D4.3 Selection of appropriate disease models for validation

116020 - ROADMAP

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

WP4 – Disease modelling and simulation

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Document History

Version	Date	Description
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V1.1	20/08/2018	Integration of comments from internal reviewers: Ron Handels (UM), Michelle Potashman (BIOGEN), Mark Belger (Eli Lilly)
V2.0	14/09/2018	Final Version with comments from consortium members addressed

Definitions

- Partners of the ROADMAP Consortium are referred to herein according to the following codes:
  - **UOXF**. The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom) – **Coordinator**
  - **NICE**. National Institute for Health and Care Excellence (United Kingdom)
  - **EMC**. Erasmus University Rotterdam (Netherlands)
  - **UM**. Universiteit Maastricht (Netherlands)
  - **SYNAPSE**. Synapse Research Management Partners (Spain)
  - **IDIAP JORDI GOL**. Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (Spain)
  - **UCPH**. Københavns Universitet (Denmark)
  - **AE**. Alzheimer Europe (Luxembourg)
  - **UEDIN**. University of Edinburgh (United Kingdom)
  - **UGOT**. Goeteborgs Universitet (Sweden)
  - **AU**. Aarhus Universitet (Denmark)
  - **LSE**. London School of Economics and Political Science (United Kingdom)
  - **CBG/MEB**. Agentschap College ter Beoordeling van Geneesmiddelen (Netherlands)
  - **IXICO**. IXICO Technologies Ltd (United Kingdom)
  - **RUG**. Rijksuniversiteit Groningen (Netherlands)
  - **Novartis**. Novartis Pharma AG (Switzerland) – **Project Leader**
  - **Eli Lilly**. Eli Lilly and Company Ltd (United Kingdom)
  - **BIOGEN**. Biogen Idec Limited (United Kingdom)
  - **ROCHE**. F. Hoffmann-La Roche Ltd (Switzerland)
  - **JPNV**. Janssen Pharmaceutica NV (Belgium)
  - **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.

Publishable Summary

Deliverable 4.1 “Catalogue of RWE relevant AD models and simplistic disease stage framework” previously provided an overview of published disease progression models. A systematic literature review identified a total of 40 models. For each model, contextual information (including data sources and size, disease stage, population characteristics, etc.), model outcome, and required input variables were extracted. Additionally, three unpublished models developed by the EFPIA Consortium members were reviewed and described in a similar manner.

In this Deliverable, we select three models for external validation:

1. Handels Kungsholmen MMSE Model (Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365)
2. Novartis Longitudinal Model (unpublished prevention longitudinal model describing time-to-MCI and time-to-dementia in correlation with biomarkers time course, ROADMAP Deliverable 4.1, 2017).
3. Eli Lilly PenTAG/GERAS Institutionalisation Model (unpublished time-to-institutionalisation model, ROADMAP Deliverable 4.1, 2017).

We also established the procedure for documenting these models. Cornerstone in the documentation of a model is the so-called “TRIPOD statement” for developers (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis, BMJ 2015;350:g7594). Review of the published papers combined with interviews enabled us to collect the required information. To structure the validation process, we will use the TRIPOD Statement for validation as a guiding principle and develop, for each model validation exercise, a dedicated statistical analysis plan.

1. Introduction

In the past decades, various disease progression models for mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia have been proposed in the literature. Disease progression models play a crucial role in both the assessment of any therapeutic intervention in the disease process and understanding the (economic) impact of these interventions, and may inform patient recruitment for randomized clinical trials (RCTs). In ROADMAP, we want to review and validate the available disease models, and to contribute to the further development of methods and data for disease modelling.

The previous Deliverable 4.1, "Catalogue of RWE relevant AD models and simplistic disease stage framework", provided an overview of published disease progression models. A total of 40 models were identified based on a systematic review of relevant literature. For each model, contextual information (including data sources and size, disease stage, population characteristics, etc.), model outcome, and required input variables were extracted. Additionally, three unpublished models developed by the EFPIA Consortium members were reviewed and described in a similar manner. In Annex I, we provide an overview of all models identified.

One of the objectives of WP4 in ROADMAP is to validate selected disease models through confirmatory analyses (ideally in diverse settings) using independent datasets provided by ROADMAP partners. In this deliverable, we will select the disease models that will be validated, provide the rationale for selecting disease models for validation, specify the variables that need to be extracted from these data sources to actually perform the validation, and specify the next steps in the validation process. The implementation of a model validation pipeline, the validation results for the selected models, and the challenges and issues encountered will be reported in Deliverable 4.4, "Results from pilot model validation exercises".

2. Disease Models to be Validated

In a series of bi-weekly telephone conferences, a number of the models identified in Deliverable 4.1 were presented by members of WP4. Based on the experience gained in these presentations and subsequent discussions, it became apparent that three main criteria should be used in selecting the models that should be the subject of external validation: (a) data availability, (b) detailed understanding of the model, and (c) of significant interest to one or more partners. We will discuss each of these criteria.

Data availability is an important criterion for selecting a model for validation. As reported in Deliverable 4.1, the number of input variables per model varies from one to nine. The majority of models contain five variables or fewer, while a third has only one or two variables. When comparing the specific variables required to the data recorded in the available data sources, we observe that different instruments are often used to measure the same phenomenon. Sometimes transformation algorithms exist that allow mapping one scale onto another – for other scales there is no such option. As a result, the needs of a model could be so specific that none of the data sources in ROADMAP would be able to provide the right data. In order to ensure that we test our ability to validate models on a significant number of data sources, one of the models to be selected for validation should have low data requirements (that is, many data sources should be able to provide the data required for model validation). By selecting a model with limited data requirements, we will be able to test our validation pipeline with a significant number of data sources.

A *detailed understanding of a model* is required when we wish to perform an external validation of that model. In practice, the documentation provided in publications is often insufficient. Critical components or details of the model are frequently lacking. For a validation, however, that level of detail is critical. In the ideal situation, the model's original developer is involved with (or available to) the team performing the validation.

Selection of the model to be validated should also be informed by the *specific interest of one or more partners* participating in ROADMAP. Clearly disease progression models are relevant for many partners. Individual partners, however, may have a preference for a certain model based on specific properties of that model. When selecting models for validation, partners' preferences should be taken into consideration.

For external validation, we selected the following 3 models.

First, the *Handels Kungsholmen MMSE Model (Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365).* The authors provide two distinct models: (a) AD-free survival time in people with MCI, and (b) decline of cognitive and physical function in AD cases. For validation, we focus on the second model developed in this study: the model that estimates the changes of cognition (as assessed by the MMSE) in incident AD dementia cases.

The *reasons* for selecting this model were, firstly, the limited data requirements. For validation, only age, date of diagnosis, and MMSE measurements are need. As a result, we believe many data sources will be able to provide this information and can participate in the validation. As a result, this

would be an ideal model to test the validation pipeline on these data sources. Secondly, the original author of the paper (Ron Handels) is a member of WP4 and will be able to provide the detailed information needed for validation.

Second, the *Novartis Longitudinal Model (Model for APCC time profile and time to first diagnosis of mild cognitive impairment or dementia due to Alzheimer's disease (AD) in elderly, cognitively normal individuals at risk to develop symptoms of AD, ROADMAP Deliverable 4.1, 2017)*. In this model, developed under leadership of Novartis, the objective was to model the pre-symptomatic timecourse in the AD prevention setting.

