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

Work Package EM11

Objective(s):

The development of a stochastic probability transition model for Alzheimer's disease (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
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.

Overview Summary:

Alzheimer's disease (AD) is a progressive neurodegenerative disease. The projections of AD and findings are disappointing; the age specific AD incidence and prevalence increase almost exponentially with increasing age, and all clinical trials of disease-modifying therapies for AD have failed to date. Mathematical, statistical and computational tools can be employed to improve understanding of the progression of Alzheimer's disease and to assist in the improvement of trial design in order to enhance the chances of success of potential new therapies.

Executive Summary:

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 is 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, 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 CTS has incorporated continuous and composite outcomes which are used as primary endpoints in clinical trials. 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.

Summary of Outputs: (as per Researchfish categories)

Publications:

Published

- Lawrence E, et al. **A Systematic Review of Longitudinal Studies Which Measure Alzheimer's Disease Biomarkers.** J Alzheimers Dis. 2017;59(4):1359-1379. doi: 10.3233/JAD-170261.

We reviewed the literature for studies that measured cerebrospinal fluid or plasma amyloid-β and tau, or took magnetic resonance image or fluorodeoxyglucose/Pittsburgh compound B-positron electron tomography scans, in longitudinal cohort studies. We summarised the properties of the major cohort studies in various countries, commonly used diagnosis methods and study designs.

- Ower AK, et al. **Temporal association patterns and dynamics of amyloid-β and tau in Alzheimer's disease.** Eur J Epidemiol. 2018 Jul;33(7):657-666. doi: 10.1007/s10654-017-0326-z.

We performed a correlation analysis of biomarkers CSF $A\beta_{1-42}$ and t-tau, and longitudinal quantile analysis. We also developed the trajectories of these biomarkers to describe the rate of change across disease development.

- Hadjichrysanthou C, et al. **The development of a stochastic mathematical model of Alzheimer's disease to help improve the design of clinical trials of potential treatments.** PLoS One. 2018 Jan 29;13(1):e0190615. doi: 10.1371/journal.pone.0190615.

We developed a Markov model to describe the clinical progression of individuals towards AD dementia and facilitate the development of computational tools to assess the effect of hypothetical treatments on the risk of developing the disease.

- Chibnik LB, et al. **Trends in the incidence of dementia: design and methods in the Alzheimer Cohorts Consortium.** Eur J Epidemiol. 2017 Oct;32(10):931-938. doi: 10.1007/s10654-017-0320-5. Epub 2017 Oct 23.

We aggregated data from nine international population-based cohorts to determine changes in the incidence of dementia since 1990.

- Evans S, et al. **The importance of endpoint selection: How effective does a drug need to be for success in a clinical trial of a possible Alzheimer's disease treatment?** Eur J Epidemiol. 2018. doi:10.1007/s10654-018-0381-0.

We have calculated the minimum detectable effect size in change from baseline of a range of measures over time, and in different diagnostic groups along the AD development trajectory.

- Anderson RM, et al. **Why do so many clinical trials of therapies for Alzheimer's disease fail?** The Lancet. 2017;390:2327–9. doi: 10.1016/S0140-6736(17)32399-1.

We developed computational tools to assess the effect of potential treatments against AD and explored the reasons behind the failure of AD clinical trials.

- Hadjichrysanthou C, et al. **Potential Factors Associated with Cognitive Improvement of Individuals Diagnosed with Mild Cognitive Impairment or Dementia in Longitudinal Studies.** J Alzheimers Dis. 2018;66(2):587-600. doi: 10.3233/JAD-180101.

We developed mathematical and statistical models to explore the factors that are associated with the improvement of individuals' clinical condition as observed in many longitudinal cohort studies.

- Anderson RM, et al. **Unsuccessful trials of therapies for Alzheimer's disease - Authors' reply.** Lancet. 2019 Jan 5;393(10166):29-30. doi: 10.1016/S0140-6736(18)31897-X.

Why developed computational tools to assess the effect of potential treatments against AD and explored the reasons behind the failure of clinical trials.

- McRae-McKee K, et al. **Combining hippocampal volume metrics to better understand Alzheimer's disease progression in at-risk individuals.** Sci Rep. 2019;9(1):7499. doi: 10.1038/s41598-019-42632-w.

