D2.3.1 Stakeholder generated lists of priority real world evidence relevant outcomes for Alzheimer's disease

116020 - ROADMAP

Deliverable 2.3.1 (INTERIM REPORT)

WP2 – outcome definition

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Due date	31/10/2017
Delivery date	14/12/2017
Deliverable type	R
Dissemination level	PU

Description of Work	Version	Date
	V1.0	27/10/2016

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Document History

Version	Date	Description
V1	09/11/2017	First draft
V2	30/11/2017	Second draft after internal peer review (Raphael Wittenberg, LSE; Emilse Roncancio Díaz, GE)
V3	14/12/2017	Final draft after Consortium review (Dianne Gove, AE; Christophe Bintener, AE)

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**. 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)
- **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

A series of stakeholder activities is in process to define a priority set of real world dementia focussed outcomes across the disease spectrum and to define what constitutes a meaningful delay in disease progression.

Effective collaboration with international partners in WP2 was undertaken to design and validate three separate surveys and workshop activities. Piloting the surveys has facilitated design improvements and identified potential technical issues, enabling surveys that will increase response rates at final implementation stage. Access to numerous distribution lists and memory clinics for Europe-wide survey distribution has been successfully negotiated. Data collection has commenced in a memory clinic in Girona, European-wide data collection from electronic surveys will commence shortly.

Separate stakeholder workshops have been conducted with people with dementia (PwD) and with carers. These workshops produced 11 hours of data that support and guide the production of the prioritised list of outcomes and inform the interpretation of meaningful delay in disease progression. Workshops with professionals are currently under way.

All the findings will be compiled by March 2018 and will be used to produce the prioritised list of outcomes, stratified by stakeholder relevance, at the end of April 2018.

1. Introduction

The health care challenge facing Europe of an ageing population, rising costs, and more specialised treatments is nowhere more acute than for dementia, with Alzheimer's disease (AD) as a leading cause of this neurodegenerative condition. Real world evidence (RWE), produced from the effective use of real world data, can potentially help better inform regulators (efficacy & safety), healthcare providers and payers (cost effectiveness and budget impact), industry (pricing & manufacturing), and scientists (mechanisms & pathways) in decision making regarding the re-purposing of current treatments and development of new treatments. Real world data exist in multiple sources beyond clinical research settings, such as patient healthcare records, disease registries, and claims or billing records. Currently, there is a lack of an integrated data environment in addition to guidance for the use and interpretation of RWE.

The European Union, with the world's most diverse and sophisticated health care systems, is uniquely positioned to develop and exploit technologies to support the collection and use of RWE. ROADMAP has brought together 22 partners from across Europe to develop a set of consensual key outcome measures and data integration tools related to AD, as well as specific guidelines on the handling and interpretation of RWE data. The work being undertaken by the ROADMAP consortium has been divided into eight work packages, each being co-led by a partner from academia and a partner from industry, with the exception of WP7 which is co-led by a partner from a patient association and a partner from industry.

WP2 aims to identify a priority set of real world dementia outcomes, focussing on AD, across the disease spectrum from the pre-clinical to severe stages from a diversity of stakeholder perspectives. WP2 also aims to identify what constitutes a meaningful delay in disease progression from clinical, humanistic and economic perspectives.

There are four specific activities being undertaken to achieve these aims:

- Pragmatic literature review to generate initial list of outcomes
- Systematic literature review to evaluate what is already known about outcome priorities and criteria for meaningful delay in disease progression
- Stakeholder engagement activities to determine a priority set of outcomes and criteria for meaningful delay in disease progression including questionnaire surveys and Patient and Public Involvement (PPI) workshops
- Gap analysis, undertaken in collaboration with WP3, to identify priority outcomes not adequately captured using currently available real world data.

The pragmatic literature review has been completed and was made public as deliverable D2.1. A separate interim report has been produced for documentation of progression made on the systematic literature review. This report provides an interim account of progress with the research surveys and the PPI workshops activities to date.

2. Stakeholder engagement – surveys

2.1. Introduction

Eliciting the views of patients, informal carers and professionals concerned with dementia, in particular AD, is an important part of ROADMAP Work Package 2's (WP2) stakeholder engagement work. Surveying stakeholder groups will provide the opportunity to efficiently evaluate the relative importance of various potential priority outcomes for assessing meaningful change in disease progression, from early through to late stages of the condition. As distributing surveys will have wider reach than other types of planned stakeholder engagement activities, we will be able to better capture the diversity of perceptions and values that are held by different stakeholder representatives.

Our survey work stream is designed to build on work which identified the 'universe' of outcomes and progression markers for AD across the spectrum relevant for real world evidence generation in deliverable D2.1, the initial list of priority AD related outcomes and outcome measures as output from this WP. We will now prioritise identified outcomes that indicate meaningful change in disease progression, which will also be further investigated qualitatively.

To our best knowledge, brief surveys to elicit perceptions of priority AD-related outcomes and meaningfulness of a delay in disease progression from all stakeholder groups, as defined by ROADMAP WP2 group members, have not yet been developed. However, we have so far identified a few survey studies related to key AD outcomes from a joint patient and caregiver perspective [1], lay person perspective [2] and general practitioner (GP) perspective [3, 4], in addition to a 30 minute online questionnaire study implemented to assess current opinions and perceptions surrounding AD and dementia from a multi-stakeholder perspective [5]. There are also qualitative studies whose investigators used interviews and focus groups to establish key outcomes relating to AD diagnosis, treatment and care [6], most of which are from patient and carer perspectives [7-9]. All but two of these papers were retrieved by the SLR search and will be screened and appraised as part of that process. The others will be checked for relevance.

2.2. Methods

2.2.1. Survey participants

Our intended participants for our online surveys are individuals from a broad range of stakeholder groups of interest, including: patients, carers, clinicians, scientists, health economists, Health Technology Assessment (HTA) bodies, regulators, payers, industry, charities, advocacy groups and ethicists [10].

We also intend for patients and carers to complete our paper surveys. The paper surveys are to be distributed in memory clinics and via postal survey to enable us to extend our reach among hard-to-reach stakeholders or those who do not have internet access. These participants may have different sociodemographic characteristics and healthcare utilisation patterns compared to those who may complete an online survey.

2.2.2. Survey development and piloting

Through working sessions held via several teleconferences, we have developed separate surveys for patients, carers and professionals, collaborating with colleagues from WP2 partners such as Alzheimer Europe (AE), London School of Economics (LSE), F. Hoffmann-La Roche Ltd (Roche), Eli Lilly and Company Ltd (Eli Lilly), GE Healthcare Ltd (GE), Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAP JORDI GOL), Biogen Idec Limited (Biogen), University of Gothenburg (UGOT) and University of Oxford (UOXF). Alzheimer Europe's European Working Group of People with Dementia (EWGPWD) also contributed to the development and refinement of the patient and carer surveys during consultation workshops held on 4 and 5 September 2017.

Our surveys are in English, Spanish and Catalan. The patient survey has been designed to be dementia-friendly in its layout and use of language. As much as possible, we have avoided profuse use of technical language so then the surveys are accessible to all. The surveys are translated into Spanish and Catalan as our colleagues from IDIAP JORDI GOL offered translation as they saw it fit for the purpose of survey distribution.

To check content validity as well as wording of questions, their logic and technical aspects, we have piloted the online survey for professionals among the members of the ROADMAP consortium and colleagues of WP2 partners from Takeda, Lilly, Roche, UGoT and UOXF. The survey for professionals, created in SurveyMonkey, was open between 22 August to 8 September. Paper versions of the patient and carer surveys were also piloted by AE's EWGPWD on 5 September 2017, where we asked them to complete our surveys before providing oral feedback.

We also submitted the patient and carer surveys, in addition to the participant information sheet, to the Plain English Campaign to evaluate our use of lay language and to ensure there are minimal abbreviations and use of jargon.

Section 3.2., the results section, and documentation in the Annex give more details on the results of the pilot survey, and explain why some changes were made to the final versions of the surveys.