The *reasons* for selecting this model were, firstly, the interest of a number of partners in exploring this model with its underlying objectives (e.g., inclusion of pre-symptomatic period) shared among partners. Secondly, Novartis, who developed the model, is participating in WP4 and will be able to provide detailed information for validation.

Third, the Eli Lilly PenTAG/GERAS Institutionalisation Model *(Healthcare and societal costs related to the time to institutionalisation in a community-based cohort of patients with Alzheimer's disease dementia, ROADMAP Deliverable 4.1, 2017).* In this model, developed as an extension of the PENTAG model under leadership by Eli Lilly, the emphasis is on costs aspects of the disease.

The *reasons* for selecting this model were, firstly, the interest of a number of partners in exploring the validation of a model that included a disease cost component. Secondly, Eli Lilly, which leads the extension of the original PENTAG model, is participating in WP4 and will be able to provide the detailed information for validation.

3. Documenting the Models

To prepare for an external validation of the selected models, we need to collect detailed information about the properties and data requirements of these models.

To structure the reporting requirements of models, a collective of researchers and representatives of several medical journals developed the so-called TRIPOD Statement a few years ago (Collins et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement. Ann Intern Med. 2015;162:55-63). The TRIPOD Statement includes a 22-item checklist, which aims to improve the reporting of studies developing or validating a model. The TRIPOD Statement checklist for model development is partially different from the checklist for validation -- reflecting the differences between developing and validating models. To document the three selected models, we used the TRIPOD development checklist. It is should be noted that the TRIPOD statement was developed for prediction models that aid health care providers in estimating the probability or risk that a specific disease or condition is present (diagnostic models) or that a specific event will occur in the future (prognostic models). Although these models have dichotomous outcome variables, whereas disease progression models usually have a continuous outcome variable, the checklist items are sufficiently general to document the development and validation of disease progression models.

To collect the information regarding the development of the selected models, we set out to fill in the TRIPOD Development checklist for each selected model. Based on the available publications, we (JK) filled in the statement as far as possible. To complement the data collection for each model, we subsequently contacted the experts for the missing information (that is, the information not available from the publications on the model).

Table 1 shows the TRIPOD Development checklist for *Handels Kungsholmen MMSE Model.* The TRIPOD checklist is divided in several sections: Title and Abstract, Introduction, Methods, Results, Discussion, and Other Information. Each section contains a number of specific topics that must be addressed. In the column 'Page', a reference to the page number of the original publication is included.

Table 1: TRIPOD Development checklist for Handels Kungsholmen MMSE Model

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	357
		Natural Progression Model of Cognition and Physical Functioning among People with Mild Cognitive Impairment and Alzheimer's Disease (Handels RL, Xu W, Rizzuto D, et al. J Alzheimers Dis. 2013;37:357-65)	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	357
		Objective: We aimed to estimate AD-free survival time in people with mild cognitive impairment (MCI) and decline of cognitive and physical function in AD cases.	

		Methods: Within the Kungsholmen project, 153 incident MCI and 323 incident AD cases (international criteria) were identified during 9 years of follow-up in a cognitively healthy cohort of elderly people aged ≥75 at baseline (n = 1,082). Global cognitive function was assessed with the Mini-Mental State Examination (MMSE), and daily life function was evaluated with the Katz index of activities of daily living (ADL) at each follow-up examination. Data were analyzed using parametric survival analysis and mixed effect models. **Results: Median AD-free survival time of 153 participants with incident MCI was 3.5 years. Among 323 incident AD cases, the cognitive decline was 1.84 MMSE points per year, which was significantly associated with age. Physical functioning declined by 0.38 ADL points per year and was significantly associated with age, education, and MMSE, but not with gender.** **Conclusion: Elderly people with MCI may develop AD in approximately 3.5 years. Both cognitive and physical function may decline gradually after AD onset. The empirical models can be used to evaluate long-term disease progression of new interventions for AD.** **In the following, we focus on one of the models developed in this study, which estimates the changes of cognition (as assessed by the MMSE) in incident AD dementia cases.**	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	358
		Natural progression models in AD have been developed in several studies, mostly among clinical samples or prevalent AD dementia cases. However, disease modifying treatments are supposed to be effective in early (pre-dementia) AD, thus long-term data on the natural course are required to evaluate their effectiveness. Such target populations have not been reflected by previous studies, leaving an urgent need for population-based empirical models that describe the long-term natural progression of the dementia and pre-dementia phases of AD.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	358
		Objective: Estimate the changes of cognition (MMSE) in incident AD dementia cased from a population-based cohort. **The study describes the development of the model.**	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	358
		Source of data is the Kungsholmen Project, a population-based cohort study on aging and dementia	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	358
		The Kungsholmen project started in 1987. Data were collected at baseline and at 3-, 6-, and 9-year follow-ups.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	358
		General population	
	5b	Describe eligibility criteria for participants.	358
		All registered inhabitants of the Kungsholmen district of Stockholm, Sweden, who were aged ≥75 years in October 1987, had no dementia, MCI, or an MMSE < 20 at baseline, with incident AD-type dementia (either AD or mixed AD &	

		vascular dementia) during follow-up. **A diagnosis of dementia (including both questionable and definite diagnoses) was established by the examining physicians, based on a comprehensive clinical examination and cognitive tests according to the DSM-III-R criteria. The diagnostic criteria applied were equivalent to probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, and according to those of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences.**	
	5c	Give details of treatments received, if relevant.	
		Not reported	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	358
		Outcome MMSE. Assessment at baseline and follow-ups with a targeted 3-year time interval.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
		Not reported	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	359
		Predictors tested: Age, Gender, Education, and Time after being diagnosed with AD. The onset of AD was assumed to have taken place in the middle of each follow-up interval (each lasting an average of 3 years). This was operationalized by adding a time correction of 1.5 years. Only Age and Time after being diagnosed turned out to be significant predictors.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
		Not reported	
Sample size	8	Explain how the study size was arrived at.	359
		No sample size calculations done, entire cohort used	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
		The mixed model with random effects takes missing or censored data into account.	363
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
		No categorization or transformation was performed. Only for the covariate time non-linearity was explored by stepwise adding a higher-order polynomial of time	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	359
		Mixed model with random effects. **A stepwise procedure was used and predictors were included if the goodness-of-fit statistics −2 log likelihood change and Wald z of the predictor were significant. The following steps were used to determine the final MMSE prediction model: (1) include time, as years after being diagnosed with AD; (2) include a random intercept; (3) determine if time is non-linear by stepwise adding a higher-order polynomial of time; (4) include a random time factor; (5) include gender, age, and education and all 2-way interactions and remove interactions with highest p-values first until $p < 0.05$, followed by predictors. No internal validation was performed.**	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	

