D6.3 Guiding principles and recommendations for the development and incorporation of RWE into clinical and market access development plans for AD

116020 - ROADMAP

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

WP6 - Regulatory and HTA Engagement

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Definitions

- **Real World Evidence (RWE)[1].** RWE is the evidence derived from the analysis and/or synthesis of real-world data (RWD).
- **Real World Data[1].** An umbrella term for data regarding the effects of health interventions (e.g. safety, effectiveness, resource use, etc.) that are not collected in the context of highly-controlled RCTs. Instead, RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data.
- 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. Aagentschap 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)
    - TAKEDA. Takeda Development Centre Europe LTD (United Kingdom)

[1] Definitions taking from the IMI GetReal 'Glossary of Definitions of Common Terms'.

- HLU. H. Lundbeck A/S (Denmark)
- LUMC. Academisch Ziekenhuis Leiden – Leids Universitair Centrum (Netherlands)
- Memento. CHU Bordeaux (France)

- **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

Although there are a growing number of well-reported late stage clinical trial failures in Alzheimer's disease (AD), the introduction of a disease modifying therapy within the next 5 years may be anticipated. These treatments are likely to target AD in the earlier disease stages, unlike drugs that are currently available that treat symptoms of moderate to severe dementia. Therefore, there is a need to establish a consensus on regulatory and health technology assessment (HTA) requirements for AD as a new drug will have to go through regulatory and HTA assessments before it becomes available to patients. This paper reports the discussions and activities of the regulatory and HTA expert advisory group (EXAG) of the 2-year ROADMAP (real-world outcomes across the AD spectrum – a multimodal data access platform) project. The EXAG discussions identified a lack of consensus on validated outcomes in the earliest AD disease stages, the need for filling gaps between outcomes used across clinical trials and real-world settings, and the role real-world evidence might have in characterising the impact of a possible disease-modifying therapy on caregivers, resource use, and long-term outcomes.

Key points

- Although a number of disease-modifying drugs for Alzheimer's disease are under development, none have made it to the market yet. These new treatments are targeting earlier stages of the disease and therefore, the HTA and regulatory experience with currently licenced AD drugs will only be partially applicable to the approval and reimbursement of newer drugs.
- There is a need for validated and widely accepted outcomes that capture the early stages of AD, including prodromal disease and mild cognitive impairment
- Real-world evidence will be needed to better characterize the impact new treatments will have on outcomes, caregivers, and healthcare systems.

1. Introduction

It has been more than a decade since the last drug therapy for the symptomatic treatment of dementia received a marketing authorisation in Europe. Since then, there has been a move towards the development of disease-modifying drugs in Alzheimer's disease (AD). We now know that AD is characterised by a long preclinical phase during which the disease starts developing in the brain prior to any detectable cognitive or functional changes[1]. Following the pre-clinical phase there is a variable but relatively short prodromal period - typically between 4 and 5 years - when early cognitive and functional changes emerge prior to a diagnosis of AD. It is likely that initial disease-modifying treatments will be offered to people with prodromal AD who have positive AD markers (amyloid and/or tau) and mild cognitive impairment (MCI) but have not yet developed sufficient functional impairment for a dementia diagnosis[1,2].

Broadly, a new drug will need to demonstrate a positive benefit-risk profile before a marketing authorisation will be granted by a regulatory agency such as the European Medicines Agency (EMA) or the Swiss Agency for Therapeutic Products, Swissmedic. Health technology assessment (HTA) bodies will subsequently perform assessments to advise healthcare payers whether a new drug provides added value and should be made available in a publicly-funded healthcare system. As disease-modifying drugs will be targeting earlier disease stages than currently licensed treatments, it is not apparent what type of evidence base might be required for these products to go through regulatory and HTA procedures, or whether there is alignment in expectations of regulators and HTAs regarding evidence supporting the value of disease-modifying drugs.

Although there are a growing number of well-reported late stage clinical trial failures[3], the introduction of a disease modifying therapy within the next five years may be anticipated. As people with AD generally will not have access to new drugs unless they reimbursed by healthcare payers, there is an urgency to establish a consensus on these regulatory and HTA requirements if Europe's healthcare systems are to be ready to facilitate access to these important treatments. This paper reports the discussions and activities of the regulatory and HTA expert advisory group (EXAG) of the ROADMAP (real-world outcomes across the AD spectrum – a multimodal data access platform) project.