2.2.3. Survey content and format

Quantitative surveys have been designed to maximise the response rate. They should take 5 and 10 minutes to complete. A short cover page provides instructions for survey completion. A participant information sheet will be accessible via a hyperlink.

In the main section of each survey, there are questions about the importance of different aspects of mild cognitive impairment (MCI) and dementia at different stages of disease progression for assessing meaningful change in disease progression. The broad range of aspects that feature are based on outcomes listed in deliverable D2.1, the initial list of priority AD related outcomes and outcome measurement tools. We have not asked any questions on outcome measurement tools. The term dementia is preferred over AD for reasons of inclusivity and to appeal to many potential survey respondents from a diverse range of stakeholder groups. From a scientific point of view, this decision is justified as most cases of dementia are caused by AD.

Background questions seeking general information on the survey respondent are included. They will help us understand differences within and between groups that may be factors for determining the

importance of priority outcomes. In the surveys designed for patients and carers, we ask for information such as: date of birth, sex, country of residence, dementia diagnosis and disease severity. Professionals who work on dementia as a healthcare issue will answer questions about occupation and (the nature and extent of their) professional exposure to patients. Identifiable personal information will not be sought as part of the survey.

There will be an opportunity for survey respondents to provide comments in a free text section at the end of the survey.

The Annex includes screenshots of the online patient, carer and professional surveys.

2.2.4. Survey distribution

We will not at any point collect or hold identifiable personal data in UEDIN. For distribution of our surveys, we are co-ordinating the distribution of surveys through WP2 partners and affiliates to reach individuals who are subscribed to receive communications from bodies such as professional medical societies or networks. We have ensured that members of these email distribution have agreed to receive communications from third parties. Our surveys will mostly be distributed via e-newsletters in English.

We also plan to distribute paper surveys to patients and carers via memory clinics. Again, we will not be collecting or holding identifiable personal data in UEDIN.

In Spain, WP2 collaborators from IDIAP JORDI GOL are co-ordinating survey related activities, with a focus on Girona. In Oxford, a WP2 collaborator at UOXF is carrying out processes to secure the capability of distributing surveys in memory clinics and via post in Oxford. In Edinburgh, we are exploring the possibility of distributing surveys in one or more of our memory clinics.

In Table 1 below, we list information on distribution lists/clinics who have agreed or may agree to distribute our stakeholder surveys. Further details are provided on estimated reach, key contact person, possible timing of survey distribution, and target stakeholders.

Table 1 Distribution lists

Target stakeholders	Target distribution	Via	N (approx.)	Contact	When
Distribution agreed					
Researchers and clinicians (UK)	DPUK	Email/E-newsletter	800	Anna Myers, Bea Shelley, Jennie Hall	TBC
Researchers and clinicians, (Europe)	AMYPAD	Email	100	Emilse Roncancio-Diaz	TBC
Psychiatrists (UK)	Royal College of Psychiatrists	UK wide E-newsletter. Full sized article or one page 'advert'	4000	Helen McCormack	January 2018. Mid November deadline for article submission
Geriatricians (UK)	British Geriatrics Society	E-newsletter	2400	Marina Mello, Recia Atkins	Early-mid January. Send docs/links asap
Mix of professionals, PwD and carers (Europe)	Alzheimer Europe	E-newsletter. 'Top story' article	7700	Kate Ellis	Beginning of January
Researchers and clinicians (Sweden)	AgeCap centre, Sweden	Email	50	Silke Kern	Flexible
Psychiatrists (UK)	British Neuropsychiatry Association	E-newsletter. Ad may be possible.	2000	Jackie Ashmenall	They have monthly bulletins that go out at the end of each month. Increased no of emails to readership in the run-up to conference. Submit docs asap
Neurologists (UK)	British Neuroscience Association	eBulletin	2000	Alex Collcutt	Last Weds of Nov, possibly again in Jan 2018
PwD and carers (Spain)	Girona memory clinics	Paper	~100 over 1-2/ months	Anna Ponjoan and Josep Garre-Olmo	Ethics obtained and data collection commenced
PwD and carers	Oxford (UK) memory clinics and postal address list	Paper	~100 over several weeks	Alex McKeown	NHS ethics required before start
PwD and carers (UK)	Join Dementia Research	Online	~ 1000	Emma Law	Once ethical approvals in place
Mix of professionals (UK)	Dementia and Neuroprogressive Network	Online	370	Emma Law	Once ethical approvals in place
PwD and carers	Memory clinic in Edinburgh	Paper	? ~ 100 over several weeks	Suvankar Pal	Distribution plan to PwD and carer to be finalised
Distribution possible					
Researchers and clinicians (Europe)	EPAD	Email/E-newsletter	150	Craig Ritchie	

Researchers and clinicians (Europe)	MOPEAD	Email/E-newsletter	100	Christophe Bintener	
Researchers and clinicians (Europe)	Other IMI funded AD projects	Email/E-newsletter	?	? CSA centre at LSE? Synapse?	There are 11 IMI funded AD projects in total.
Various, incl. PwD, carers & charity reps (UK)	Alzheimer Scotland	Email/E-newsletter	6000	?	It is more than enough to go through AE but can approach AS if instructed
Various, incl. PwD, carers & charity reps (UK)	Alzheimer's Society	Email/E-newsletter	?	?	It is more than enough to go through AE but can approach AS if instructed
Mix of professionals, incl. routes to regulatory bodies (Europe)	Institutions ROADMAP partners belong to	Email?	?	Various	

2.2.5. Data collection and analysis

We will collect electronic data via SurveyMonkey. Identifiable information will not be collected. The survey will be accessible via a web link in an email invitation or an e-newsletter. We will export online data in csv format, which will be saved within a restricted access secure location on a University of Edinburgh server.

Paper surveys designed for self-completion by patients and carers will be distributed in memory clinics and/or by post to memory clinic patients and their carers. Pre-paid envelopes will be provided for the return of surveys to the following freepost address:

ROADMAP team at the Usher Institute
Nine Edinburgh Bio Quarter
9 Little France Road
Edinburgh
EH16 4UX

Our inclusion criteria for patients recruited via memory clinics are as follows:

- must be over 18 years of age
- must have a clinical diagnosis of MCI, dementia or AD
- survey participation must be voluntary

Willingness and ability to complete the survey will be taken to indicate capacity. A reason for declining survey response will not be required. Those with co-morbidities will not be excluded unless the co-morbidities render them unable to complete a survey.

In the memory clinics, patients and their carers will be invited to complete the survey after they have checked for their appointment. Completed surveys are to be collected in a return box close to the

reception desk or sent via a postage paid return envelope, should patients and carers wish to take the survey home. Return boxes will be collected by a member of the ROADMAP team on a regular basis. Completed surveys collected in Oxford will be sent to Edinburgh. All completed surveys will be stored in a locked secure file cabinet.

In Girona, some surveys will be interviewer-led as it has been judged appropriate to do so by our colleagues in IDIAP JORDI GOL.

Non-identifiable data from paper surveys will be manually entered and stored in a Microsoft Excel workbook within a restricted access secure location on a University of Edinburgh server. Data entry will be conducted by a member of the ROADMAP team. A proportion of the data entered will be spot checked by another member of ROADMAP team. Data cleaning will also take place in-house. Data from surveys completed in Spain will be entered locally by a member of the IDIAP JORDI GOL ROADMAP team; these colleagues also translated the surveys into Spanish and Catalan previously. They will be returned by secure electronic data transfer to the ROADMAP team in Edinburgh. Paper surveys that are completed in Spain will also be returned in batches to the ROADMAP team in Edinburgh by a member of the IDIAP JORDI GOL team.

We envisage that basic descriptive analyses of online and paper survey data will be conducted using statistical analysis software (e.g., R or STATA) to include means, medians, ranges, and 95% confidence intervals. Separate analyses of online and paper survey responses will be conducted, and analyses will be stratified by stakeholder groups. Outcomes will also be cross-tabulation by other variables such as:

- self-reported disease severity (patient survey)
- carer-reported disease severity (carer survey)
- age
- sex
- country of residence/work
- relation of carer to patient (carer survey)
- whether they live with the person with dementia (carer survey)
- hours spent caring or supporting the person with dementia (carer survey)
- whether or not a survey respondent interacts with people living with dementia in their professional capacity (professionals survey)
- how many years they have been in their profession
- how many years they have been working with AD or dementia (professionals survey)

UEDIN and UOXF are currently working together to prepare for statistical analysis and presentation of the findings.