		No measures used, model performance not assessed	
Risk groups	11	Provide details on how risk groups were created, if done.	
		Not applicable	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	358, 359
		At baseline, 225 of the 1,810 participants were diagnosed with dementia and 110 participants refused the extensive evaluations. Of the remaining 1,475 dementia-free persons, 355 with MCI (130 with amnestic MCI (aMCI) and 225 with other cognitive impairment not demented (OCIND)) at baseline and 38 with very low global cognitive status in the absence of a dementia diagnosis (MMSE) <20) were excluded, leaving 1,082 cognitively healthy subjects at baseline. Out of those, 323 developed AD during 9-year follow-up.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	359
		Age at diagnosis 86.7 (4.1) yrs, 83% female, education 8.2 (2.9) yrs, MMSE at diagnosis 19.7 (5.0), Katz ADL at diagnosis 1.2 (0.7). No specific information on missing data.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	360
		For the 323 participants who developed AD during follow-up, 313 MMSE scores were available at the moment of AD diagnosis, 109 at 3 years after diagnosis, and 28 at 6 years after diagnosis. Forty-nine percent of the participants died during follow-up.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	362
		Regression parameters estimates (95% CI) of univariate mixed effects regression model to predict MMSE: Age -0.41 (-0.57 to -0.26), Time after being diagnosed -1.84 (-2.10 to -1.57), Gender -1.14 (-2.89 to 0.60), Education -0.05 (-0.29 to 0.19).	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	360
		MMSE = 26.87 – 3.26 Time – 0.35 (Age – 75) + 0.10 Time (Age – 75), in which Time is years after being diagnosed with AD.	
	15b	Explain how to the use the prediction model.	
		Not reported, but straightforward	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
		Model performance not assessed	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	363
		The Kungsholmen project included persons aged 75 and older, which resulted in attrition due to death and refusal. However, this reflects reality, since most demented people are older than 75, and the mixed model with random effects and the survival analysis take missing or censored data into account. Nonetheless, generalization to a younger population should be done with caution, A second limitation is that the Kungsholmen project started in 1987, when the current cholinesterase inhibitors and memantine treatments that affect cognitive decline were not available. Thirdly, the empirical models were not adjusted for comorbidities, as this information was not available to	

		the researchers. Furthermore, the 1.5 year correction might limit the precision of the time-to dementia conversion. **The regression and survival models have not been validated by external datasets, or by predicting the progress of similar patients in current clinical practice. The data available at follow-up was limited, resulting in uncertain predictions. Finally, generalizability to other countries is limited because differences in life expectancy might lead to differences in average disease progression rates or the effect of age.**	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	361-363
		A population-based study including 95 incident dementia participants [20, 21] found an average rate of cognitive decline of 1.71 MMSE points per 6 months, whereas we found a lower average rate of decline (1.84 / 2 = 0.92 points per 6 months). The difference could be explained by the inclusion of a higher proportion of moderately severe dementia participants in the Kungsholmen Project, who decline less quickly due to the floor effect of the MMSE. According to the multivariate model using average age, subjects decline by 1.2 MMSE points in the first 6 months after being diagnosed. Mendiondo et al. [22] and Mohs et al. [23] parameterized the annual rate of cognitive decline and found a U-shaped pattern with low decline rates in mild and severe dementia and a higher decline rate in between. We explored this model, but the results were not significant and could be attributed to the use of a population-based sample instead of a clinical sample, as the latter probably includes persons with a poorer prognosis because consulting a medical professional is probably initiated by the person's memory complaints. Han et al. [24] reviewed studies largely based on clinical samples of prevalent cases with an average of 2 years of follow-up, and found a mean annual rate of decline of 3.3 MMSE points per year. Our estimates are at the lower bound of their confidence interval. Besides the use of incident community participants, this difference could be explained by the long follow-up time, in which some participants reach the floor level of the MMSE.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	363
		The empirical models developed in this study (including the MMSE model) could be used to simulate the natural disease progression in a cohort and compare this with a scenario where a hypothetical future treatment is available. Such predictions can be integrated with evidence on health care resource usage and quality of life, and enable policy makers to address questions about the potential of new diagnostic or treatment interventions from a cost-effectiveness point of view. Such analyses could provide added value to randomized controlled trials which are limited in terms of follow-up time or the number of scenarios to compare.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
		No supplemenary resources mentioned	
Funding	22	Give the source of funding and the role of the funders for the present study.	364
		Dutch Alzheimer's Society, Center for Translational Molecular Medicine	

Table 2 shows the TRIPOD Development checklist for the *Novartis Longitudinal Model.*

Table 2: TRIPOD Development checklist for the Novartis Longitudinal Model

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
		Model for APCC time profile and time to first diagnosis of mild cognitive impairment or dementia due to Alzheimer's disease (AD) in elderly, cognitively normal individuals at risk to develop symptoms of AD	-[1]
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
		OBJECTIVES: **Shifting the focus of clinical trials testing disease-modifying interventions against Alzheimer's disease from the dementia stages of the disease to pre-symptomatic stages may increase the likelihood of success for these trials. The aim of this research was to develop a model for the pre-symptomatic time course in the AD prevention setting to inform clinical trial design.** **METHODS: We developed a statistical model describing time to first diagnosis of mild cognitive impairment (MCI) and dementia diagnosis using a Weibull parametric survival model and the progression of the Alzheimer's Prevention Initiative Preclinical Composite (APCC, see Langbaum et al. 2014[2]), a measure for cognitive decline, using a non-linear mixed-effects model. We chose model covariates based on clinical relevance, goodness of model fit and statistical tests. We trained the model on cohorts from the Rush Alzheimer's disease center (Rush) (ROS, MAP and MARS) and the National Alzheimer's Coordinating Center (NACC), US databases including healthy as well as cognitively impaired and demented subjects. For the time-to-diagnosis model, we used N=2159 subjects from Rush and N=8535 subjects from NACC who were cognitively normal at baseline and were diagnosed with MCI or dementia due to AD during follow-up. For the APCC model, we used N=2336 subjects from Rush who were cognitively normal at baseline and had no other diagnoses than MCI or dementia due to AD during follow-up.** **RESULTS: We identified age, apolipoprotein E ε4 (APOε4) status, APCC at baseline and education level as important model covariates. Patient simulations showed a good fit between model predictions and observed values, for both time to first diagnosis and progression of APCC. Simulations also showed that an enrichment strategy focusing on elderly participants yielded a higher power for a given hazard ratio of the investigated interventions.** **CONCLUSIONS: The 2-step model linking APCC decline and time to MCI or AD diagnosis is the first AD disease progression model for pre-symptomatic stages of the disease. It can be used in the context of optimizing design of clinical trials in the prevention setting. Further refinements of the model, e.g. including biomarkers such as amyloid-beta and tau as covariates and covering other relevant endpoints, external validation of the model, and incorporation into a health economic model to evaluate interventions in the prevention setting, are objectives of future research.**	

[1] No publication available.

