EM 11

The development of an Alzheimer's disease clinical trial simulator, parameter estimation from international patient cohorts and standardizing epidemiological measurement platform for cohort studies.

Start date:1 January 2019 **Completion date: 30 June 2020**

Overall work package objectives:

Objectives

The development of a stochastic probability transition model for AD development describing the start and rate of development over time of the neurodegenerative process that results in the clinical diagnosis of AD. The model permits many stratifications for risk groups dependent on factors such as age, educational attainment and genetic background. The development of a dynamic model for AD describing the changes over time of blood-based AD associated biomarkers, brain scan measures and the development of cognitive decline towards AD.

1. Construction of mathematical models of the progression of patients from cognitively normal, via various stages of morbidity, to Alzheimer's disease (AD)
2. Identification of longitudinal cohort patient databases that include quantitative data on time series of AD biomarkers aiming at parameter estimations to be used in models
3. New analyses of AD-related epidemiological patterns recorded in the databases (as described in other WPs)
4. Construction of a clinical trial simulator to facilitate the design of phase II and III clinical trials of possible therapies that slow the progression of AD

EM11a- Construction of mathematical models of the progression of patients from cognitively normal, via various stages of morbidity, to Alzheimer's disease (AD)

Overall objectives: The development of a transition model for AD effectively describing the start and pace of development of the neurodegenerative process that results in the clinical diagnosis of AD. The development of a dynamic model for AD describing the changes over time of blood-based AD associated biomarkers and the development of cognitive decline towards AD.

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective 1:				
D1.1 Mathematical model framework for AD, allowing for studying variation of time to the first and next stages of incubation and progression to AD	M1.1.1 Testing/improving the model (ongoing); presenting the model and model outcomes for evaluation (ongoing); report in Q3/Q4 2019	M1.1.1 Complete	EM11b	CH (ADERG), Imperial
	M1.2.1 Adding dynamics of blood-based biomarker into the mathematical model; Testing/improving the model; report/paper in Q4 2019	M1.2.1 Dec 2019	EM11b	CH (ADERG), Imperial
Objective 2:				
D2.1 Model parameterization and estimation of parameters using data obtained through EM11b from existing cross-sectional and clinical cohort data	M2.1.1 Adapting models and rerunning models; reporting in Q4 2019	M2.1.1 Dec 2019	EM11b	CH (ADERG), Imperial
D2.2 Publication of (a) the model frameworks and (b) the outcomes of the model fit in peer-reviewed journals	M2.2.1 Papers	M2.2.1 Jun 2020	EM11b	CH (ADERG), Imperial

D2.3 Incorporating the mathematical models into the Trial Simulator (EM11d)	M2.3.1 Programming and (re-)running of the trial simulator for a variety of trial designs and outcomes	M2.3.1 Jun 2020	EM11b	CH (ADERG), Imperial
EM11b-Identification of longitudinal cohort patient databases that include quantitative data on time series of AD biomarkers aiming at parameter estimations to be used in models **Overall objective:** To obtain access to existing (published) databases and data sets of cross-sectional and clinical studies on AD. To obtain access to databases and data sets of existing longitudinal prospective population based studies that are part of the Harvard Cohort Consortium on AD.				
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 Access to data and addition of data to database of cross-sectional and clinical AD studies	M1.1.1 contracts/agreements with owners of data and databases (ongoing)	M1.1.1 Complete		KMM
Objective 2:				
D2.1 Analysis of distribution of age, gender, education, and risk factors within the study population with particular emphasis of how these factors are associated with cognitive ability/state. Visual analyses (scatterplots, histograms) and statistical tests (including chi-squared test, two-way ANOVA) will be performed	M2.1.1 Data preparation and analyses reports	M2.1.1 Dec 2019	EM11a	KMM
Objective 3:				
D3.1 Access to data and addition of data to database of longitudinal prospective population-based cohort studies such as Framing Heart Study and Rotterdam Study. Additional data will be generated in in the Rotterdam Study regarding	M3.1.1 Agreements with owners of data/databases of longitudinal studies	M3.1.1 Sep 2019		KMM (ADERG)
D3.2 Predictive value AD-related antigens in plasma Rotterdam cohort study: *Time series (extended) of quantitative measures of NfL, Aβ40, Aβ42 and (T/p-) tau in approx 1000 plasma* samples	M3.2.1 Agreement with the Rotterdam study re the use of longitudinally measured AD related proteins in plasma	M3.2.1 Complete		KMM (ADERG)
EM11c-New analyses of AD-related epidemiological patterns recorded in the databases (as described in other WPs) **Overall objective:** To analyse and describe AD-related epidemiological patterns using the longitudinal prospective cohort data including the AD related biomarker data.				
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 Analysis of cross-sectional and clinical data in preparation for model parameterization	M1.1.1 Data preparation and statistical analysis; reporting	M1.1.1 Jun 2019	EM11b	KMM (ADERG)
D1.2 Analyses of longitudinal data in preparation of model fit	M1.2.1 Data preparation and statistical analysis; reporting	M1.2.1 Dec 2019	EM11b	KMM (ADERG)