2.2.6. Ethics Review

Research ethics committee review is being undertaken separately for each method of participant recruitment. Review for the online survey, for Europe wide distribution, is being undertaken by ACCORD Medical Research Ethics Committee (AMREC) at the University of Edinburgh. Review for

the UK postal and NHS clinic recruitment is being undertaken through the NHS Health Research Authority. Review for the clinic recruitment in Spain has been undertaken locally, coordinated by IDIAP JORDI GOL.

2.2.7. Output

Thereafter, we will produce deliverable D2.3, a summary report in the form of stakeholder generated lists of priority outcomes and disease progression markers. Our survey findings will form the foundation of deliverable D2.3 with findings from other stakeholder engagement activities constituting the remaining part.

2.3. Results

2.3.1. Pilot survey results

A pilot survey study was conducted in order to test the suitability of the survey itself in addition to the process of carrying out a survey study. This is a summary of what we did, feedback we received, including pilot survey results, and what changes we have made to improve the survey. What our surveys do not cover is also be addressed.

2.3.2. Results from the online pilot survey for professionals

Responses

We received 71 responses. Out of the 71 respondents who participated in the pilot survey, 47 completed all required questions, and thus the completion rate was 66.2%. The average amount of time spent on the survey was 11 minutes. At an aggregate level, attrition increased as respondents progressed through the survey. Out of the 71 respondents, 68 accessed the survey via the web link. The remainder accessed the survey via the SurveyMonkey email invitation. Initial problems with the SurveyMonkey email invitation on the first day may have been the reason for a preference for the web link.

Out of all the individuals (47/71) who completed all required questions about the pilot survey, 59.6%, or 28 respondents, were able to provide accurate answers ‘most of the time’. Eight respondents (17%) were able to answer accurately ‘about half of the time’.

A breakdown of the results from questions answered is detailed a document that can be accessed in the Annex.

Feedback

Some professionals reported that the survey would benefit from a clear definition of ‘meaningful change in the disease’.

It was also highlighted that the terms ‘MCI’, ‘mild AD’ and ‘moderate-severe AD’ are confusing as we mix terminology used for syndromic diagnosis and aetiological diagnosis. This contributed to some of the difficulty of answering the first main questions about types of clinical information.

Out of the 71 respondents, 67.6% (48/71) responded to questions about types of clinical information, symptoms and experiences, and personal and economic aspects. Respondents may have become fatigued after background questions were completed. Respondents had to complete most rows of question (2 out of 3 or 3 of out 5 questions in each of the set of questions) in order to move on to the next page; this may have caused attrition too.

The first question about 'confirming a clinical diagnosis' may have thrown some respondents off as the overarching key question does not fit these questions about clinical information as well as subsequent questions.

The questions that follow for which respondents must only choose three most important aspects at each disease stage was answered by 66.2% (47/71) of all respondents. These questions seemed to better differentiate the importance of all aspects at each stage of the disease.

The question beginning, "Please provide further details on clinical, symptomatic, personal and economic aspects," yielded 9 responses; 4 of those responses were 'N/A' or none. Seven out of eight responses to the question, "Is there anything else you would like to tell us?" was no.

2.3.3. Results from the paper pilot survey for patients and carers

Responses

One of the carers did not complete the survey as she was not a close relative of a PwD. All carers provided oral feedback to AL, DG and AD. The PwD did not complete the surveys, instead opting for extensive discussion of suggestions for improvement with MN and CBi.

Feedback

Carers thought that it was absolutely appropriate to send online surveys in addition to paper versions. They also highlighted the need for details of a dementia or carers helpline to assist anyone who may feel emotionally overwhelmed by questions in our survey. PwD would prefer online surveys over paper surveys that are completed in memory clinics. Going to memory clinics can be a stressful experience which involves undergoing multiple types of assessments.

Overall, the use of language in the survey was viewed as passive, repetitive and somewhat patronising. The overall advice was, "keep the language short, simple and direct." PwD suggested that 'severe' was a 'bad' word with too many negative connotations that might be distressing. 'Advanced' was suggested, as was 'stage'. Some members were happy with 'severe.' Other suggestions pertaining to the writing style were provided. For example, underlining and text in bold was not considered necessary. The carers did not seem to have a problem with the language used.

For the carers, the questions about approximate hours spent on the different types of support or care was not well received. They did not know or responded with 'full-time', '24/7' or they left it blank. It was reported that time spent on each activity also did not take into account emotional impact of caring responsibilities or impact on other areas of their lives. The question about their paid employment does not take into account reduced productivity or efficiency, only loss of paid employment and reduced/increased hours.

The PwD did not think that the questions about types of clinical information, such as 'confirming a medical diagnosis' was of highest priority as an outcome. The carers did not have any strong feelings

about this question. However, the carers were confused by the request to pick the one most important aspect in the questions that followed the questions for which rating was required they found it repetitive. They asked why we decided to have ratings on a scale of importance instead of ranking options.

The phrase 'significant events in your/their life' was interpreted in a way that has not been encountered during the survey design process with WP2 researchers and clinician researchers. The carers thought we meant significant milestone events in the life course, e.g. not being physically or mentally present at a daughter's or son's wedding, rather than milestone events in the disease course, e.g. starting antipsychotic medication.

The longevity versus Quality of Life (QoL) question was considered very important and should be kept. QoL was considered most important: this opinion was unanimously held. Carers described the importance of QoL during the mild and moderate stages as most important.

The question beginning with, "Please provide further details on medical, symptomatic, personal and financial aspects…" was considered to be redundant as it is too long and confusing. The carers did not think to add any other thoughts in these free text boxes.

The PwD and carers expressed resentment when they realised that our surveys would be addressing AD focussed outcomes only. Some members of AE's EWGPWD have dementia due to other aetiology and they felt that the aspects (outcomes) of dementia we list are also experienced by them and their exclusion from survey participation was not particularly kind nor just.

The documents we sent to the Plain English Campaign have all received 'Crystal Marks' for clarity. They were received after two rounds of revisions of documents were made.

Changes that have been made

As the PwD had strong opinions about the language used and the length of the patient survey, it has been shortened and the language simplified. The surveys for carers and professionals have also been modified accordingly in order to resemble the patient survey as closely as possible.

To address the issue of increasing attrition as respondents progress through the survey, the survey questions have been re-ordered so that background questions will come after the main questions focusing on outcome priorities. We have now omitted the question about 'confirming a clinical diagnosis' as coded medical diagnoses, like mortality, are outcomes we will necessarily be looking for in real world data. Other questions about types of clinical information, symptoms, experiences and personal and economic aspects have been combined to avoid a sense of repetitiveness.

We have also changed terms MCI, mild AD and moderate-severe AD. After much deliberation, we have chosen to use the terms MCI, mild dementia and moderate-severe dementia. The term dementia is preferred over AD in general throughout the surveys.

We have also defined 'meaningful change in disease', slightly modifying it to 'disease progression' to clarify that we are interested in identifying the types of aspects/outcomes that are most impactful and would indicate clear disease progression from different stakeholder perspectives. Postponing a change in the severity of the disease in order to allow a person with dementia to continue living their life as they want to live it would constitute a 'meaningful delay' in disease progression. We provide a definition in the participant information sheet and survey introductory page.

What the surveys do not address

Some questions about psychosocial aspects of disease impact are not featured in our surveys but this dimension of impact became apparent in the focus group consultations with EWGPWD through their interpretations of some questions. Meaningful delay in disease progression meant, for example, having ‘a sense of self’ and ‘staying connected with the world.’ The event they dreaded most was not recognising family members and anticipating the look of pain in their eyes. ‘Significant events in your/their life’ was interpreted as significant milestone events in the life course. The ability to capture such insights extending beyond the survey content reaffirms the need for focus group consultations.