[2] http://www.sciencedirect.com/science/article/pii/S1552526014000636

Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
		Shifting the focus of clinical trials testing disease-modifying interventions against AD from the dementia stages of the disease to pre-symptomatic stages may increase the likelihood of success for these trials. Various models describing cognitive decline in later stages of AD exist so far, but a model describing cognitive function in the pre-symptomatic phase of the disease and predicting time to first diagnosis of MCI or dementia is lacking. Hence, there is an urgent need of such a model to e.g. inform the design of trials targeting patients at risk to develop dementia.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
		The aim of this study was to develop a model for the pre-symptomatic time course in the AD prevention setting. The study describes the development of the model.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
		Source of data are the Rush and the NACC longitudinal cohorts. **Rush: Cohort study cohort study of common chronic conditions of aging with emphasis on decline in cognitive and motor function and risk of AD.** **NACC: Prospective cohort study with participants from Alzheimer's Disease Centers (ADCs).**	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
		Rush: Started in 1997, still ongoing. **NACC: Started in 2005, still ongoing.**	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
		Rush: Participants are older adults recruited from 37 retirement communities and subsidized senior housing facilities throughout Chicagoland and north-eastern Illinois. **NACC: Participants are followed at 39 past and present U.S. ADCs (with or without dementia). Subjects may come from clinician referral, self-referral by patients or family members, active recruitment through community organizations, and volunteers who wish to contribute to research on various types of dementia. Most centers also enrol volunteers with normal cognition.**	
	5b	Describe eligibility criteria for participants.	
		Rush: - **older persons without known dementia** - **must agree to an assessment of risk factors, blood donation, and a detailed clinical evaluation each year** **NACC:** - **participant at a contributing ADC**	
	5c	Give details of treatments received, if relevant.	
		Not reported	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
		Outcomes: - **APCC, assessed continuously throughout the study (from Rush)** - **Diagnosis of MCI and dementia due to AD, assessed throughout the**	

		study (from Rush and NACC)	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
		Not reported	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
		Tested predictors are APCC at baseline, age at baseline or at time of diagnosis, gender, APOε4 status and educational level (years of education).	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
		Not reported	
Sample size	8	Explain how the study size was arrived at.	
		No sample size calculations done, entire cohort used	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
		APCC model: The mixed effects model takes missing data into account. Time-to-first-diagnosis model: The Weibull survival regression model takes censored data into account, but removes subjects with missing covariates.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
		Continuous predictors were log transformed and centered around their median.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
		APCC model: Non-linear mixed effects model (power model). Time-to-first-diagnosis model: Weibull survival regression model. Model structures were chosen because of their flexibility to fit the data. Covariate were chosen based on investigating the predictive value of a set of candidate predictors in a systematic way. No internal validation performed.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
		Model performance was assessed using diagnostic plots.	
Risk groups	11	Provide details on how risk groups were created, if done.	
		Not done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
		APCC model: We evaluated a total of N=2336 subjects from Rush who were cognitively normal at baseline, had at least two visits and had no other diagnoses than MCI or dementia due to AD during follow-up. Of those subjects, 732 were first diagnosed with MCI or dementia within eight years, and 1604 stayed cognitively normal within eight years of follow-up. **Time-to-first diagnosis model: We evaluated a total of N=10694 subjects from Rush and NACC who were cognitively normal at baseline, had at least two visits and had no other diagnoses than MCI or dementia due to AD during follow-up. Of those subjects, 2870 were first diagnosed with MCI or dementia, and 859 were first diagnosed with dementia.**	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
		APCC model: Mean APCC at baseline 61.0, mean education 16.1 years, 1.1%	

		homozygote carriers of APOε4 and 23.6% heterozygote carriers (8.3% missing values) for subjects diagnosed with MCI or dementia. Mean APCC at baseline 64.9, mean education 16.0 years, no homozygote carriers of APOε4 and 18.0% heterozygote carriers for subjects staying cognitively normal. **Time-to-first diagnosis model: Mean age at baseline was 74.4 years, mean APCC at baseline was 63.5 (16.4% missing values), 1.7% homozygote carriers of APOε4 and 20.6% heterozygote carriers (39.7% missing values).**	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
		APCC model: APCC was available for all subjects diagnosed with MCI or dementia at baseline, at four subsequent follow-up visits on average, and maximally at seventeen subsequent follow-up visits. APCC was available for all subjects staying cognitively normal at baseline, at three subsequent follow-up visits on average, and maximally at eight subsequent follow-up visits. **Time-to-first diagnosis model: 2870 subjects were first diagnosed with MCI or dementia (7824 censored), 859 were diagnosed with dementia (9835 censored).**	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
		Not reported	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
		APCC model for converters, i.e. subjects diagnosed with MCI or dementia within eight years: mixed-effects power model with predictor APCC at baseline for the intercept and the slope, and predictors education and APOε4 carrier status for the slope. **APCC model for non- or late-converters, i.e. subjects staying cognitively normal within eight years: linear mixed-effects model with predictors education and age at baseline for the intercept, and predictors APCC at baseline, APOε4 carrier status and age at baseline for the slope.** **Time-to-first-diagnosis of MCI or AD model: Weibull survival regression model with predictors age at baseline, APCC at baseline and APOε4 carrier status.** **The formulas for these models are still to be added.** **For clinical trial simulations, the models were linked in the following way: first, time to first diagnosis of MCI or AD was simulated. Second, if a subject was diagnosed within 8 years, the APCC model for converters was applied to simulate APCC progression for that subject. If a subject was *not* diagnosed within 8 years, the APCC model for non-/late-converters was applied to simulate APCC progression for that subject. A further link between the two models exists via the time to event: The APCC models the time course using TTE minus 8 years as the baseline and not calendar time t=0.**	
	15b	Explain how to the use the prediction model.	
		Straightforward	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
		Model performance not assessed	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
		- **APCC in the NACC database is just a proxy** - **Number of subjects in specific subgroups of interest is rather small. Example: APOE4 homozygote carriers**	

		- **No biomarker data available, hence, no information on important prognostic factors** - **Model structure needs to be justified, i.e. compared with other model structures** - **Choice of model covariates needs to be justified, i.e. should be done systematically**	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
		The 2-step model linking APCC decline and time to MCI or AD diagnosis is the first AD disease progression model for pre-symptomatic stages of the disease. It can be used in the context of optimizing design of clinical trials in the prevention setting, although results have to be considered with care since a validation of the model is lacking. Some limitations of the model may be due to the fact that the model was originally not developed as a disease model with a broader and more general interpretation, but as a basis for trial simulations in a specific setting. Hence, the strategy of the model development and model fit was tailored to the requirements of the clinical trial setting. These limitations need to be investigated and modifications of the model may be explored to leverage the model to a broader application and interpretation.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
		APCC starts to decline in cognitively normal individuals ~5 years before MCI/dementia diagnosis, therefore the model could also be used to predict time to MCI/dementia diagnosis in healthy individuals once APCC decline has started, i.e. ~2 years before.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
		None	
Funding	22	Give the source of funding and the role of the funders for the present study.	
		The model was developed within Novartis.	

Table 3 shows the TRIPOD Development checklist for the Eli Lilly PenTAG/GERAS Institutionalisation Model.

Table 3: TRIPOD Development checklist for the Eli Lilly PenTAG/GERAS Institutionalisation Model

Section/Topic	Checklist Item		Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
		Healthcare and societal costs related to the time to institutionalization in a community-based cohort of patients with Alzheimer's disease dementia Mark Belger, Josep Maria Haro, Catherine Reed, Michael Happich, Josep Maria Argimon, Giuseppe Bruno, Richard Dodel, Roy W. Jones, Bruno Vellas, Anders Wimo. Submitted for Publication. **The Modeling structure (PENTAG model) is also described in:** **Green, C., Shearer, J., Ritchie, C.W., Zajicek, J.P.: Model-based economic evaluation in Alzheimer's disease: a review of the methods available to model Alzheimer's disease progression. Value Health 14(5), 621–630 (2011). doi: 10.1016/j.jval.2010.12.008.** **Bond, M., Rogers, G., Peters, J., Anderson, R., Hoyle, M., Miners, A., Moxham,**	

