D4.6 Report on results from analysis of pharmacological interventions

116020 - ROADMAP

Real world Outcomes across the AD spectrum for better care: Multi-modal data Access Platform

WP4 – Disease modelling and simulation

Lead contributor	Christoph Jindra (01 – UOXF)
	christoph.jindra@psych.ox.ac.uk
	Nemanja Vaci (01 – UOXF)

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Document History

Version	Date	Description
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Definitions

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  - **UM**. Universiteit Maastricht (Netherlands)
  - **SYNAPSE**. Synapse Research Management Partners (Spain)
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  - **AE**. Alzheimer Europe (Luxembourg)
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  - **GE**. GE Healthcare Ltd (United Kingdom)
  - **AC Immune**. AC Immune SA (Switzerland)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ROADMAP project (116020).
- **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 ROADMAP Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement.** Agreement concluded amongst ROADMAP 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.
- **MTA.** Material Transfer Agreement

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Publishable Summary

The possibility of using published clinical trial data from CAMD for a comparison of the development of MMSE scores in patients with AD in cohort studies was investigated. A research design for such a comparison was developed. CAMD trial data were accessed and cleaned for the analysis and Whitehall II was identified as a cohort study containing the relevant information for a comparison. Due to delays in the access to relevant Whitehall II data, the final analysis could not be conducted.

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1. Introduction

The aim of the deliverable was to evaluate the impact of dementia-related interventions and to identify gaps and variations across datasets. The possibility to use, for example, the introduction of cholinesterase inhibitors and the use of anti-inflammatories as natural experiments to study how interventions can affect disease trajectories was investigated. Due to stringent data requirements for such a design, the research question was adapted to a comparison of the development of MMSE scores in patients with AD in clinical trials compared to cohort studies. This report provides a development overview of the research question, refinements based on data availability as well as results in the follow up to the writing of the report.

2. Background

Whilst there is no cure for AD, two types of drugs have been licensed for the treatment of its symptoms. The first line of treatment are often the acetylcholinesterase inhibitors (AcEIs) donepezil, rivastigmine, and galantamine. A further option is the NMDA receptor antagonist memantine. Donepezil, rivastigmine and galantamine all work via their effect on the levels of the neurotransmitter acetylcholine in the brain, of which reduced levels are found in people with AD. AcEIs increase the concentration of acetylcholine in the brain by preventing the enzyme acetylcholinesterase from breaking it down. According to the cholinergic hypothesis, this should improve communication between the cells and consequently, stabilise or slow down cognitive decline.

There is increased evidence of beneficial, though modest, effects from clinical trials for all three AcEIs and different outcomes and measures (Birks, Chong, and Grimley Evans 2015; Campbell et al. 2008; Hansen et al. 2008; D. Jiang et al. 2015; Lockhart, Orme, and Mitchell 2011; C.-C. Tan et al. 2014). However, due to small effect sizes, the clinical relevance of the drugs is still controversial (C.-C. Tan et al. 2014). Additionally, while clinical trials are good at establishing efficacy and have high internal validity, they usually have low external validity and perform less well as indicators of the performance of drugs under real world conditions (Parkinson 2014).

The deliverable investigated the possibility of enriching the evidence on AcEIs by looking at their effectiveness in different settings. The aim was to utilise a variety of real world data (RWD) and different outcome measures to produce evidence on how effective the drugs are outside of the setting of clinical trials. A second goal was to compare disease trajectories, found in the RWD, to those of more homogenous populations from the placebo arms of randomised control trials.

The main questions were thus:

1. How can evidence from clinical trials be enriched with RWE?
2. How effective are the drugs outside of clinical trials?
3. How does information from clinical trials compare to the information from cohorts?

3. Development of the research questions

Given the emphasis of the original research proposal, we explored ways to exploit a natural experiment. One option that was originally further scrutinised shares some similarities with a

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regression discontinuity design. Figure 1- A natural experiment approach shows how such an approach could look like