We do not ask questions about outcome measurement tools specifically, as this could not be addressed by all stakeholder groupings, would increase the length of the survey and would affect the response rate and attrition. In previous iterations of the survey for professionals, we included some follow-up questions about biomarkers and different assessment tools. Suggestions from some ROADMAP partners to cover outcome measurement tools and biomarkers go beyond the aims of our work but could potentially be included in future surveys as part of the next phase of ROADMAP.

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3. Stakeholder engagement – Patient and Public Involvement (PPI) Workshops

3.1. Introduction

Stakeholder consultation is a fundamental part of the work of the ROADMAP project. The research questions of WP2 will be addressed through quantitative surveys of stakeholder populations. PPI workshops will be undertaken to support the survey design and ensure that the priorities of the stakeholders remain central in WP2's research activity, enhancing the relevance and credibility of the work package results.

The aim of the workshops is to ensure that members of the stakeholder groups PwD, carers, and professionals working with dementia and Alzheimer's disease) are actively involved in the design, analysis and interpretation of the WP2 research activities. The workshops aim to facilitate productive interaction between the research team and stakeholders and ensure that stakeholder priorities are not only identified through the research but also inform and guide the translation of the survey results into a representative set of priority outcomes and Alzheimer's disease progression criteria.

At the point of writing this interim report, the PPI workshops involving PwD and the workshop involving carers have been conducted. The PPI workshops involving professionals are yet to be conducted.

3.2. Methods

The workshop activities have been designed to enable a nuanced interpretation of the outcomes prioritised by different stakeholders and how these outcomes relate to a meaningful delay in disease progression. The workshops are achieving this by gaining an insight into potential rationales and reasoning in stakeholders' differentiation of Alzheimer's disease progression criteria, both within and between stakeholder groups.

3.2.1. PPI Workshop Objectives

The PPI workshops have two overarching objectives:

a) To provide constructive criticism of the survey design in general and specific feedback on the design, content, layout and accessibility of survey tool.

b) To support the interpretation of survey study by providing elucidations based on personal experience of:

I. why specific outcomes might or might not have been prioritised by stakeholders in the survey, in relation to AD across the spectrum, and why prioritised outcomes might matter most to different stakeholders.

II. how prioritised outcomes can potentially be translated into a definition of 'meaningful delay' in disease progression in AD across the spectrum.

3.2.2. PPI Workshop Members

The workshop members are intended to be individuals from the broad range of stakeholder groups identified across the ROADMAP project as a whole [1]. These are:

1. People with mild cognitive impairment, dementia or Alzheimer's disease.
2. Informal carers of people with mild cognitive impairment, dementia or Alzheimer's disease.
3. Professionals working in the field of mild cognitive impairment, dementia or Alzheimer's disease, including: clinicians and allied health professionals, scientists, health economists, HTA bodies, regulators, payers, industry, charities, advocacy groups and ethicists.

3.2.3. Workshop process

Several one-off workshops are being held with separation of the three different stakeholder groups (people living with the condition/carers/professionals working in this field). The workshops are mainly being conducted face-to-face, with location and timing set to maximise attendance of relevant stakeholders. However, the wide range of stakeholder types required for this process and the importance of obtaining input from all groups requires a flexible approach to ensure that all stakeholder views are taken into consideration, and that input from those unable to attend face-to-face workshops can be captured. Thus, additional remote interactions will be held to enable discussion over video and audio links. These remote interactions will predominantly be conducted as individual interviews, following the same general discussion guide as the larger face-to-face workshops. The individual interactions will be held at a time convenient to the individual. In this way we hope to ensure adequate representation in the PPI activities of all relevant stakeholder groups.

Recruitment of Workshop Members

a) Informal carers and people living with mild cognitive impairment, dementia or Alzheimer's disease

Members for the workshops involving carers and people living with mild cognitive impairment, dementia or Alzheimer's disease were identified and provisional agreement to be involved was negotiated in advance at an organisational level. Members were representatives of the European Working Group of People with Dementia (EWGPWD). The group is composed of 10 PwD from different European countries and with different types of dementia. The EWGPWD works to ensure that the activities, projects and meetings of Alzheimer Europe (a member of the ROADMAP consortium) duly reflect the priorities and views of PwD. All members of the EWGPWD are in the early to mid-stages of dementia and have capacity to understand what is being asked of them and to decide if they wish to contribute to this work. Members of the EWGPWD are accompanied to meetings by a friend, relative or member of an Alzheimer association, and the accompanying individual was invited to be involved in the separate workshop for carers. The workshops were held in Luxembourg at the EWGPWD meeting on the 4th and 5th of September 2017.

b) Professionals working in the field of mild cognitive impairment, dementia or Alzheimer's disease

Members for the professionals' workshops will be recruited using purposeful selection and snowballing strategies. These sampling techniques will help ensure identification of individuals with the required level of expertise and specialist knowledge in the area of interest, and will facilitate

recruitment through the use of personal referral and introduction to networks that are otherwise difficult to access. Initial recruitment will start with the experts already working within the ROADMAP consortium and will span outwards.

There will be several face-to-face workshops for professionals. Some will be held in the UK and the others will be held in mainland Europe. These are planned to take place from December 2017 to February 2018. Further remote interactions will be held after the face-to-face groups and will be limited to a maximum of 6 individual interviews.

Conduct

Confidentiality and respect between the group members will be discussed and agreed at the start of the workshop. The ground rules of the group will include:

- What is said in this room/group stays here and is not repeated outside the group.
- There are no right or wrong answers.
- Every person's experiences and opinions are important and we want to hear a wide range of opinions.
- Speak up whether you share the experience or want to put a different point of view.

a) Group size

Each PPI workshop will have a minimum of 6 and maximum of 10 members. This group size will be large enough to generate rich discussion but not so large that some members are left out. The only exception to this is the already conducted workshop for people living with mild cognitive impairment, dementia or Alzheimer's disease where a couple of members chose to have their carer present for support during the discussions. In this case, the carers were not acting in the discussion on their own behalf but on behalf of the individual living with the condition in a facilitative role.

b) Language

All the workshops will be held in English. The EWGPWD conduct their meetings in English as a standard practice and the members and their carers are used to discussing the type of issues that will be covered by the research in English. Two members of the EWGPWD are regularly supported by a person of their choice in the meetings and help them to express themselves in English.

We have also been advised by our European partners that it is common practice to use English in the scientific workplace in international meetings and that undertaking the PPI workshops in English will not present a barrier to involvement for these members.

c) Time

The consultation with the members of the EWGPWD and carers was held as part of their meeting in Luxembourg. One and a half days was dedicated to the discussions with the group. The discussions were broken down into sessions, which allowed for a rest and for refreshments. The duration of each session was dependent on the particular topic to be explored and related tasks planned, but overall sessions lasted between 1.5 to 2 hours. Additional breaks were taken as need and while the workshops would have been brought to an earlier close if necessary, this was not needed.

The workshops for professionals working with mild cognitive impairment, dementia or Alzheimer's disease will last between two and three hours, with a break for refreshments. Supplementary individual interviews will take up to one hour.

d) Discussion topics

Discussion topics relate directly to the objectives of the PPI workshops. Members have already been asked to feed back on the survey design, content, layout and accessibility of survey tool and all workshop members have been/will be asked to discuss:

I. why specific outcomes might or might not have been prioritised by stakeholders in the survey, in relation to AD across the spectrum, and why prioritised outcomes might matter most to different stakeholders.

II. how prioritised outcomes can potentially be translated into a definition of 'meaningful delay' in disease progression in AD across the spectrum.

e) Facilitation

The role of the WP2 researchers in the workshop is to facilitate and stimulate discussion on a topic between the members, rather than eliciting a group's direct response to a question. Therefore, the researchers will take a peripheral, rather than a central role in the discussion. Two researchers will be present at each group. One researcher will act as moderator and will facilitate discussions while the other researcher takes notes.