		T., Davis, S., Thokala, P., Wailoo, A., Jeffreys, M., Hyde, C.: The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. Health Technol. Assess. 16(21), 1–470 (2012). doi: 10.3310/hta16210.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
		Objectives: To examine the costs of caring for community-dwelling patients with Alzheimer's disease (AD) dementia in relation to the time to institutionalisation. **Methods: GERAS was a prospective, non-interventional cohort study in community-dwelling patients with AD dementia and their caregivers in three European countries. Using identified factors associated with time to institutionalisation, models were developed to estimate the time to institutionalisation for all patients. Estimates of monthly total societal costs, patient healthcare costs and total patient costs (healthcare and social care together) prior to institutionalisation were developed as a function of the time to institutionalisation.** **Results: Of the 1495 patients assessed at baseline, 307 (20.5 %) were institutionalised over 36 months. Disease severity at baseline (based on Mini-Mental State Examination [MMSE] scores) was associated with risk of being institutionalised during follow-up ($p < 0.001$). Having a non-spousal informal caregiver was associated with a faster time to institutionalisation (944 fewer days versus having a spousal caregiver), as was each one-point worsening in baseline score of MMSE, instrumental activities of daily living and behavioural disturbance (67, 50 and 30 fewer days, respectively). Total societal costs, total patient costs and, to a lesser extent, patient healthcare-only costs were associated with time to institutionalisation. In the five years pre-institutionalisation, monthly total societal costs increased by more than £1000 (€1166 equivalent for 2010) from £1900 to £3160 and monthly total patient costs almost doubled from £770 to £1529.** **Conclusions: Total societal costs and total patient costs rise steeply as community-dwelling patients with AD dementia approach institutionalisation.**	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
		The PENTAG model has been used for economic models to assess the cost effectiveness of ACHEi's. During these submissions NICE identified a number of weaknesses to the submitted model, these focused around the relevance of the data used to build the models. The recent work has focused on developing models using the GERAS study data for both time to Institutionalisation, time to death and costs and quality of life related to pre-institutionalisation time.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
		The work is an update on the PENTAG model, using more recent data from The GERAS study. No external validation has been performed on the equations used within the model. **The publication includes equations to predict the time to institutionalisation and equations for cost as a relationship to pre-institutionalisation. These are taken from the three-year follow-up data from the GERAS study. Additional models are available based on 60 month follow up data from GERAS, and including models on time to death, and the relationship of pre-Institutionalisation to to quality of life (EQ-5D)**	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or	

		registry data), separately for the development and validation data sets, if applicable.	
		The data comes from the GERAS study (Wimo, A., Reed, C.C., Dodel, R., Belger, M., Jones, R.W., Happich, M., Argimon, J.M., Bruno, G., Novick, D., Vellas, B., Haro, J.M.: The GERAS Study: a prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in three European countries – study design and baseline findings. J. Alzheimers Dis. 36(2), 385–399 (2013). doi: 10.3233/JAD-122392)	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
		GERAS is an 18-month, multicentre, observational study designed to assess the direct and indirect country costs associated with AD for patients and their caregivers in France, Germany and the UK. Patients in France and Germany were being followed for a further 18 months. An addendum to the study collected information on Date of death and date of institutionalisation. Recent database lock on the 60-month follow up data is available. **The study enrolled patients between October 1 2010 and September 31 2011.** **Patients and caregivers were evaluated at baseline and every six months**	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
		Patients enrolled were in a community dwelling with a probable AD diagnosis according to the National Institute of Neurological and Communicative Disorders, and stroke and Alzheimer's disease and related disorders association (NINCDS-ADRDA) 94 sites were enrolled from three countries	
	5b	Describe eligibility criteria for participants.	
		Community dwelling **Age ≥55 years;** **Probable AD (NINCDS-ADRDA)** **An MMSE score of ≤26** **Presented within the normal course of care** **Patients were excluded if they had a history, clinical signs or imaging of stroke or transient ischemic attack, patients with an history of Parkinson's disease prior to or at the start of AD onset; Probable Lewy-body disease.** **Patients were required to have a caregiver who was willing to participate in the study, and were defined as an informal carer who would normally take care of day to day activities (not for a health care professional)**	
	5c	Give details of treatments received, if relevant.	
		Patients were on standard of care, there was no requirement for patients to be treated with any specific AD medication at study entry.(78% received ACHEi's; 21% were receiving Memantine at study enrolment)	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
		Time to Institutionalisation **Total societal cost as a function of Pre-Institutionalisation** **Patient medical cost as a function of Pre-Institutionalisation** **Patient medical and social care cost as a function of Pre-Institutionalisation** **Models are also available for the outcome Time to death, but not in publication.** **Quality of life as a function of Pre-Institutionalisation**	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
		Not reported.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	

		Two models were considered one including only patient characteristics, and a second model which included both patient and caregiver characteristics: **All predictors measured at baseline:** **Patient characteristics considered:** **Age** **Gender** **Years of education** **Time since diagnosis of AD** **Number of comorbidities** **MMSE score** **Total ADCs-ADl** **Instrumental ADCS-ADL** **Basic ADCS-ADL** **NPI** **AD medication** **Caregiver factors considered** **Age** **Gender** **Relationship with patients (spouse yes/no)** **Caregiver working for pay** **Sensitivity analysis were considered which looked at interaction terms, and sub-domains of the ADL and the NPI** **Details of the scales used can be found in the Wimo publication**	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
		No blinding	
Sample size	8	Explain how the study size was arrived at.	
		Enrolment was over a 12 month period, with sample size based on country and MMSE severity group. Sites were selected within the three countries to aim for approximately equal numbers of patients in each MMSE severity group. **Sample size was based on the precision obtained for estimating costs** **Further details are provided in the Wilmo publication.**	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
		Survival analysis was used for models predicting time to Institutionalisation, patients were censored at last visit or at time of discontinuation from the study **No imputation was performed on missing baseline data as over 97% of baseline data available** **Missing Cost data was imputed based on the reason for missing cost data.The following rules were applied:** **For institutionalised patients, mean monthly costs from the last visit were used for the period until institutionalisation and monthly costs for institutionalisation were used from institutionalisation up to 18 months for the UK and up to 36 months for France and Germany.** **For patients who died, last observation carried forward was used such that costs from the last known visit were extrapolated up to the date of death (no costs after death were computed).** **For patients with other reasons for discontinuation, the multiple imputation regression method [19] stratified by MMSE group and country was applied to missing costs.** **The list of factors used in the multiple imputation procedure was selected from those identified by Dodel et al. (Dodel, R., Belger, M., Reed, C., Wimo, A., Jones, R.W., Happich, M., Argimon, J.M., Bruno, G., Vellas, B., Haro, J.M.:**	