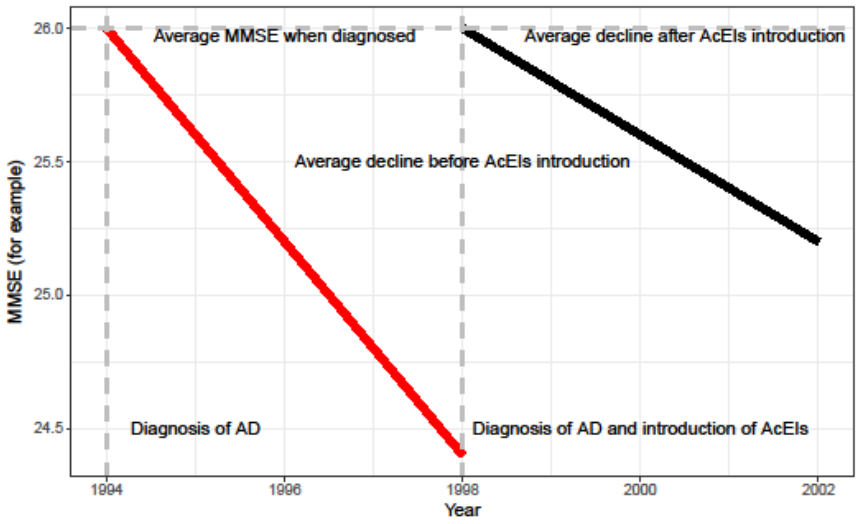

Figure 1- A natural experiment approach

If data were available on the exact date of the introduction of AcEIs, one could look at the average decline in people who were diagnosed just before the introduction, thus not receiving the drugs, and compare it to people diagnosed just after their introduction. Under several strict assumptions, like exchangeability of groups around the cutoff, differences in the slopes could provide information on the effectiveness in real world circumstances. However, the design would require data that are available just around the date of the introduction of the first AcEIs and several, frequent measures of a specific outcome in relatively small intervals to increase the plausibility of the results. Due to the data requirements implied even by such a simple design as well as the stringent assumptions necessary to interpret the results, the research question was developed in a different direction.

Subsequently the main objectives of the study were defined as a descriptive analysis of the prescription of the drugs across types of data and a comparison using standard demographic and other variables. A second objective was defined as describing, and modeling trajectories of outcome measures in people with AD in clinical trial placebo data and RWE looking at within and between variation. The last objective was defined as a comparison and assessment of the consistency of the findings across data. A natural way of finding a common time-scale for this type of question would be date of DX or date of the first prescription of the drug. However, after investigating the CAMD clinical trial data as well as information available in Whitehall II, the research questions had to be further adjusted. The main reason being that date of DX was not consistently available in the clinical trial data and, while the individual drug history is available in the clinical trial data, information within the cohorts seems not sufficient enough to use this as a time anchor.

This led to the decision to use age as the common time scale and the final objectives were defined as follows:

1. Describe the prevalence of the prescription of AcEIs in the samples and compare the characteristics of the group of people who are being treated with the drugs to the group who do

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not take any of the anti-dementia drugs using standard demographic and other relevant variables.

2. Comparison of shape and location of the cognition-age distribution
    a. Using age as the common anchor in time, the age-cognition distribution will be described separately for clinical trials and cohort data by looking at location and shape parameters.
    b. In a second step, differences in shape and location will be analysed.

4. Methods

4.1. Study design and population

The design of the study is observational. While data from clinical trials were included, only information from the control groups is available. Additionally, people in the RCTs were randomly assigned to treatment and control for an unknown intervention. The clinical trials are thus effectively observational.

The study population was defined as individuals who are clinically diagnosed with AD. Only people who are older than 65 years, when they were diagnosed, are included to exclude people with early onset AD. People with other types of dementia, like dementia due to Lewy bodies or vascular dementia, are excluded from the sample. People with mixed dementia are however included in the study as long as one of the causes of their dementia is AD. People with comorbidities and different types of medication, except other anti-dementia drugs, are going to be included in the sample.

Inclusion criteria for the study are thus

- Clinically diagnosed with dementia due to AD when older than 65 years.

Exclusion criteria are

- Patients receiving anti-dementia drugs other than AcEIs (memantine)
- Patients with single aetiologies of dementia other than AD.

The following variables describe the minimal set of variables that each dataset has to have to be relevant for the study (variable in parenthesis are not mandatory for the analysis). The selection of variables was partially informed by what was available in the clinical trials. The clinical trial data have

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for example no information on education and thus education was not strictly necessary in the cohort studies:

1. Demographics
    a. Age, Gender, (Education)
2. At least one of the following outcome measures
    a. MMSE, ADAS-Cog, NPI, CIBIC+
3. Biomarkers
    a. (APOE e4 status)
4. Clinical variables:
    a. Status on diagnosis of AD-type dementia or mixed dementia with one of the causes being AD, AcEIs prescription status, (Comorbidities)

A dataset can contribute to the analysis if at least some of the individuals have at least three or more repeated observations for some of the relevant outcomes after they were diagnosed with AD. As long as some individuals have three observations, the remaining individuals in the specific dataset contribute with two repeated measurements. However, in order to be able to apply random effect models, some observations must be observed three times or more.

4.2. Data sources

The following population cohorts, identified through the DPUK platform and CAMD for appropriate datasets, were identified as being potentially relevant for the present research and are explored in more detail:

1. Whitehall II (DPUK)
2. Clinical trials from CAMD

4.3. Planned analyses

4.3.1. Analysis for objective 1

All analyses are carried out for each dataset separately. Each dataset is described in terms of the main variables of interest as well as socio-demographic characteristics and covariates. The population of each dataset is further described separately for two subgroups, the group who is taking the drugs and those who are not taking any of the AcEIs. If applicable, the proportion of missing values is calculated for each variable and systematic differences between the group assessed.

4.3.2. Analysis for objective 2

Standard regression techniques and regression models allowing a better approximation of the underlying shape of the distributions are used for objective 2.1, depending on the suitability of the data.