2. The ROADMAP project

The ROADMAP project provides the foundation for a European data platform for real-world evidence in AD. Funded through the Innovative Medicines Initiative (IMI), the 2-year project running from November 2016 to October 2018 was a public-private partnership that brought together academic partners, manufacturers (including those with disease-modifying drugs currently under development), data providers, a patient advocacy organisation, a regulatory agency, and an HTA body[4]. The objective of ROADMAP was to provide the foundation for an integrated data environment and framework for real-world evidence in AD. The project consisted of different work streams, organised in work packages on the following topics: outcome definitions; identification, mapping and integration of real-world evidence; disease modelling and simulation; and health economics. ROADMAP outputs can be found on the project website (www.roadmap-alzeimer.org).

ROADMAP recognised that in order to ensure the project produces outputs that are not merely of high scientific quality but might also be usable in a regulatory and HTA context, it will be paramount to consider European regulatory and HTA requirements. Therefore, ROADMAP established the EXAG consisting of regulatory and HTA experts from different European countries that provided the project with periodic input and feedback. The EXAG discussions were confidential, non-binding, and experts participated as individuals rather than as official representatives of their employers. During the course of the project, EXAG meetings were held every three months and different topics were discussed at these meetings, including priority outcomes across a range of stakeholders in AD, validation of a disease-progression model currently under development, and pharmacoeconomic modelling considerations.

The EXAG meetings followed a common format, with ROADMAP researchers presenting ongoing work from the different work streams, followed by discussion with the EXAG members who would comment on the findings presented. Some of the discussions were had with a hypothetical disease-modifying therapy for AD in mind, but none of the discussions at EXAG meetings were product-specific. Minutes of all EXAG meetings were drafted and checked by the EXAG members before being finalised and shared with the ROADMAP consortium partners. The EXAG meeting minutes of five separate meetings that took place throughout the ROADMAP project were used to develop this paper.

2.1. Data cube

ROADMAP had access to a large number of data sources including population-based databases, national registries, electronic health records (primary and secondary care), disease registries, and randomised controlled trial (RCT) data. All of these data sources might contain valuable information about people with AD or dementia, but not all data sources will contain the same information or cover all the stages of the disease. ROADMAP visualised this problem as a data-cube with data sources, disease stages and outcomes as the three

axes (Figure 1). Populating the cells of the cube for each data source enabled the available data to be described with gaps in the data becoming apparent, providing all stakeholders with a rapid and convenient summary of the evidence base.

Identifying gaps in the AD evidence base will inform scientific, clinical, and regulatory activity as it will direct thinking on the collection and evaluation of further evidence. By identifying gaps now, rather than once the first disease-modifying drug becomes available, ongoing and future work can begin to fill the gaps. The goal was to provide a sufficient evidence base to facilitate rapid decision making by HTA bodies and regulators. Given the potentially significant public health impact of a disease-modifying treatment for AD, many HTA bodies and regulators have a keen interest in this field.

2.2. Priority outcomes

An ‘outcome' can be defined as the result of an intervention[5] and for a drug the most important outcome is the extent to which it maintains or improves health and wellbeing. The EXAG agreed that regulators will usually approve drugs based on a demonstrated effect on a certain clinical endpoint (preferably measured within an RCT) whereas HTA bodies will also consider and tend to prefer long-term outcomes that will include health-related quality of life, life expectancy, healthcare costs, and (depending on the HTA body) societal costs. For a new disease-modifying therapy in AD, these are the outcomes that can be expected to be considered relevant.

Late-stage AD is characterised by cognitive impairment, functional decline and behavioural disturbances[6] and with further progression of the disease, institutionalisation/full-time care also becomes an important outcome. In the National Institute for Health and Care Excellence (NICE) appraisal of ‘Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease’[7], outcomes of interest included measures of disease severity, response to treatment, behavioural symptoms, mortality, the ability to remain independent, admission to full-time care, the health-related quality of life of patients and carers, and adverse effects of treatment. The four drugs covered by the appraisal were approved either by national regulatory agencies (donepezil, galantamine) or the EMA (rivastigmine, memantine). The primary outcomes cited in the regulatory assessments related to cognition - which is usually measured by the Alzheimer’s disease assessment scale - cognition (ADAS-cog) - and functioning; quality of life and other drivers for HTA were not included. Cognition was not considered as a primary outcome for memantine as in people with moderate to severe AD, cognition would be difficult to assess and minor changes would be inconsequential unless they translated into global and functional improvements[8].

For the earlier disease stages of pre-clinical and prodromal AD, outcomes related to cognition and the rate of cognitive decline may be more important than functioning, as functioning might not yet be severely affected in the earliest disease stages. This has implications for the regulatory and HTA context as the primary outcomes of RCTs, as well as their patient

populations, might well differ from those used for the approval of currently marketed drugs. For example, the phase III trials for solanezumab (a disease-modifying drug that failed to demonstrate efficacy) all had cognitive decline as measured by ADAS-cog as a primary endpoint[9]. Due to the variety and complexity of cognitive-related outcomes, the EXAG discussed that a new consensus may be required which will lead to the development of new pharmacoeconomic models that are able to model the entire disease spectrum, including the prodromal and early-AD stages.