An introductory 'ice breaker' question, tailored to each group will be used at the start of the workshops to help ease the group into the discussions. A number of standard conversation prompts to encourage further elaboration of a topic will also be used, including "Can you tell me a bit more about that?"; "Help me understand what you mean"; and "Can you give an example?" Other prompts and probes specific to the on-going discussion will be used as appropriate at the time.

f) Recording and transcription

All workshops and individual interviews will be audio recorded. Field notes will also be made during the discussions by the researchers present. The field notes will record non-verbal aspects such as body language and group dynamics, including nodding/shaking of heads, eye contact between specific members, physical excitement, tears, and movement towards or away from a speaker.

Field notes will be written up and audio recordings will be transcribed. The field notes and the transcripts will then be linked. Transcription will be conducted out-of-house. Two transcription services that have been used before by researchers in the university and have proven to be trustworthy and efficient in the past will be used in this study. The transcription services are bound by confidentiality agreements and secure transfer arrangements are in place for the recordings and the completed transcript documents. Transcripts will be anonymised before analysis and long-term storage.

Analysis of the interactions

A thematic analysis of the data will be undertaken in order to take an exploratory, rather than confirmatory, approach to the data [2]. The analysis will be generally directed by research objectives with themes related to the PPI workshop objectives. However, an open coding procedure will be used for themes within these areas, given the lack of established knowledge and published literature in this

area, with codes to be created as required to capture appropriately the experiences and issues raised in the texts [2,3,4]. The NVIVO software package will be used to store the data and share the analysis and thematic interpretations with the research group. Regular analysis meetings will be held with the study partners to discuss the analysis in general and the interpretations made, and to refine the scope and definitions of the emerging themes.

Each of the stakeholder groups' transcripts will first be examined in isolation to identify themes common within the group. These individual analyses and interpretations will then be compared across the stakeholder groups and across the different discussion groups to identify differences and similarities in themes and interpretations across the groups.

The practical process of data analysis will be guided by the writings of Braun and Clarke [5] and the principles of analytic induction, constant comparison and comprehensive data treatment will be adhered to in order to maximise the quality, rigour and reliability of the work [6].

Application of the interactions

The findings of this PPI workshop activity will feed into the work of the larger ROADMAP project and will specifically contribute to building the comprehensive stakeholder generated lists of priority RWE relevant outcomes. The findings will also support the development of the data RWE progression marker and outcome classification matrix for AD and will be used to guide the development of the survey tool.

A report will be produced and, if considered appropriate by the ROADMAP executive committee, published on the ROADMAP website. Additional publications will be sought in academic and professional journals. Results of the study will also be presented at academic and professional conferences, and will be given as a presentation to the EWGPWD.

Ethical considerations

The inclusion of stakeholders in the design, conduct, analysis and interpretation of health-related research studies is encouraged as part of good practice [7], enhancing the effectiveness and credibility of the research projects undertaken. This stakeholder involvement does not require review by ethics committee and is instead required by most UK research ethics committees as proof of appropriate design of studies in advance of application for approval. WP2s PPI workshops are being undertaken to support the effectiveness and credibility of the survey work and the application for ethical approval for it.

Agreement to be involved

Provisional agreement to be involved was negotiated in advance with the members of the EWGPWD and with their informal carers. The aim and purpose of the workshops and the ROADMAP project was explained by the core team of Alzheimer Europe and this was reiterated at the start of the workshops. As this stakeholder involvement is not considered research the members of the PPI workshops for PwD and carers were not and, members of the professionals' workshops will not, be asked to sign consent forms. However, informed agreement was and will be verbally obtained from members and members of the workshops were and will be free to stop their involvement at any point without giving a reason.

In any PPI activity involving PwD, on-going negotiated agreement can make involvement more meaningful for and inclusive of PwD [8]. This approach includes considering different aspects of negotiating involvement such as the way in which the information is provided to the members and also on-going monitoring of the initial agreement provided by each member as this will ensure that visual or verbal signs from members expressing unease or distress are addressed and that initial agreement is not taken for granted as the person being willing to be involved at all times. These principles were adhered to throughout the conduct of the PPI workshops involving members of the EWGPWD alongside the awareness of their extensive experience of undertaking such consultations, with members of the EWGPWD having been involved in many other consultations in the context of EU projects. Researchers from AE, who know the members of the group well were also present to co-moderate the workshops.

All members involved in the workshops and individual interviews will need to have sufficient mental capacity to understand what involvement will comprise and judge if involvement is right for them. It has been established that all the members of the EWGPWD are in the early to mid-stages of disease progression and have capacity to make such decisions.

3.3. Results

The PPI workshops involving PwD and carers were conducted in September 2017. The consultations ran over the course of two days. The full schedule of consultation activities is given in Annex II. In brief, the discussion topics included:

- Disease staging – benefits and drawbacks; alternative ways of staging; how to differentiate stages
- Understanding meaningful delay – delaying the onset of dementia and slowing the progress of the disease
- Real world data and evidence – how to use it to monitor treatment benefit and disease progression
- Survey design – layout, questions, language and distribution (participant recruitment)

The workshops produced 11.5 hours of data. Transcription of the consultation discussions is now complete and anonymization of the transcripts is currently being undertaken.

The discussions specific to the survey design have been analysed. The workshop members advised that the survey be shortened and simplified and certain sections, perceived as repetitive, were removed from the survey. One outcome aspect was also removed from the survey as a result of the consultation and analysis. The outcome removed was ‘Having a confirmed medical diagnosis’. This was identified as an outcome that was likely to be collected regardless, but irrelevant to monitoring disease progression. As such it was perceived as confusing and unhelpful when undertaking the survey.

In the participant demographics section, the question related to ‘age’ was recommended to be changed to ‘date of birth’. This change was suggested as the workshop members with dementia identified that an individual’s age changes each year and so was more difficult for PwD to answer

whereas date of birth remains consistent. Aspects of text layout and format were also discussed and the recommendations were similarly enacted.

The preliminary analysis of the remaining discussion topics is underway and is being undertaken by the core UEDIN and AE research team. A wider WP2 analysis team will advise on the application of the workshop consultations to the survey results once the preliminary analysis is complete. A full write up of the workshop analysis will be produced and the results will be incorporated with the survey results in order to provide a comprehensive stakeholder generated lists of priority RWE relevant outcomes for AD.

The early preliminary analysis of the workshop notes has provided insights relevant to the development of the data RWE progression marker and outcome classification matrix for AD, lay measures of disease progression and definitions of meaningful delay in terms of both disease onset and progression. As this preliminary analysis is at an early stage, it is based predominately on the researcher field notes, and is likely that the interpretations will develop further in the light of full transcript. As such, detailed insights are not being provided in this interim report. The full analysis and write up of the workshop interactions will be completed by March 2018 and, once agreed within WP2, will be made available as part of D2.3 (Stakeholder generated lists of priority RWE relevant outcomes for AD) and D2.4 (RWE progression marker and outcome classification matrix for AD).

3.4. References

1. Guest, G.S., MacQueen, K.M. and Namey, E.E. Applied Thematic Analysis. London: Sage Publications. 2012.
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4. Conclusion and next steps

The stakeholder engagement work continues to make progress by gathering high quality robust evidence from multiple sources on the outcomes of AD which matter most to a range of stakeholder groups.

All of the findings will be compiled by March 2018 and will be the basis for a series of consultations with partners in WP2 and WP3 during which the matrix of progression markers and outcome classifications stratified by stakeholder relevance and impact will be developed (D2.4).

ANNEXES

Annex I. Survey materials

(Materials submitted as separate pdf documents)

- Results from WP2 pilot questions
- WP2 carer survey
- WP2 patient survey
- Survey for professionals
- SPANISH Survey for professionals
- CATALAN Survey for professionals
- Invitation to participate
- SPANISH invitation to participate in the online survey
- CATALAN invitation to participate in the online survey
- Online survey information sheets
- SPANISH Online survey information
- CATALAN Online survey information
- Screenshots of online surveys
- Paper survey information sheet

Annex II. PPI workshop schedules

ROADMAP Discussion Schedule for consultation with the European Working Group of People with Dementia (EWGPWD) - PwD

4-5 September 2017, Munsbach, Luxembourg

Background to the EWGPWD

The EWGPWD (European Working Group of People with Dementia) was set up by Alzheimer Europe (AE) in 2012 and is currently comprised of 10 people with different kinds of dementia. Each member is nominated by a national Alzheimer Association and participates in quarterly meetings in Luxembourg or Brussels to provide feedback and advice to Alzheimer Europe in relation to its own work and its involvement in various EU projects.

