trials. |
| The group suggested that more work should be done to identify markers that represented different stages of the presymptomatic period, particularly so-called proximity markers i.e. markers that identify a period in proximity to onset of symptoms (the immediate preclinical stage). |
| The group supported the use of adaptive clinical trial designs in presymptomatic trials. These |

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| are likely to be more efficient and allow trialling of more drugs in a shorter period of time. It was noted that a number of aspects of the design may be adapted. The involvement of experienced trial statisticians is recommended. |
| The group also supported run-in clinical trial designs. With this in mind, the group recommends that natural history observational studies should aim to be run to GCP standard so that data from these studies can then be used in a run-in design. |
| The group recognized that more work needs to be done in assessing feasibility prior to trials e.g. whether enough participants can be identified in certain rare diseases, whether the intervention/design is acceptable to participants etc. |
| b) Inclusion criteria |
| The group noted the need to identify the appropriate participants for each trial. For diseases where there is clear autosomal dominant inheritance participants could be identified by the presence of a known pathogenetic genetic mutation but other groups may be identified by a particular risk marker (or combination of risk markers) e.g. amyloid PET imaging in Alzheimer's disease. |
| The group discussed the time in the disease process at which trials should ideally be performed. It was felt that the earlier the better when there is likely to be a minimum of irreversible neuronal loss (and possibly greater chance of success). However the group recognized that entering participants into trials who were distant from their likely symptom onset would depend on the risk-benefit ratio of the particular intervention. |
| The group could not reach consensus about whether trials should be performed in patients who are not aware of their genetic status i.e. to allow trials in which at-risk family members who have not undergone presymptomatic genetic testing can be participants (with the gene-negative family members automatically entering the placebo group). In the observational studies within the different genetic disorders that the group were part of around 15-20% of participants were aware of their status. It was felt that although an increased number of people are likely to undergo presymptomatic testing if aware of a clinical trial, this number will still be relatively low. Allowing entry of subjects without knowledge of their status is therefore likely to produce a significant increase in recruitment to presymptomatic trials. However the occurrence of side-effects in participants receiving an active compound risks inadvertent unblinding of genetic status and it is essential that this is made clear in the consent process of any trial involving such participants. |
| The group supported the development of disease registries to identify people with rare neurodegenerative disorders, and felt that observational studies should ensure consent to act also as a registry with the ability to recontact participants and families at a later date. |
| c) Use of biomarkers |
| The group supported the use of imaging and fluid biomarkers in early phase trials and to explore how they may be best used in later phase trials. |
| The group also noted and supported the efforts to validate and standardize imaging and fluid biomarkers e.g. standardization of CSF collection, harmonization of MR imaging protocols and of measurement of key markers such as hippocampal volume in AD. |

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| As noted above the group suggested that more work needs to be done in the development of proximity markers. These may be imaging or fluid biomarkers but may also include composite cognitive measures such as those designed for upcoming AD trials, or quantitative motor recording in movement disorders. |
| In some disorders, biomarkers can be used to enrich a presymptomatic group with those likely to develop the disorder e.g. RBD in PD or amyloid PET in sporadic AD. |
| The group noted that more work needs to be done in terms of developing biomarkers of target engagement prior to clinical trials. |
| *2) Ethical issues in presymptomatic clinical trials* |
| The group noted the need for ethical issues to be considered at an early stage of presymptomatic trial design. Ethical issues include the following:<br>• As mentioned above, there is a possibility of inadvertent unblinding of genetic status to participants in trials of an active compound e.g. because of specific side-effects. It is essential that the design of the consent process in such a trial incorporates this.<br>• Similarly in presymptomatic studies of sporadic disorders, work needs to be done to further understand the ethics of disclosure of investigation results that reveal disease status e.g. a positive amyloid PET scan in sporadic AD.<br>• Further work is also required on the provision of information to potential participants in presymptomatic trials when only those who are gene-positive will be entered; it will be important to ensure that appropriate information is provided to currently untested individuals who may consider genetic testing to allow themselves to enter the study. |
| Integration of support mechanisms such as rare disease support groups and genetic counselling should be considered within all natural history observational studies of presymptomatic disease as well as presymptomatic trials. |

## Contributors

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