		Determinants of societal costs in Alzheimer's disease: GERAS study baseline results. Alzheimers Dement. 11(8), 933–945 (2015). doi: 10.1016/j.jalz.2015.02.005)	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
		No transformations were conducted on the continuous variables. The caregiver relationship categorical variable was dichotomised into spouse (yes/no).	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
		Factors associated with time to institutionalisation were explored using Cox proportional hazards models of the 36-month data; time to institutionalisation was censored at the time of last follow-up or time to death for those subjects who did not report being institutionalised. One hundred different models using forward and backward selection were run, selecting 67 % of subjects at random for inclusion in the model, and the factors identified in each model summarised. Entry and exclusion of individual factors was based on a significance level of 0.05. Any factor found to be significant in over 75 % of the models was included in the parametric models used to predict time to institutionalisation. To allow for different assumptions around the distribution of the data, the parametric models considered exponential, log-logistic, Weibull, log-normal and gamma distributions. Model fit was assessed using AIC and BIC model fit statistics, and the best fitting model was selected for use in the model that estimated societal and patient costs as a function of time to institutionalisation. Models were fitted to estimate costs (y) as a function of time to institutionalisation (x). Separate models were developed for total societal costs, total patient costs (patient healthcare plus social care costs) and patient healthcare costs. For each patient, the predicted time to institutionalisation (Pred_Inst) was calculated from the parametric model. Then, for each 6-month visit, the patient's time to institutionalisation (Pre-Inst) was calculated as: Pre-Inst = Pred_Inst – visit. Each individual subject time point was treated as independent, had an associated cost and any missing cost visits used the imputation methods described earlier.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
		See above, Time to institutionalisation models were assessed by AIC and BIC, and then a visual inspection of the extrapolated curves.	
Risk groups	11	Provide details on how risk groups were created, if done.	
		No risk groups created	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
		1495 patients were enrolled into the study, 307 were institutionalised during the 36-month follow up, while 152 patients died before being institutionalised. 298 patients discontinued the study before end of follow up period.(18 months UK, and 36 months France and Germany)	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
		1495 patients enrolled; 566 with Mild AD, 472 moderate and 457 with moderate severe/sever AD at baseline. Mean (sd) age 77.6 (7.7) years , 55% female; 72% married/cohabitating; 76% living in urban area; 96% living in own home; 10.4(3.2) years of education; 2.2 (2.2) years since AD diagnosis; baseline MMSE score 17.4 (6.3); ADLscore 46.5 (19.5); NPI_12 score 15.1	

<table>
<tr><td></td><td></td><td>(15.3)</td><td></td></tr>
<tr><td rowspan="3">Model development</td><td>14a</td><td>Specify the number of participants and outcome events in each analysis.</td><td></td></tr>
<tr><td></td><td>1495 patients enrolled
307 institutionalised in first 36 months
152 died in first 36 months

Updated figures using the 60 month addendum data are available</td><td></td></tr>
<tr><td>14b</td><td>If done, report the unadjusted association between each candidate predictor and outcome.</td><td></td></tr>
<tr><td></td><td></td><td>Not available</td><td></td></tr>
<tr><td rowspan="3">Model specification</td><td>15a</td><td>Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).</td><td></td></tr>
<tr><td></td><td>Submitted publication uses just the 36-month data and is reporting the model including caregiver factors. The equations using just patient factors and the 60-month addendum data can be provided. The models using just patient factors and the 60 month addendum data may be more appropriate for use in external validation:
Models from submitted publication:

<table>
<tr><th>Variable</th><th>Regression coefficient[a]</th><th>Standard error</th><th>95 % confidence limits</th><th>Chi-square</th><th>p value</th><th>Change in time to institutionalisation, days (months)[b]</th></tr>
<tr><td>Intercept</td><td>7.600</td><td>0.209</td><td>7.190; 8.010</td><td>1321.79</td><td>< 0.0001</td><td>–</td></tr>
<tr><td>MMSE total score[c]</td><td>0.034</td><td>0.009</td><td>0.016; 0.052</td><td>13.75</td><td>0.0002</td><td>−67 (2.3)</td></tr>
<tr><td>Instrumental ADCS-ADL[c]</td><td>0.025</td><td>0.005</td><td>0.015; 0.036</td><td>23.44</td><td>< 0.0001</td><td>−50 (1.7)</td></tr>
<tr><td>Basic ADCS-ADL[c]</td><td>−0.044</td><td>0.014</td><td>−0.071; −0.017</td><td>10.13</td><td>0.0015</td><td>+89 (3.0)[d]</td></tr>
<tr><td>NPI-12 total score[c]</td><td>−0.015</td><td>0.003</td><td>−0.021; −0.010</td><td>27.35</td><td>< 0.0001</td><td>−30 (1.0)</td></tr>
<tr><td>Spousal caregiver, No (Ref = yes)</td><td>−0.640</td><td>0.095</td><td>−0.826; −0.453</td><td>45.18</td><td>< 0.0001</td><td>−944 (31.5)</td></tr>
<tr><td>Scale</td><td>1.206</td><td>0.054</td><td>1.105; 1.317</td><td>–</td><td>–</td><td>–</td></tr>
</table>
Analysis of maximum likelihood parameter estimates of patient and caregiver factors associated with time to institutionalisation from the log-normal model

Models showing the relationships of costs to pre-Institutionalisation (pre_Inst)

Q1: Total societal costs (£) = 3159.68 – (334.03 Pre-Inst) + (18.57 Pre-Inst^2) – (0.43 Pre-Inst^3)
Q2: Total patient costs (£) = 1528.96 – (208.53 Pre-Inst) + (12.73 Pre-Inst^2) – (0.28 Pre-Inst^3)
Q3: Patient healthcare costs (£) = 348.31 – (14.88 Pre-Inst) + (0.35 Pre-Inst^2)</td><td></td></tr>
<tr><td>15b</td><td>Explain how to the use the prediction model.</td><td></td></tr>
<tr><td>Model performance</td><td>16</td><td>Report performance measures (with CIs) for the prediction model.</td><td></td></tr>
<tr><td></td><td></td><td>Within the economic model alternative parametric models are run in the form of sensitivity analysis
(These models are available for both the 36 and 60 month analysis)</td><td></td></tr>
<tr><td colspan="4">Discussion</td></tr>
<tr><td>Limitations</td><td>18</td><td>Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).</td><td></td></tr>
<tr><td></td><td></td><td>Patients with no formal caregiver were not eligible for the study
In the model with patient and caregiver factors, patient age was not selected. If caregiver factors were excluded then model uses:</td><td></td></tr>
</table>

		Patient age, NPI, ADL and MMSE **Other factors not collected may influence the likelihood of institutionalisation are not considered, also reasons for institutionalisation may be country specific (UK model is available)** **There is a possibility of selection bias due to the recruitment of the study participants mostly from memory clinics, which may limit the generalisability of the findings as the sample is not fully representative of all AD patients living in the community**	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
		The economic model framework described in PENTAG, also has models for time to death, and QoL as a function of pre-Institutionalisation. Within the model there is also an equation looking at MMSE over time. **The submitted publication described above is just focusing on the methods used to take a model for predicting time to Institutionalisation and relating that to costs.** **For the development of the economic models to update the PENTAG model we have the following information available that makes use of the 60 month follow up data:** **Time to Institutionalisation** **Time to death** **Costs as a function of pre-Institutionalisation** **Qol as a function of pre-Institutionalisation** **MMSE over time** **Models for UK only cohort have also been developed**	
Funding	22	Give the source of funding and the role of the funders for the present study.	
		The GERAS study was sponsored by Eli Lilly, and analysis was conducted by Eli Lilly	

4. Discussion and Next Steps

The previous Deliverable 4.1, “Catalogue of RWE relevant AD models and simplistic disease stage framework”, provided an overview of published disease progression models. In this Deliverable, we selected the models for external validation.