Members of the group, who have all been diagnosed with dementia, serve a two-year renewable term of office on a voluntary basis. They have the capacity to contribute meaningfully to consultations (in the context of patient and public involvement - PPI) organised by Alzheimer Europe and in collaboration with its project partners. Each person has the right to be supported by a person of his/her choice to ensure safe travel and to provide support during meetings.

On 4-5 September, the EWGPWD will participate in a consultation, co-moderated by the University of Edinburgh and AE, to provide advice / feedback on some of the key aspects that the project is focused on (meaningful delay of disease progression, real-world data / evidence) and on the survey that has been developed for people with dementia and carers.

Monday

- 10.40 – 10.45 Welcome to the ROADMAP consultation
- 10.45 – 10.55 Introduction to key concepts
- 10.55 – 11.15 Introduction to the ROADMAP project
- 11.15 – 11.30 Questions and answers
- 11.30 – 12.40 Group discussion about disease progression and treatment

Explain the topic: namely that we are going to discuss whether it makes sense to you to see the progression of dementia in terms of stages. But first, before we start talking about how dementia progresses, we'd like to briefly consider what dementia is. This is also a bit of an ice-breaker so just feel free to say what comes to mind without worrying whether it is technically correct or the most helpful response.

Introduce the following ice-breaker activity to get the ball rolling (10 minutes)

So here's the activity: I'd like you to imagine you are in a lift and are carrying a bag from a dementia conference with "dementia" written on it. Someone gets in the lift, sees your bag, and says, "Oh dementia! My mother has just been diagnosed with dementia but I'm not sure really what it is". You

haven't got much time to go into detail. What would you say (in a nutshell) to give them a good general understanding of what it is?

So that was helpful in helping us to understand broadly speaking what you feel it is important to know in order to understand what dementia is. We'd now like to move on to the first question which is about the progression of dementia.

Question 1 (10 minutes): Dementia has been traditionally described in terms of stages (also in the context of healthcare and in research). Which ones are you familiar with? Are there any others? (open question, see what comes up)

- propose a few examples if nothing forthcoming (e.g. mild, moderate, severe; early, middle, late; end-stage; 1-3; 1-7 etc.)
- just in relation to Alzheimer's disease, new terms are now being used to describe stages before the development of symptoms of dementia. Are you familiar with this and how do you feel about pre-dementia stages being used?

Question 2 (20 minutes): Is this way of dividing dementia up into different stages helpful to you? (If so, in what way? If not, in what way is not helpful?)

- Do you think that is helpful, overall, to talk about dementia in terms of stages?
    - If so, for whom? If your doctor uses terms like that when talking about your condition, how do you feel about it?
- If referring to stages doesn't work for you, how could the progression be more meaningfully described?

Co-moderator: for Q1 and Q2 to make notes on the flip chart.

Question 3 (20 minutes): How can you tell that someone's dementia is progressing/getting worse? (could be based on your own experience or based on your observations of other people you have encountered with dementia). Explain that we are going to brainstorm for examples of changes which you think might indicate that a person's condition is progressing to a more advanced stage (tell them not to worry about which stages as we will look at that next). The person supporting the co-moderators should write the responses clearly on the flip chart. We need to try to ensure that we leave enough time for discussion.

Activity 3a: give each person three green sticky labels/dots and ask them to put them next to changes which might indicate:

- a progression from a mild/early stage to a mid/moderate stage of dementia?

Activity 3b: give each person three red sticky labels/dots and ask them to put them next to changes which might indicate:

- a progression from a mid/moderate to a later/more advanced stage of dementia?

If any time left, discuss reasons for choice.

- 12.40 – 14.00 Lunch at the hotel
- 14.00 – 15.00 Group discussion about treatment and research

Explain the topic, namely that we are going now to discuss pharmacological treatments for dementia. Remind the group that we would like them to think about drugs for dementia, not other drugs, such as antipsychotics, that are sometimes prescribed to some people with dementia but are not specific for dementia.

Question 4 (10 minutes): Existing treatments for AD (e.g. cholinesterase inhibitors and memantine) are currently limited to alleviating various symptoms. However, there is a lot of research going on at the moment into delaying the onset of dementia and/or slowing down its progression. What do you think of this change of focus?

- Are you familiar with this type of research?
- Why is this important?
- Are there any disadvantages to this new focus?

Question 5 (20 minutes): Let's now imagine that there are two new drugs that are about to come out and that can a) delay the onset of dementia, b) slow the progression of dementia. We are going to split the group in two smaller groups to each think about one of these hypothetical drugs.

GROUP 1: Drug that can delay the onset of dementia.

- When you hear the sentence "delay the onset of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- Is delaying the onset of dementia more meaningful for some people than for others?
- When or in which circumstances would delaying the onset of dementia not be considered meaningful?

GROUP 2: Drug that can slow the progression of dementia.

- When you hear the sentence "slow the progression of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- For the impact of the drug to be considered meaningful, what kind of difference do you think it should make?
- Is slowing the progression of dementia more meaningful for some people than for others?
- When or in which circumstances would slowing down the progression of dementia not be considered meaningful?

(15 minutes) On the flipchart, a representative of each group to write the main ideas discussed in the group in relation to why / when delaying or slowing progression of dementia is or not meaningful

Question 6 (15 minutes): Do you agree with what is written on the flipchart? Is there any other thing/ aspect that should be included?

To wrap up this session, and after the discussions that we have had, how would you briefly explain to that same person that you met this morning in the lift, what a "meaningful delay in the progression of the disease" means.

- 15.00 – 15.15 Coffee/tea break
- 15.15 – 16.30 Focus group discussion on topic of meaningful real world evidence of disease

In this last part of today's discussion, we'd like to hear your views about how to measure the possible impact of a drug, not through tests and scales typically used by researchers, but by other sources of information which are readily available in the real word (or could be made available without too much difficulty).

Imagine that a pharmaceutical company is carrying out a clinical trial for a new drug which is showing signs of slowing down the progression of dementia.

In the trial, they have used tests like the MMSE, scales measuring Activities of Daily Living such as ADCS-iADL and cognitive performance such ADAS-Cog13 (e.g. over a 2-year period).

They'd now like to look at the possible benefits of the new drug in the "real world" and measure the impact on people's lives using information that is not typically collected by researchers but may also be accessible and useful in helping determine whether the drug is effective.

Question 7: What kinds of things (e.g. events, outcomes, data etc.) do you think they should be looking at?

Prompt: use the examples listed on the WP2 list as examples and have handouts ready in case needed.

Question 8: How might these be collected and used?

- 16.30 – 17.00 Joint session (feedback about the day and main conclusions) – All

Joint session with people with dementia and carers. One person from each group to explain in 10 minutes how the day went and what they thought was important.

Tuesday

- 09.00 – 10.30 Feedback on the questionnaire and areas covered with a focus on the identification of gaps

Pre – activity: Remind the group of what 'outcomes' are.

Outcome

In general, an outcome is a specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumour size and improvement of disease.

In research, outcomes are events that can be measured objectively to determine the impact of an intervention.

In the context of ROADMAP, outcomes include, but are not limited to, cognition (measured with pen and paper tests such as the Mini Mental State Examination), disease-specific scales, like the Alzheimer's Disease Related Quality of Life (ADRQL) and health resource utilization or cost measures.

Explain the topic, namely that WP2 in ROADMAP is developing a survey in order to identify which outcomes are most important to different stakeholders in assessing a meaningful change in disease progression and its impact on the person's life. Three different versions of the survey are being designed for three different types of stakeholders. One of these surveys is for people with dementia. We would like you to have a look at the survey and imagine you are a person with dementia who is going to complete it. During the morning we are would like to have your feedback about a number of aspects related to the survey

Question 1 (15 minutes): what do you think of the idea of having a survey specifically for people with dementia? What are the main challenges of this approach? What should be take into account?