The EXAG discussions (Table 1) identified that valid and well-established outcome measures in the early, often asymptomatic, disease stages are lacking, making defining and measuring the most relevant outcomes in the pre-clinical and prodromal disease stages a key priority for ROADMAP. A review of priority outcomes for key stakeholder groups that was performed by ROADMAP has been published.[10] The effectiveness of a disease-modifying drug in the pre-clinical disease stage will be driven by the ability to either prevent or delay clinical symptoms, resulting in a higher prominence for cognitive symptoms rather than functional impairment which normally only becomes more apparent during the later stages of the disease. The EXAG discussed what a meaningful delay in disease progression might look like, but agreed that once a drug might go through regulatory and HTA processes, this would depend on whether the drug's effect would be considered clinically relevant and what evidence would be available to support this. Therefore, the EXAG found that further work is needed to establish the best instruments to reliably measure cognition in people with AD in the pre-clinical stages. Furthermore, it will be essential to ensure that these instruments will not just be applicable in RCTs but ideally, cognition should be measured using instruments that can measure cognition across settings including in the home environment.

Existing regulatory procedures can help validate and build consensus on new outcome measures in AD. The EMA offers a procedure for qualification of novel methods that can assess new methods for use in drug development, and joint qualification advice with HTA bodies is offered. The EXAG stressed the importance of pursuing such strategies once ROADMAP's outputs had matured, as the EXAG discussions are not intended to replace official procedures or advice. Therefore, existing routes for validation of endpoints, instruments, and disease models will need to be followed.

2.3. Disease progression and economic modelling

With the identification of changes in the brain that can be identified many years before first AD symptoms develop, the disease staging of AD has shifted and is now understood to have a long preclinical phase during which people show no signs of the disease but can test positive for disease markers that can be used to identify people at risk of developing AD and therefore might be candidates for treatment with disease-modifying therapies. AD disease stages across the disease continuum and AD outcomes are closely related, as within models, disease stages are usually defined by outcomes, although the people in the preclinical disease stage are defined by testing positive for amyloid, tau, or both.

Disease stages in previous disease progression models have been defined by mini mental state examination (MMSE) score or by institutionalisation. For many diseases, economic modelling will see the amount of uncertainty surrounding outcomes increasing over the model's time horizon. In AD the situation is the reverse: there is high uncertainty – due to a lack of data - about the disease and how it affects outcomes in the pre-clinical and earlier disease stages – the starting point of a full disease progression model - whereas at the moment, the later stages of the disease are relatively better characterised. This has a big impact on extrapolations of long-term effects based on short-term outcomes and therefore having data available that can mitigate some of this uncertainty is critical. The EXAG found that there is a role for real-world evidence to mitigate some of this uncertainty, but the data cube identified gaps between the outcomes relevant across the disease stages and those commonly measured in clinical practice.

2.4. Regulatory versus HTA considerations

The EXAG has members with regulatory as well as with HTA expertise which proved helpful in discussing divergent requirements. The use of different endpoints for regulatory and HTA purposes was discussed, especially the preference for health-related quality of life from the HTA perspective whereas historically this is not a prominent endpoint in regulatory assessments that tend to focus more on clinical endpoints. Yet, it was noted that from a regulatory point of view, health-related quality of life could be considered in regulatory assessments if manufacturers would choose to make it a more prominent endpoint in their studies. The EXAG stipulated that impacts on cognition and functioning will be important from a regulatory perspective, and that HTA bodies will be interested in the clinical significance of such impacts and the cost-effectiveness of the treatment.

Several HTA bodies will not merely consider the impact of AD on people with the disease but will also include the impact the disease has on a caregiver's quality of life in their assessments. Regulators will assess whether they consider benefit-risk of a product positive or not. The EXAG noted that in theory regulators could consider the impact on caregivers, if there is compelling evidence that this should be considered as part of the benefit-risk profile of the product. These discussions illustrate the benefit from having a multi-disciplinary advisory group where questions are considered by regulatory and HTA experts simultaneously.

2.5. Differences in national and regional healthcare settings

Once AD has progressed to a more severe disease stage, people generally will need various types of care, including unpaid and long-term formal care provided at home or in an institutional setting. The delivery and availability of different types of care will vary considerably between countries. However, within countries there can also be substantial differences in the availability of care, or even, in the impact the disease might have on patients

and carers. The EXAG found that a health economic model would need to be adapted according to the setting it will be used to evaluate a disease-modifying drug, given the differences in preferences between HTA bodies.