Data availability is an important criterion for selecting a model for validation. The number of required input variables varies between models. In the literature review, the majority of models contains five variables or fewer, while a third has one to two variables (see Deliverable 4.1). There is, however, a significant issue with the diversity in the way each variable has been measured – multiple options are available even for the same phenomenon/concept of interest. Transformation algorithms sometimes exist that support the mapping of one scale onto another. The data needs of a model, however, could be so specific that none of the data sources in ROADMAP would be able to provide the required data. These issues will be further exemplified and discussed in Deliverable 4.4, “Results from pilot model validation exercises”.

A *detailed understanding of a model* is required when we want to perform an external validation of that model. Published models are available in the literature, but the level of detail provided in the publications (and their supporting material) may be incomplete. From a validation perspective, the publications often provide insufficient documentation. Critical components or details that are mandatory for external model validation are often lacking. However, a team performing the external validation needs these details to be available. In the ideal situation, the original developer of the model is involved with (or directly available to) the team performing the validation.

Selection of the model to be validated was also informed by the *specific interest of one or more partners* participating in ROADMAP. Clearly, disease progression models in general are relevant for many partners. Partners, however, may have a preference for a certain model based on specific properties of that model. These preferences were taken into account when selecting the models for validation.

The *first model* we selected was the *Handels Kungsholmen MMSE Model (Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365).* For validation, we focus on the model that estimates the changes of cognition (as assessed by the MMSE) in incident AD dementia cases. The model poses limited data requirements. To perform the validation, only age, date of diagnosis, and MMSE measurements are needed. As a result, we believe many data sources will be able to provide this information and can participate in the validation. This would be an ideal model to test the validation pipeline in many environments. Moreover, the original author of the paper (Ron Handels) is a member of WP4 and will be able to provide detailed information we need for validation.

Although the data required for validation may be available in a given data source, differences in study populations and different data collection methods may severely hamper validation efforts. Validation of the Handels MMSE model will, in all likelihood, be in principle possible with many data sources – a number of data sources will have MMSE measurements for patients with AD. We must address during validation a number of issues relating to the source population and methods used in

data collection. The data used to derive the Handels MMSE Model were obtained from inhabitants registered in the Kungsholmen district of Stockholm, Sweden, who were aged ≥75 years in October 1987, had no dementia, MCI, or an MMSE < 20 at baseline, with incident AD-type dementia (either AD or mixed AD & vascular dementia) during follow-up. If the validation is performed in, for example, the IPCI data base, one needs to consider differences in the source population and data collection processes. IPCI is a GP-based data source in the Netherlands, where the GP has a gatekeeper role. Restricting the analysis to individuals in IPCI who are 75 or older, to match the sample with the Kungsholmen one, is easy. Matching for education or socioeconomic factors, for example, is not possible. Moreover, the process of collecting data in Kungsholmen involved a screening assessment followed by regular follow-up visits. In IPCI, the data are the result of routine care being delivered and as a result, the structure that characterises a cohort study with timed visits is absent. When interpreting the validation results, these aspects need to be taken into account. In general, the purpose of the validation exercise is to assess the performance of the model in a population that is different from the development cohort, but with characteristics that match that cohort as closely as possible.

The second model we selected was the *Novartis Longitudinal Model (Model for APCC time profile and time to first diagnosis of mild cognitive impairment or dementia due to Alzheimer's disease (AD) in elderly, cognitively normal individuals at risk to develop symptoms of AD, ROADMAP Deliverable 4.1, 2017)*. In this model, developed under leadership of Novartis, the objective was to model the pre-symptomatic time course in the AD prevention setting. Compared to the Handels MMSE model, this model addresses a different disease stage: the pre-symptomatic period. Novartis, who developed the model, is participating in WP4 and will be able to provide the detailed information that is needed for validation.

The model requires, amongst others, APCC and APOE-ε4 status. EHR data sources typically do not have information on APOE-ε4. Moreover, the use of APCC in cohorts is uncommon. As a result, further exploration of data sources is required to determine which data sources would, in principle, be able to participate in the validation exercise.

The final model we selected was the Eli Lilly PenTAG/GERAS Institutionalisation Model *(Healthcare and societal costs related to the time to institutionalisation in a community-based cohort of patients with Alzheimer's disease dementia, ROADMAP Deliverable 4.1, 2017).* The validation will focus on the model that estimates time to institutionalisation. The model incorporates measures of cognition, function, and behaviour. The challenge will be to find data sources that contain these measures, or apply algorithms or statistical methods to align different scales. Eli Lilly, who lead the extension of the original PENTAG model, is participating in WP4 and will be able to provide detailed information we need for validation.

The next steps in the validation are to develop Statistical Analysis Plans for each validation, and to discuss in detail with the various data sources the data requirements of each validation. To structure the validation process, we will use the TRIPOD checklist for validation as a guiding principle and specify, for each model validation exercise, a dedicated TRIPOD validation checklist. A validation pipeline will then be implemented to perform various validation exercises. The results of these exercises, and the challenges and limitations of the validation methodology will be discussed in ROADMAP Deliverable 4.4.

Annexes

Annex I. Models Identified in Deliverable 4.1

Table 1 provides an overview of the models identified in the literature. Table 2 shows the unpublished models provided by industry. For details on the methods used in the literature review and a more detailed description of each model, we refer to Deliverable 4.1.

Table 1. Disease progression models identified in the literature.

1	Stern ADAS-Cog Model (1994)
	Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiat. 1994;151:390-396.
2	Stern Growth Model (1996)
	Stern Y, Liu X, Albert M, et al. Application of a growth curve approach to modeling the progression of Alzheimer's disease. J Gerontol A-Biol. 1996;51:M179-184.
3	Smith ADAS-Cog Model (1996)
	Smith F. Mixed-model analysis of incomplete longitudinal data from a high-dose trial of tacrine (Cognex) in Alzheimer's patients. J Biopharm Stat. 1996;6:59-67.
4	Stewart MMSE Model (1998)
	Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. Int J Geriatr Psych. 1998;13:445-453.
5	Fenn and Gray MMSE Model (1999)
	Fenn P, Gray A. Estimating long-term cost savings from treatment of Alzheimer's disease. A modelling approach. Pharmacoeconomics. 1999;16:165-174.
6	O'Brien MMSE Model (1999)
	O'Brien BJ, Goeree R, Hux M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc. 1999;47:570-578.
7	Kungsholmen-MMSE Model 1 (Jonsson et al 1999)
	Jonsson L, Lindgren P, Wimo A, Jonsson B, Winblad B. Costs of Mini Mental State Examination-related cognitive impairment. Pharmacoeconomics. 1999;16:409-416.
8	CERAD-MMSE Model 1 (Mendiondo et al 2000)
	Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. Stat Med. 2000;19:1607-1616.
9	CERAD-MMSE Model 2 (Ashford and Schmitt 2001)
	Ashford JW, Schmitt FA. Modeling the time-course of Alzheimer dementia. Curr Psychiat Rep. 2001;3:20-28.