Activity (20 minutes): now we would like you to read through the survey instruction page and complete survey so that you can tell us what it is like to complete the survey.

Question 2 (30 minutes): how do you feel about the:

- Layout of the survey?
- Sections suggested?
- Questions asked?
- Language used?
- Other aspects?

Activity (20 minutes): There are hundreds of different outcomes collected as part of real world evidence and we want to understand which ones are most important. We have drawn 3 concentric circles on the wall – like an archery target. Like in archery the centre circle is the most important. The outer circle is the least important. We grouped all the different outcomes into 13 types of outcomes.

Question 3: We would like you to decide as a group where on the target each of these different types of outcomes should go.

Remind the group

- In the future, these outcomes will be used to identify if there has been a meaningful change in disease progression.
- As well as wanting to understand which types of outcomes we should prioritise, we really want to understand why we should prioritise them.

- 10.30 – 10.50 Coffee/tea break
- 10.50 – 11.30 Discussion about the question regarding long life versus quality of life in the questionnaire

Tell them that we are going to discuss the topic of long life and then give each person a handout. Explain that this provides general information on the topic to remind them that dementia has an impact on life expectancy, and also that the topic is very complex as many other factors can also affect longevity.

- Dementia is a 'life limiting' condition.
- Life expectancy varies for each person with dementia. Several factors may influence this: e.g. type of dementia, age, sex, health, where the person lives etc.
- Some people may also die from some other causes.
- The impact of existing drugs for dementia on longevity is not clear.

Question 4: (15 minutes) How would you feel about a drug that would give you some extra years' life (on top of what you would have normally lived with dementia)?

+ 1 year

+ 10 year

+ 20 years

- What would make this extra time worthwhile?
- What would be the reason for you not to choose this option (i.e. extra years)?
    - Would your answer be dependent on the stage of the disease? (e.g. how would you feel if this extra time was at the mild stage of dementia, at moderate stage or at severe stage)
    - Would your answer be different if the drug had side effects?

Question 5: (10 minutes) How would you feel about a drug that would not give you extra time, but would make it possible to live longer at the mild stage and reduce the time at the moderate and severe stages of dementia?

We wanted to have this discussion with you today, because we'd like to hear your views about one specific question in the survey. It is as follows:

Which is of greater importance – longevity (number of years lived) or quality of life?

The research team is strongly divided about whether or not it should be included in the survey.

Question 6 (15 minutes): we would like to know:

- how did you feel when you first read the question?
- do you think this question is appropriate in the context of dementia?
- if you do not consider it appropriate, what approach do you think would be useful to address this topic in the survey?

Question 7 (5 minutes): (time permitting)

Activity: we will give you sticky dots again. We will ask you to stick your dot on a chart next to your preference – include the question in the survey, or exclude the question.

- 11.30 – 12.30 Feedback about the day's activities and the project in general

Joint session with people with dementia and carers. One person from each group to explain in 10 minutes how the morning went and what they thought was important.

As a group to identify the top 5 messages that they want to pass on to ROADMAP researchers.

- 12.30 – 12.45 Close of the meeting

ROADMAP Discussion Schedule for consultation with the European Working Group of People with Dementia (EWGPWD) - Carers

4-5 September 2017, Munsbach, Luxembourg

Background to the EWGPWD

The EWGPWD (European Working Group of People with Dementia) was set up by Alzheimer Europe (AE) in 2012 and is currently comprised of 10 people with different kinds of dementia. Each member is nominated by a national Alzheimer Association and participates in quarterly meetings in Luxembourg or Brussels to provide feedback and advice to Alzheimer Europe in relation to its own work and its involvement in various EU projects.

Members of the group, who have all been diagnosed with dementia, serve a two-year renewable term of office on a voluntary basis. They have the capacity to contribute meaningfully to consultations (in the context of patient and public involvement - PPI) organised by Alzheimer Europe and in collaboration with its project partners. Each person has the right to be supported by a person of his/her choice to ensure safe travel and to provide support during meetings.

On 4-5 September, the EWGPWD will participate in a consultation, co-moderated by the University of Edinburgh and AE, to provide advice / feedback on some of the key aspects that the project is focused on (meaningful delay of disease progression, real-world data / evidence) and on the survey that has been developed for people with dementia and carers.

Monday

- 10.40 – 10.45 Welcome to the ROADMAP consultation
- 10.45 – 10.55 Introduction to key concepts
- 10.55 – 11.15 Introduction to the ROADMAP project
- 11.15 – 11.30 Questions and answers (all)
- 11.30 – 12.40 Group discussion about disease progression and treatment

Explain the topic, namely that we are going to discuss whether it makes sense to you to see the progression of dementia in terms of stages. But first, before we start talking about how dementia progresses, we'd like to briefly consider what dementia is. This is also a bit of an ice-breaker so just feel free to say what comes to mind without worrying whether it is technically correct or the most helpful response.

Introduce the following ice-breaker activity to get the ball rolling (10 minutes)

So here's the activity: I'd like you to imagine you are in a lift and are carrying a bag from a dementia conference with "dementia" written on it. Someone gets in the lift, sees your bag, and says, "Oh dementia! My mother has just been diagnosed with dementia but I'm not sure really what it is". You haven't got much time to go into detail. What would you say (in a nutshell) to give them a good general understanding of what it is?

So that was helpful in helping us to understand broadly speaking what you feel it is important to know in order to understand what dementia is. We'd now like to move on to the first question, which is about the progression of dementia.

Question 1 (10 minutes): Dementia has been traditionally described in terms of stages (also in the context of healthcare and in research). Which ones are you familiar with? Are there any others? (open question, see what comes up)

- propose a few examples if nothing forthcoming (e.g. mild, moderate, severe; early, middle, late; end-stage; 1-3; 1-7 etc.)
- just in relation to Alzheimer's disease, new terms are now being used to describe stages before the development of symptoms of dementia. Are you familiar with this and how do you feel about pre-dementia stages being used?

Question 2 (20 minutes): Is this way of dividing dementia up into different stages helpful to you? (If so, in what way? If not, in what way is not helpful?)

- Do you think that is helpful, overall, to talk about dementia in terms of stages?
    - If so, for whom? If your doctor uses terms like that when talking about the condition of your relative or friend, how do you feel about it?
- If referring to stages doesn't work for you, how could the progression be more meaningfully described?

Co-moderator: for Q1 and Q2 to make notes on the flip chart.

Question 3 (20 minutes): How can you tell that someone's dementia is progressing/getting worse? (could be based on your experience within your family or based on your observations of other people you have encountered with dementia). We are going to brainstorm for examples of changes which you think might indicate that a person's condition is progressing to a more advanced stage (tell them not to worry about which stages as we will look at that next). The person supporting the co-moderators should write the responses clearly on the flip chart. We need to try to ensure that we leave enough time for discussion.

Activity 3a: give each carer three green sticky labels/dots and ask them to put them next to changes which might indicate:

- ☞ a progression from a mild/early stage to a mid/moderate stage of dementia?

Activity 3b: give each carer three red sticky labels/dots and ask them to put them next to changes which might indicate:

- ☞ a progression from a mild/moderate to a later/more advanced stage of dementia?

If any time left, discuss reasons for choice.

- 12.40 – 14.00 Lunch at the hotel
- 14.00 – 15.00 Group discussion about treatment and research

Explain the topic, namely that we are going now to discuss pharmacological treatments for dementia. Remind the group that we would like them to think about drugs for dementia, not other drugs, such

as antipsychotics, that are sometimes prescribed to some people with dementia but are not specific for dementia.

Question 4 (10 minutes): Existing treatments for AD (e.g. cholinesterase inhibitors and meantime) are currently limited to alleviating various symptoms. However, there is a lot of research going on at the moment into delaying the onset of dementia and/or slowing down its progression. What do you think of this change of focus?

- Are you familiar with this type of research?
- Why is this important?
- Are there any disadvantages to this new focus?