Objective 2:				
D2.1 Trial Simulation analysis	M2.1.1 Running and rerunning models and statistical analysis of model outcomes. reporting	M2.1.1 Jun 2020	EM11b	KMM (ADERG)
EM11d- Construction of a clinical trial simulator to facilitate the design of phase II and III clinical trials of possible therapies that slow the progression of AD **Overall objective:** To construct, using the mathematical model for AD- resulting from EM11a. a clinical trial simulator to facilitate design of clinical trials of possible therapies that slow the progression to AD				
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 Code of the AD trial simulator	M1.1.1 writing/rewriting code and testing; reporting and paper preparation	M1.1.1 Jun 2020	EM11a, b, c	SB (ADERG)
Objective 2:				
D2.1 Produce detailed instructions	M2.1.1 report	M2.1.1 Jun 2020	EM11 a, b, c	SB (ADERG)

Updates on delivery against milestones since last report

- M1.1.1 Testing/improving the model (ongoing); presenting the model and model outcomes for evaluation (ongoing); report in Q3/Q4 2019 (Jun 2019):

  The mathematical model presented in the previous report has now been finalised. The model describes the clinical progression of individuals towards Alzheimer's disease and it has been used for the description of the temporal dynamics of a large number of cognitive and biological markers during disease progression. The model outcomes are presented in a manuscript that has been submitted for publication.

- M3.1.1 Agreements with owners of data/databases of longitudinal studies (Sept 2019):

  A data transfer agreement is currently being negotiated between Imperial College London and J&J to access CHARIOT:PRO data. Final discussions to be had with study investigators at CTAD conference in December 2019. We anticipate this to complete by the end of Q4 2019. An initial payment has been made to UK Biobank and the process is underway to access relevant data within this resource. This process can take up to 4 months. Submitted an EOI to the AIBL study to gain access to data relating to amyloid PET scans, demographics, and longitudinal cognitive testing. If successful, the process can take up to 2 months (Dec 19).

- M3.2.1 Agreement with the Rotterdam study re the use of longitudinally measured AD related proteins in plasma (Sept 2019):

  Data from the Rotterdam study has been analysed and submitted as a paper which is currently under review "Plasma total-tau, neurofilament light chain and amyloid-β levels and risk of Alzheimer's disease: a population-based prospective cohort."

Summary of plan to deliver on outstanding work (with dates)

- To continue to work towards deliverables and milestones
- S Bajaj will attend the Conference on Cognitive Reserve in Dementia and Other Disorders (ResDem), (Oct 2019) and has submitted an abstract
- K McRae-McKee will attend the Conference on Clinical Trials in Alzheimer's Disease (CTAD), Dec 2019 and will identify key groups with relevant trial data to facilitate the progression of the clinical trial simulator
- To publish current papers in preparation:
  - K McRae-McKee, Improving the use of amyloid inclusion criteria in clinical trials of Alzheimer's disease: a composite score
  - S Bajaj et al; Longitudinal plasma NFL and neurodegeneration in ADNI

- The team are synthesising individual projects and working towards compiling a functional clinical trial simulator (Jun 2020)

Risks	**Mitigation**
1) The ADERG team may not get contracts for access to further datasets	1) Keep in regular contact with key stakeholders on progress of dataset applications to eliminate issues as they arise
2) Papers may not be accepted in target journals	2) Write high quality manuscripts with novel concepts and establish a journal hierarchy i.e. which journal to try if the first fails
3) Time taken to have a functional working clinical trial simulator with an established user interface	3) Identify a developer who can code the user interface and start discussions on how this can be incorporated to the final simulator

Team members <u>funded</u> (full or part-time) by DPUK

Roy Anderson, Frank de Wolf, Christoforos Hadjichrysanthou, Kevin McRae-McKee, Sumali Bajaj, ~~Emily McNaughton~~

Team members involved with the project but <u>not</u> funded by DPUK

David Thomas (Visiting researcher), Stephanie Evans (previous team member)

Outcomes

Papers accepted:

1. K. McRae-McKee, et al. **Perspective: Clinical relevance of the dichotomous classification of Alzheimer's disease biomarkers: Should there be a "gray zone"?** Alzheimer's and Dementia: The Journal of the Alzheimer's Association - Using data from the Alzheimer's Disease Neuroimaging Initiative with a focus on cortical amyloid binding, we discuss the limitations of applying the biological definition of disease status as a tool to define the increased likelihood of the onset of the Alzheimer's clinical syndrome and the effects that this may have on trial study design.
2. S. Evans, et al. **Alzheimer's disease progression and risk factors: A standardised comparison between six large datasets.** Alzheimer's and Dementia: Translational Research & Clinical Interventions - There exist a large number of cohort studies that have been used to identify genetic and biological risk factors for developing Alzheimer's disease (AD). However, there is a disagreement between studies as to how strongly these risk factors affect the rate of progression through diagnostic groups toward AD. We have calculated the probability of transitioning through diagnostic groups in six studies and considered how uncertainty around the strength of the effect of these risk factors affects estimates of the distribution of individuals in each diagnostic group in an AD clinical trial simulator.

Papers under review:

1. S. Evans, et al. **The effect of cognitive reserve on the rate of cognitive decline in the Cardiovascular Health Study.** Neurobiology and Ageing - This study developed a composite score of cognitive reserve, an important modifier of the relationship between AD pathology and clinical diagnosis of disease, and the score significantly predicted cognitive performance over time for older adults who were cognitively normal at baseline.
2. F. de Wolf, et al. **Plasma total-tau, neurofilament light chain and amyloid-β levels and risk of Alzheimer's disease: a population-based prospective cohort.** BRAIN - Higher levels of NfL and lower levels of Aβ42 plasma concentrations at baseline are each independently associated with a higher risk of developing clinical AD. These markers may be used to identify people at high risk of AD while the disease is still in its pre-clinical phase, and to guide clinical trial design for possible preventative treatments.
3. D. X. Thomas, et al. **Association of TDP-43 proteinopathy, cerebral amyloid angiopathy, and Lewy bodies with cognitive impairment in individuals with or without Alzheimer's disease neuropathology.** JAMA Neurology - Investigate the associations between trajectories of cognitive decline and neuropathological signature in a clinical population of individuals with or without Alzheimer's disease neuropathology and to estimate the prevalence of each combination of co-morbid neuropathologies in the same population.

4. C. Hadjichrysanthou, et al. **Revisiting the natural history of Alzheimer's disease: dynamics of biomarkers along the disease continuum**. PNAS. - This study presents a novel method to estimate continuous long-term changes of such markers throughout the AD continuum, and determine their rate of change and temporal order. The methodology is founded on the development of stochastic models to estimate the expected time to a clinical state for different risk groups and synchronise short-term individual data onto a disease progression timeline.
5. L. Chibnik, et al. **Time trends in the incidence of dementia over three decades in Europe and the USA: The Alzheimer Cohorts Consortium.** Neurology - The incidence rate of dementia in Europe and North America is very similar for men and women and has declined by 17% per decade over the past 25 years, consistent across available studies. This observation calls for even more strenuous efforts in finding the reasons for this decline.

Project narrative

Alzheimer's disease (AD) is a progressive disease, with no effective treatments or cure. Over 98% of clinical trials of AD drug candidates have failed or been discontinued and the failure rate of clinical trials for AD treatments is far higher than that of trials in other therapy areas. The high variability in the measurement of cognition and diagnostic markers may be one of the most important reasons for the high failure rate. Mathematical, computational and statistical tools can be employed to investigate why AD clinical trials fail, to improve the design of trials of potential treatments and to enhance the chances of success. Employing these tools, the overall aim of this project is to develop a clinical trial simulator (CTS) of potential prophylactic and therapeutic treatments of AD.

The CTS will be founded on a stochastic mathematical model that has been developed to describe the movement of individuals through distinct health and disease states (e.g. Cognitively Normal (CN), Mild Cognitively Impaired (MCI) and AD) and predict the development and progression of AD. Probabilities of transitioning from one state to another are estimated employing a wide variety of longitudinal observational studies in Europe and North America that the team has access to. The dataset, comprising of multiple, consistent follow ups, will allow identification and quantification of variability within and between patients in measurement for markers of disease progression. Understanding the source of variance within currently employed measures will ultimately improve trial design, facilitate detecting a signal in the trial, shorten the trial times for detecting an effect and reduce the number of patients enrolled. The development of a CTS therefore, will help to improve the design of clinical trials by providing insight to the most relevant trial endpoints and the optimal time point to administer treatment. This could help to deliver a novel therapeutic option to a therapy area of high unmet need.