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In order to analyse differences in the shape and location, we will use interactions. In case of a random coefficient model, the following model, linear in time, will be estimated:

$$Y_{it} = \alpha + \beta_1 * Group + \beta_2 * Age + \ \beta_3 * Age * Group + \epsilon_{it} + u_i$$

Where Group refers to a dummy identifying people taking the drug. A significant β_3 would be indication of different slopes while β_1 implies differences in the location. Three-way interaction effects will be used to distinguish between trajectories in the cohort study and those in the clinical trials.

4.3.3. Confounding variables

The selection of the variables was based on the existing literature on response to AcEIs (e.g. Perera (2014), Van Der Putt (2006), Wallin et al (2011), Raschetti et al. (2005), Wattmo et al (2012)). However, data availability in the clinical trials implied that important confounders could not be included.

5. Data

5.1. CAMD clinical trial data

CAMD AD/MCI provides access to a clinical trial database with focus on Alzheimer's disease (Neville et al 2015). Data from the control arms of 24 trials are currently freely available for researchers from the CAMD Online Data Repository. Together, these trials have information on 6500 subjects. Main outcome is ADAS-Cog, however MMSE are and other outcomes are available for most trials. Additional available information is APOE4 genotype, limited demographic information and medical history. According to CAMD, the data are standardised to a common data standard (CDISC SDTM v3.1.2) to allow analysis across trials.

5.1.1. Preparation and issues

Medication names in CAMD trials are provided as verbatim, carrying forward spelling mistakes and international brand names. While CAMD insisted on a standardized nomenclature for AcEIs, given their importance for the specific subject of the trials, it was found that this did could not be assumed to hold for all trials equally. Hence, to minimise measurement error, all the variables related to drugs were used to identify instances of AcEIs. Drug libraries were constructed based on DrugBank (https://www.drugbank.ca/drugs) and Jaro-Winkler distance was used to find instances close enough to be identified as potential AcEIs instance. This reduced the number of cases sufficiently to be able to manually screen problematic instances. However, while this approach can deal with spelling mistakes and instances where the brand name was used instead of the component, the drug library is likely anglocentric and will still miss instances of international brand names.

5.2. Whitehall II

By the time of the writing, access to Whitehall II data was granted. However, the dataset that was provided did not correspond to the data that were originally asked for and important information was missing by the time of the writing of the report. This applied particularly to the age of the respondent,

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information on medication and HES that were going to be used to ascertain AD diagnosis. Thus, Whitehall II could finally not be analysed.

6. Results

Given that the access to Whitehall II was not yet granted by the writing of the report, we only report basic summary statistics for the CAMD clinical trial data.

6.1. Descriptive results for CAMD data

CAMD clinical trial data vary in sample size between 57 and 719 individuals. The average age at the first recorded measurement is between 69.7 and 82.1 years, while overall mean is 73.7. While most studies recruited people with MMSE scores of around 20 on average, some trials include participants who are either more severely cognitively impaired or less. Not all studies have MMSE measurements at the first recorded visit.

Table 1- Summary statistics for the CAMD trials

studyid	N	Av. obs per individual	Female share	Av. age at 1 visit	Av. MMSE at 1 visit
1000	102	7.8	58.8	74.8	20.4
1009	164	6	55.5	74.2	20.6
1013	719	11	50.2	74.2	20.6
1014	644	10	56.2	74.8	21
1055	140	4.4	58.6	73.3	19.4
1056	494	7.8	55.9	72.7	19.8
1057	500	7.9	61.4	74.2	19.6
1058	166	6.3	59	72.5	19.3
1105	326	9	50.9	73.1	20.6
1107	146	6.6	61	73.9	12.1
1131	57	5.6	59.6	74.9	24.3
1132	412	7.4	43.4	69.7	26.9
1133	162	6.4	61.1	72.6	19.2
1134	105	7.2	81.9	82.1	13.9
1135	274	7.4	55.1	70.8	19.8
1136	144	6.5	59	72.9	19.4
1137	216	6.7	50.5	75.7	16.9
1138	202	6.5	57.4	76.5	17
1139	167	4.5	67.7	77.5	7.4
1140	137	5.6	42.3	72.7	NA
1141	492	8.5	55.3	69.9	NA
1142	409	7.6	56	75.9	NA
1143	105	5.6	82.9	79.1	8
1144	217	6.4	64.5	75.1	14

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7. Conclusion and next steps

The project investigated the possibility of using natural experiments to investigate the effectiveness of AcEIs in more natural settings, thus looking at the effectiveness outside of clinical trials. However, such a design would be very demanding, requiring information on people with AD around the introduction of the drugs. Given that some of the drugs are already available for a long time, many cohort studies could not be used for this type of exercise as the participants in those studies are too young at the relevant time. Furthermore, many cohort studies have long intervals between waves, thus not providing information around a specific time point that could be exploited. Thus, further options were explored, and the research design was developed into a comparison of the development of MMSE scores in clinical trial patients compared to a more heterogenous population in cohort data. Due to data availability, the final analyses could not be conducted at the time of writing of this report.

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