10	AHEAD Model (Caro 2001)
	Caro JJ, Getsios D, Migliaccio-Walle K, Raggio G, Ward A. Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. Neurology. 2001;57:964-971.
11	CERAD-CDR Model (Neumann 2001)
	Neumann PJ, Araki SS, Arcelus A, et al. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. Neurology. 2001;57:957-964.
12	Rotterdam MMSE Model (McDonnell 2001)
	McDonnell J, Redekop WK, van der Roer N, et al. The cost of treatment of Alzheimer's disease in The Netherlands: a regression-based simulation model. Pharmacoeconomics. 2001;19:379-390.
13	Fuh CDR Model (2004)
	Fuh JL, Pwu RF, Wang SJ, Chen YH. Measuring Alzheimer's disease progression with transition probabilities in the Taiwanese population. Int J Geriatr Psych. 2004;19:266-270.
14	Jones Memantine MMSE Model (2004)
	Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drug Aging. 2004;21:607-620.
15	Teipel MCI MMSE Model (2007)
	Teipel SJ, Mitchell AJ, Moller HJ, Hampel H. Improving linear modeling of cognitive decline in patients with mild cognitive impairment: comparison of two methods. J Neural Transm. 2007;Suppl 72:241-247.
16	Ito AChEI ADAS-cog Model (2010)
	Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, Tensfeldt T. Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement. 2010;6:39-53.
17	CERAD-SIB Model (Weycker et al 2007)
	Weycker D, Taneja C, Edelsberg J, et al. Cost-effectiveness of memantine in moderate-to-severe Alzheimer's disease patients receiving donepezil. Curr Med Res Opin. 2007;23:1187-1197.
18	Wattmo ADAS-Cog/MMSE Model (2008)
	Wattmo C, Hansson O, Wallin AK, Londos E, Minthon L. Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer patients in a naturalistic setting. Dement Geriatr Cogn. 2008;26:203-211.
19	CERAD-MMSE Model 3 (Getsios 2010)
	Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28:411-427.
20	Rive ADAS-cog Model (2010a and b)
	Rive B, Le Reun C, Grishchenko M, et al. Predicting time to full-time care in AD: a new model. J Med Econ. 2010;13:362-370.
21	Ito ADNI ADAS-cog Model (2011)

	Ito K, Corrigan B, Zhao Q, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. Alzheimers Dement. 2011;7:151-160.
22	Kavanagh Galantamine MMSE Model (2011)
	Kavanagh S, Van Baelen B, Schauble B. Long-term effects of galantamine on cognitive function in Alzheimer's disease: a large-scale international retrospective study. J Alzheimers Dis. 2011;27:521-530.
23	Lachaine Institutionalization Model (2011)
	Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Can J Psychiat. 2011;56:596-604.
24	Abner MCI Model (2012)
	Abner EL, Kryscio RJ, Cooper GE, et al. Mild cognitive impairment: statistical models of transition using longitudinal clinical data. Int J Alzheimers Dis. 2012;2012:291920.
25	Djalalov aMCI Model (2012)
	Djalalov S, Yong J, Beca J, et al. Genetic testing in combination with preventive donepezil treatment for patients with amnestic mild cognitive impairment: an exploratory economic evaluation of personalized medicine. Mol Diagn Ther. 2012;16:389-399.
26	Gomeni AChEI ADAS Model (2012)
	Gomeni R, Simeoni M, Zvartau-Hind M, Irizarry MC, Austin D, Gold M. Modeling Alzheimer's disease progression using the disease system analysis approach. Alzheimers Dement. 2012;8:39-50.
27	NACC-UDS CDR Model (Spackman et al 2012)
	Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Curr Alzheimer Res. 2012;9:1050-1058.
28	Samtani MCI-AD ADNI ADAS-cog Model (2012)
	Samtani MN, Raghavan N, Shi Y, et al. Disease progression model in subjects with mild cognitive impairment from the Alzheimer's disease neuroimaging initiative: CSF biomarkers predict population subtypes. Brit J Clin Pharmaco. 2012;75:146-161.
29	Delor ADNI CDR-SOB Model (2013)
	Delor I, Charoin JE, Gieschke R, Retout S, Jacqmin P. Modeling Alzheimer's disease progression using disease onset time and disease trajectory concepts applied to CDR-SOB scores from ADNI. CPT Pharmacometrics Syst Pharmacol. 2013;2:e78.
30	Handels Kungsholmen MMSE Model (Handels 2013)
	Handels RL, Xu W, Rizzuto D, et al. Natural progression model of cognition and physical functioning among people with mild cognitive impairment and alzheimer's disease. J Alzheimers Dis. 2013;37:357-365.
31	Liu CDR/MMSE Model (2013)
	Liu W, Zhang B, Zhang Z, Zhou XH. Joint modeling of transitional patterns of Alzheimer's disease. PLoS One. 2013;8:e75487.
32	William-Faltaos ADAS-cog Model (2013)

	William-Faltaos D, Chen Y, Wang Y, Gobburu J, Zhu H. Quantification of disease progression and dropout for Alzheimer's disease. Int J Clin Pharm Th. 2013;51:120-131.
33	Yu MCI Model (2013)
	Yu H, Yang S, Gao J, al. e. Multi-state Markov model in outcome of mild cognitive impairments among community elderly residents in Mainland China. Int Psychoger. 2013;25:797_804.
34	Qiu ADNI ADAS-Cog Model (2014)
	Qiu Y, Li L, Zhou TY, Lu W. Alzheimer's disease progression model based on integrated biomarkers and clinical measures. Acta Pharmacol Sin. 2014;35:1111-1120.
35	Samtani ADNI CDR-SB Model (2014)
	Samtani MN, Raghavan N, Novak G, Nandy P, Narayan VA. Disease progression model for Clinical Dementia Rating-Sum of Boxes in mild cognitive impairment and Alzheimer's subjects from the Alzheimer's Disease Neuroimaging Initiative. Neuropsychiatr Dis Treat. 2014;10:929-952.
36	Hu Severity-Dependency Model (2015)
	Hu S, Yu X, Chen S, Clay E, Toumi M, Milea D. Memantine for treatment of moderate or severe Alzheimer's disease patients in urban China: clinical and economic outcomes from a health economic model. Expert Rev Pharmacoecon Outcomes Res. 2015;15:565-578.
37	Samtani ADAS-cog Bapineuzumab Model (2015)
	Samtani MN, Xu SX, Russu A, et al. Alzheimer's disease assessment scale-cognitive 11-item progression model in mild-to-moderate Alzheimer's disease trials of bapineuzumab. Alzheimers Dement Transl Res Clin Interv. 2015;1:157-169.
38	Green Multidomain Model (2016)
	Green C, Zhang S. Predicting the progression of Alzheimer's disease dementia: a multidomain health policy model. Alzheimers Dement. 2016;12:776-785.
39	Wattmo ADAS-Cog/MMSE/IADL/PSMS Model (2016)
	Wattmo C, Minthon L, Wallin AK. Mild versus moderate stages of Alzheimer's disease: three-year outcomes in a routine clinical setting of cholinesterase inhibitor therapy. Alzheimers Res Ther. 2016;8:7.
40	Guerrero Personalized Time-to-Conversion Model (2016)
	Guerrero R, Schmidt-Richberg A, Ledig C, et al. Neuroimage. 2016;142:113-125.

Table 2. Disease progression models developed by EFPIA Consortium members.

41	Roche Guo Model Extension (2017)
	Based on Guo et al. (Pharmacoeconomics. 2014;32:1129-39) and extended to multiple order Markov chain structure.
42	Novartis Longitudinal Model (2017)
	Unpublished prevention longitudinal model describing time-to-MCI and time-to-dementia in correlation with biomarkers time course.
43	Eli Lilly PenTAG/GERAS Institutionalisation Model (2017)
	Unpublished time-to-institutionalisation model based on Green's PenTAG model updated with recent data from the GERAS study.