We developed statistical models to explore predictive markers for identifying individuals likely to progress to AD. We focused on hippocampal volume (HV) and assessed the added benefit of combining HV and rate of hippocampal atrophy over time in relation to disease progression.

- Evans S, et al. **Alzheimer's disease progression and risk factors: A standardized comparison between six large data sets.** Alzheimers Dement (N Y). 2019;5:515-23. doi: 10.1016/j.trci.2019.04.005

We have calculated the probability of transitioning through diagnostic groups in six studies and considered how uncertainty around the strength of the effect of genetic and biological risk factors

affects estimates of the distribution of individuals in each diagnostic group in an AD clinical trial simulator.

- McRae-McKee K, et al. **Perspective: Clinical relevance of the dichotomous classification of Alzheimer's disease biomarkers: Should there be a "gray zone"?** Alzheimers Dement. 2019;15(10):1348-56. doi: 10.1016/j.jalz.2019.07.010.

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. We also suggest potential research objectives going forward.

- de Wolf F, et al. **Plasma total-tau, neurofilament light chain and amyloid-β levels and risk of Alzheimer's disease: a population-based prospective cohort.** BRAIN. DOI: 10.1093/brain/awaa054.

We reported the results of a longitudinal study of plasma biomarkers using the Rotterdam cohort. Plasma levels of Neurofilament light chain and amyloid-β42 are each independently and in combination strongly associated with risk of all cause and Alzheimer's dementia and may be useful in monitoring the progression of Alzheimer's dementia.

- Hadjichrysanthou, et al. (2020). **The dynamics of biomarkers across the clinical spectrum of Alzheimer's disease.** Alzheimer's Res. Ther. 12(1):74. DOI:10.1186/s13195-020-00636-z.

We developed stochastic models to characterise continuous changes of biological and cognitive markers and determine their rate of change and temporal order throughout the AD continuum.

- Wolters, FJ, et al. (2020). **Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium.** Neurology 95 (5) e519-e531. DOI: 10.1212/WNL.0000000000010022.

We developed statistical models to determine changes in the incidence of dementia between 1988 and 2015. This analysis was performed in aggregated data from individuals >65 years in seven population-based cohort studies in the United States and Europe.

- Thomas, DX, et al. (2020) **Association of TDP-43 proteinopathy, cerebral amyloid angiopathy, and Lewy bodies with cognitive impairment in individuals with or without Alzheimer's disease neuropathology.** Sci. Rep. 10, 14579. DOI: 10.1038/s41598-020-71305-2.

We developed cognitive trajectories for patients with common co-pathologies in the presence and absence of AD neuropathology. Cognitive trajectories were modelled in a Bayesian hierarchical regression framework to estimate the effects of each neuropathology on cognitive decline.

Under Review

- Sumali Bajaj et al; (2021). **Plasma Neurofilament Light is associated with markers of Alzheimer's disease, but does not reflect its clinical progression.**

We investigated the effects of baseline and "baseline rate of change" NfL plasma levels on rate of decline in cognition for individuals classified as amyloid positive at baseline (on the Alzheimer's disease continuum). We also studied the associations and correlations between the rate of change in NfL plasma over time and rate of change of other known markers of AD progression (cognition, brain structure, CSF and plasma markers) for amyloid positive individuals.

Collaborations & Partnerships
None
Further Funding
None
Next Destinations
None
Engagement Activities
None
Influence of policy, practice, patients & the public
None
Research Tools & Methods
None
Research Databases & Models
None
Intellectual property & licencing
None
Medical products, interventions & clinical trials
None

Artistic & creative products
None
Software & technical products
None
Spin outs
None
Awards & recognition
None
Other outputs & knowledge/future steps
None
Use of facilities & resources
None
Other:
None
Most successful outcome and what it means for future dementia research:
The most successful outcome of this project is the development of robust mathematical and statistical models that enable the prediction of the long-term temporal dynamics of a range of cognitive and biological markers associated with Alzheimer's disease utilising short-term longitudinal data. The models have been employed for the development of a clinical trial simulation for the assessment of candidate prophylactic and therapeutic treatments. Such mathematical and simulation techniques can play a pivotal role in the understanding of the pathogenesis and progression of the disease and the identification of disease biomarkers. These are also powerful tools that can facilitate the improvement of clinical trial designs and accelerate the development of treatments for Alzheimer's disease.
Lessons learned:
All the mathematical, statistical and computational tools have been developed as planned.
Date of Report:
23/02/2021