If moderators decide to split the group for this task, please follow questions 5 and 6 below, if not, please go to ALTERNATIVE to Question 5 and 6.

Question 5 (20 minutes): Let's now imagine that there are two new drugs that are about to come out and that can a) delay the onset of dementia, b) slow the progression of dementia. We are going to split the group in two smaller groups to each think about one of these hypothetical drugs

GROUP 1: Drug that can delay the onset of dementia.

- When you hear the sentence "delay the onset of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- Is delaying the onset of dementia more meaningful for some people than for others?
- When or in which circumstances would delaying the onset of dementia not be considered meaningful?

GROUP 2: Drug that can slow the progression of dementia.

- When you hear the sentence "slow the progression of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- For the impact of the drug to be considered meaningful, what kind of difference do you think it should make?
- Is slowing the progression of dementia more meaningful for some people than for others?
- When or in which circumstances would slowing down the progression of dementia not be considered meaningful?

(15 minutes) On the flipchart, a representative of each group to write the main ideas discussed in the group in relation to why / when delaying or slowing progression of dementia is or is not meaningful.

Question 6 (15 minutes): Do you agree with what is written on the flipchart? Is there any other thing/ aspect that should be included?

To wrap up this session, and after the discussions that we have had, how would you briefly explain to that same person that you met this morning in the lift, what is a "meaningful delay in the progression of the disease".

ALTERNATIVE

Question 5: (if the group is not split)

Let's now imagine that there are two new drugs that are about to come out and that can a) delay the onset of dementia, b) slow the progression of dementia. We are going to look at each of these two hypothetical drugs in turn. (Give handouts).

Co-moderator: make notes on flipchart about when each drug would be meaningful and situations where each would not be meaningful.

Let's start with the drug that could **delay the onset of dementia** (20 minutes).

- When you hear the sentence "delay the onset of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- Is delaying the onset of dementia more meaningful for some people than for others?
- When or in which circumstances would delaying the onset of dementia not be considered meaningful?

Thanks, that was very useful. Let's now think about the other drug, the one that could slow the progression of dementia. (15 minutes)

- When you hear the sentence "slow the progression of dementia", what comes to mind?
    - how do you feel?
    - what do you understand it to mean?
- For the impact of the drug to be considered meaningful, what kind of difference do you think it should make?
- Is slowing the progression of dementia more meaningful for some people than for others?
- When or in which circumstances would slowing down the progression of dementia not be considered meaningful?

Question 6 (15 minutes): Please have a look at the flipchart. Is there any other thing/ aspect that should be included?

To wrap up this session, and after the discussions that we have had, how would you briefly explain to that same person that you met this morning in the lift, what is a "meaningful delay in the progression of the disease".

- 15.00 – 15.15 Coffee/tea break
- 15.15 – 16.30 Focus group discussion on topic of meaningful real world evidence of disease

In this last part of today's discussion, we'd like to hear your views about how to measure the possible impact of a drug, not through tests and scales typically used by researchers, but by other sources of information which are readily available in the real world (or could be made available without too much difficulty).

Imagine that a pharmaceutical company is carrying out a clinical trial for a new drug which is showing signs of slowing down the progression of dementia.

In the trial, they have used tests like the MMSE, scales measuring Activities of Daily Living such as ADCS-iADL and cognitive performance such ADAS-Cog13 (e.g. over a 2-year period).

They'd now like to look at the possible benefits of the new drug in the "real world" and measure the impact on people's lives using information that is not typically collected by researchers but may also be accessible and useful in helping determine whether the drug is effective.

Question 7: What kinds of things (e.g. events, outcomes, data etc.) do you think they should be looking at?

Prompt: use the examples listed on the WP2 list as examples and have handouts ready in case needed.

Question 8: How might these be collected and used?

- 16.30 – 17.00 Joint session (feedback about the day and main conclusions) – All

Joint session with people with dementia and carers. One person from each group to explain in 10 minutes how the day went and what they thought was important.

Tuesday

- 09.00 – 10.30 Feedback on the questionnaire and areas covered with a focus on the identification of gaps

Pre – activity: Remind the group of what 'outcomes' are.

Outcome

In general, an outcome is a specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumour size and improvement of disease.

In research, outcomes are events that can be measured objectively to determine the impact of an intervention.

In the context of ROADMAP, outcomes include, but are not limited to, cognition (measured with pen and paper tests such as the Mini Mental State Examination), disease-specific scales, like the Alzheimer's Disease Related Quality of Life (ADRQL) and health resource utilization or cost measures.

Explain the topic, namely that WP2 in ROADMAP is developing a survey in order to identify which outcomes are most important to different stakeholders in assessing a meaningful change in disease progression and its impact on the person's life. Three different versions of the survey are being designed for three different types of stakeholders. One of these surveys is for the carers of people with dementia. We would like you to have a look at the survey and imagine you are a carer of a person with dementia who is going to complete it. During the morning we are would like to have your feedback about a number of aspects related to the survey.

Question 1 (15 minutes): what do you think of the idea of having a survey specifically for carers of people with dementia? What are the main challenges of this approach? What should be taken into account?

Activity (20 minutes): now we would like you to read through the survey instruction page and complete survey so that you can tell us what it is like to complete the survey.

Question 2 (30 minutes): how do you feel about the:

- Layout of the survey?
- Sections suggested?
- Questions asked?
- Language used?
- Other aspects?

Activity (20 minutes): There are hundreds of different outcomes collected as part of real world evidence and we want to understand which ones are most important. We have drawn 3 concentric circles on the wall – like an archery target. Like in archery, the centre circle is the most important. The outer circle is the least important. We grouped all the different outcomes into 13 types of outcomes.

Question 3: We would like you to decide as a group where on the target each of these different types of outcomes should go.

Remind the group

- In the future, these outcomes will be used to identify if there has been a meaningful change in disease progression.
- As well as wanting to understand which types of outcomes we should prioritise, we really want to understand why we should prioritise them.

- 10.30 – 10.50 Coffee/tea break
- 10.50 – 11.30 Discussion about the question regarding long life versus quality of life in the questionnaire

Tell them that we are going to discuss the topic of long life and then give each person a handout. Explain that this provides general information on the topic to remind them that dementia has an impact on life expectancy, and also that the topic is very complex as many other factors can also affect longevity.

- Dementia is a 'life limiting' condition.
- Life expectancy varies for each person with dementia. Several factors may influence this: e.g. type of dementia, age, sex, health, where the person lives etc.
- Some people may also die from some other causes.
- The impact of existing drugs for dementia on longevity is not clear.

Question 4: (15 minutes) How would you feel about a drug that would give the person with dementia some extra years' life (on top of what you would have normally lived with dementia)?

- + 1 year
- + 10 year
- + 20 years

- What would make this extra time worthwhile?
- What would be the reason for you not to choose this option (i.e. extra years)?
    - Would your answer be dependent on the stage of the disease? (e.g. how would you feel if this extra time was at the mild stage of dementia, at moderate stage or at severe stage)
    - Would your answer be different if the drug had side effects?

Question 5: (10 minutes) How would you feel about a drug that would not give would not give extra time to the person with dementia, but would make it possible for him/her to live longer at the mild stage and reduce the time at the moderate and severe stages of dementia?

We wanted to have this discussion with you today, because we'd like to hear your views about one specific question in the survey. It is as follows:

Which is of greater importance – longevity (number of years lived) or quality of life?

The research team is strongly divided about whether or not it should be included in the survey.

Question 6 (15 minutes): we would like to know:

- how did you feel when you first read the question?
- do you think this question is appropriate in the context of dementia?
- if you consider it appropriate, what approach do you think would be useful to address this topic in the survey?

Question 7 (5 minutes): (time permitting)

Activity: we will give you sticky dots again. We will ask you to stick your dot on a chart next to your preference.

- 11.30 – 12.30 Feedback about the day's activities and the project in general

Joint session with people with dementia and carers. One person from each group to explain in 10 minutes how the morning went and what they thought was important.

As a group to identify the top 5 messages that they want to pass on to ROADMAP researchers.

- 12.30 – 12.45 Close of the meeting