2.6. Real-world evidence

ROADMAP has mapped different possible sources of real-world evidence across disease stages and identified a number of gaps that were discussed with the EXAG. Gaps that were identified included the use of different measures for cognition and functioning in RCTs versus instruments that are used in clinical practice, limited collection of biomarker status in clinical practice, and a lack of follow-up of disease progression on disease instruments (such as MMSE) once an initial diagnosis is made. The EXAG noted that there is a lack of standardisation in the collection of real-world data and that there is a need to establish consensus on what the most important data are in the context of AD, such that improvements in data collection efforts can be made and gaps can be filled. The EXAG noted that existing procedures, such as qualification of novel method and scientific advice – offered by the EMA and with the possibility to involve HTA bodies – would allow for the validation of outcome measures and a disease progression model in AD.

Real-world evidence can be used for many different purposes and is used in HTA for establishing prevalence, long-term outcomes, and costs,[11] but is not often used for establishing comparative effectiveness of new drugs, although HTA bodies do sometimes accept real-world evidence when RCT data are not available.[12] There are limitations to the use of real-world evidence for a drug's effectiveness, and most HTA bodies place real-world evidence below RCT data in terms of quality of evidence, stipulating that it should be used to confirm or supplement, rather than substitute RCT data.[12] The EXAG highlighted these limitations in its discussions and in discussing the role of real-world evidence, but did note that there might be a role for real-world evidence in AD, for example, in providing evidence on the impact of the disease on carers, resource use, and disease progression.

3. Conclusions

During the ROADMAP project, five different meetings with its EXAG explored a number of regulatory and HTA considerations for a future disease-modifying drug, of which the most important ones are summarised in this paper (Table 1). ROADMAP was part of a group of IMI projects called the Big Data for Better Outcomes Programme and therefore the project also explored the role that real-world evidence can play in AD, and specifically, in supporting new therapies making their way to people who need them. Notwithstanding, in light of all the challenges of bringing a disease-modifying drug for AD to patients, ROADMAP and its focus on the role of real-world evidence is only a part of a bigger puzzle, and other research projects, for example those that are aimed at improving our understanding of the role biomarkers play in disease progression, are needed.

Many of the challenges that the EXAG identified could be solved by generating better real-world data and by better utilising existing data sources in AD. Therapies that target the earlier phases of the disease will have inherent uncertainties about the long-term impacts on patients, caregivers, but also on healthcare systems. Therefore, there is a clear need to agree and establish international consensus on the AD outcomes that will facilitate and inform regulatory and HTA decision-making, which has been initiated within ROADMAP. The challenge will be to ensure that data sources across Europe will be able to generate the evidence needed to support regulatory and HTA decision making. Filling the gaps in the ROADMAP data cube would provide a step-change in preparing Europe's healthcare systems for the future disease-modifying agents that are so urgently needed.

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ANNEXES

ANNEX I.

Table 1: ROADMAP's regulatory and HTA expert advisory group recommendations.

These recommendations were formulated based on meetings with the project's different work packages.

Topic	Recommendations
Priority outcomes	Establish the rationale and justification for the selection of priority outcomes in pre-clinical AD and prodromal AD/MCI
	Establish accepted outcomes for regulators, HTAs and payers for (1) defining prevention of AD and (2) delayed AD onset
	Ensure that instruments used for measuring these outcomes can distinguish between AD and other forms of dementia
	Explore how modern technology (apps, wearables) could assist in measuring cognition that could easily be used across settings
	Establish the caregiver-relevant outcomes (quality of life, health status, loss of income, carer time) that are important to capture for economic modelling
Disease progression and economic modelling	Real-world evidence will be required to support modelling assumptions as not all evidence to support modelling assumptions – including caregiver impacts, use of endpoints, correlation between disease stages and certain outcomes – can exclusively be generated from RCTs
	Sensitivity analysis will be necessary to examine the robustness and impact of modelling assumptions on outcomes
	The data cube approach will allow ROADMAP to identify current gaps in available data from different data sources and will identify activities needed to fill those gaps
	Better evidence is needed on the impact on caregivers in the *different stages* of the disease, both in the earlier stages when the impact might be minimal, and in the later stages where the quality of life of caregivers might be substantially affected, and how this impact can be valued
	The degree of uncertainty arising from a switch from patient reported to proxy reported quality of life outcomes, particularly as these perspectives are not always compatible, will need to be examined
	A pharmacoeconomic model will have to be able to accommodate for differences between national and regional settings (i.e. delivery of care, relevant costs and outcomes to include)

	Real-world data will be required to provide the required regional and national information

AD Alzheimer's disease; MCI mild cognitive impairment; HTA health technology assessment; ROADMAP Real-world outcomes across the AD spectrum: a multi-modal data access platform.

Figure 1: ROADMAP Data Cube