

## D2.5 Summary of gaps between data requirements and currently available data

### 116020 - ROADMAP

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

#### WP2 – Outcome definition

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## Document History

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V2.0	12/10/2018	Sent for external review
V3.0	24/10/2018	Final Version

## 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)
  - **TAKEDA.** Takeda Development Centre Europe LTD (United Kingdom)
  - **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.

## 1. Publishable summary

In dementia research, real-world data (RWD) is increasingly being used in accordance with data collected in intervention trials, to strengthen evidence of the effectiveness of new treatments.

In ROADMAP, Work Package 3 (WP3) has identified 300 European sources of RWD. WP2 have identified dementia-relevant, stakeholder priority outcomes for patients, caregivers, HTA and regulatory agencies and health professionals. Using a questionnaire, WP3 and WP4 have collated information from RWD custodians for 77 of these data sources, highlighting the outcomes that are or are not captured in their data source.

This report aims to highlight gaps in the available data for each outcome. It has three main objectives, to identify:

1. which outcomes can be obtained at scale from the RWD sources identified by WP3,
2. which outcomes are challenging to obtain from any of the data sources identified in WP3, and
3. which outcomes are not adequately captured in any data source, to the best of our knowledge?

Outcomes relating to cognitive abilities, functional abilities and independence, behavioural and neuropsychiatric symptoms, details of therapeutic treatment, and mortality & comorbidities are measured in many of the data sources. Fewer data sources measure significant disease related life events, medical investigations, use of health care and social services, and patient quality of life. A limited number of data sources capture information on caregiver-oriented outcomes, in particular outcomes related to the quality of the carer's and family's lives.

A number of limitations are outlined, such as the potential for overlap of outcomes across domains, and the variability of data included in each data source.

# 1. Introduction

## 1.1. Real-World Data use in the Context of ROADMAP

In dementia research, real-world data (RWD) is increasingly being used in accordance with data collected in intervention trials, to strengthen evidence of the effectiveness of new treatments (Berger et al., 2015, Eichler et al., 2011, Makady et al., 2017). RWD reflects the heterogeneous lives of the individuals who attend hospitals, general practice, and other health services, hence ‘real-world’ (Eichler et al., 2011). In theory, use of RWD in research can improve generalisability of findings (i.e. external validity), by accounting for factors like patient genetics, comorbidities, medication histories, and behaviours such as adherence to treatment regimens (Eichler et al., 2011; Makady et al., 2017). Intervention trials often use selective populations that do not account for these differences (Makady et al., 2017).

RWD includes electronic health records (EHRs) and national patient registries, such as the SIDIAP information system for research in primary care (<http://www.sidiap.org/index.php/en>), cohort data like those included in the Dementias Platform UK portal (<https://www.dementiasplatform.uk>), and more (Berger et al., 2015; Makady et al., 2017).

This report incorporates work from across WPs 2, 3 and 4, as follows:

1. WP2 identified dementia-relevant, stakeholder priority outcomes for patients, caregivers, HTA and regulatory agencies and health professionals;
2. WP3 outlined potential sources of RWD from across Europe, and;
3. WP4 collated information from data custodians on which outcomes were captured in their data sources.

This report aims to highlight gaps in the available data for each outcome. This report has three main objectives, to identify which outcomes:

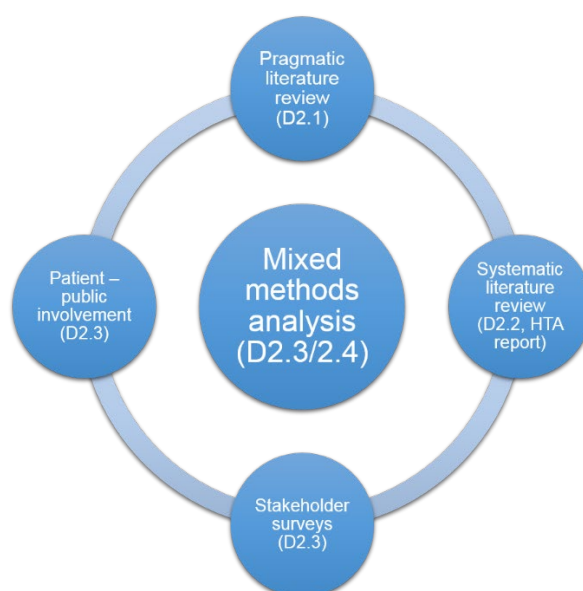
1. can be obtained at scale from the RWD sources identified by WP3?
2. Are challenging to obtain from any of the data sources identified in WP3?
3. Are not adequately captured in any data source, to the best of our knowledge?

This gap analysis will answer these questions based on the evidence gathered by WPs 2, 3 and 4. A summary of this evidence follows.

## 1.2. WP2: Development of Stakeholder Priority Outcomes

WP2 has conducted pragmatic and systematic literature reviews, patient-public involvement workshops & interviews, and stakeholder surveys (Figure 2) to develop priority outcomes lists from the perspectives of multiple stakeholders. Mixed-methods analytical techniques were then used to compile and integrate these different methods of data collection (ROADMAP consortium D2.3 & 2.4, 2018). This approach creates a robust, comprehensive evidence base (Heale & Forbes, 2018), and provides more nuance to key issues than either approach alone.

**Figure 1: Outline of workstreams that contributed to the final mixed-methods analysis, and associated deliverables**



First, a pragmatic literature review produced a preliminary outcomes list following review of published and unpublished literature. This review reports a ‘universe’ of outcomes across the AD spectrum (ROADMAP consortium D2.1, 2017).

The systematic literature review aimed to collate all primary and secondary research sources and ‘grey literature’ that elicited the views of key stakeholders regarding outcomes of priority and what constitutes a meaningful delay in disease progression. The included studies used qualitative (focus groups, semi-structured interviews and diary recordings analysed with thematic analysis, grounded theory, content analysis, interpretive phenomenological analysis, etc.) and quantitative methods (surveys, ranking of outcomes; ROADMAP consortium D2.2, 2018). Thematic analysis grouped findings into outcomes (e.g. memory) and related domains (e.g. cognitive abilities).

HTA and regulatory perspectives were gathered using case studies, interviews, and a literature review, regarding the outcomes used for legislative or guidance purposes. The report provided an in-depth understanding of the HTA processes in the Netherlands, Germany and England (ROADMAP consortium D2.3 & 2.4, 2018).

In the patient-public involvement consultations, focus groups were undertaken with the European Working Group of People with Dementia (EWGPWD) and individual interviews were conducted with a range of health professionals and research scientists with an active interest in dementia. These aimed to uncover and provide insight into (1) what constitutes a meaningful delay in disease progression, (2) outcomes that indicate that the disease is progressing, and (3) outcomes that are important for staging disease progression. Transcripts were analysed using content analysis with the aim of grouping related outcomes under overarching domains (ROADMAP consortium D2.3 & 2.4, 2018).

WP2 developed online and postal surveys that were completed by patients, caregivers and a diverse range of health professionals and research scientists. Surveys explicitly asked participants to prioritise outcomes based on those that would indicate a meaningful delay in disease progression. Data from professionals also outlined the outcomes of priority at the different stages of the disease (MCI, mild dementia, and moderate-severe dementia; ROADMAP consortium D2.3 & 2.4, 2018).

WP2 then compiled all results of the relevant workstreams using mixed methods analysis, to produce integrated lists of priority outcomes and highlight those of priority across the different stages of the disease for patients, caregivers and health professionals. Joint displays were developed in the form of Venn diagrams (for priority outcomes) and matrices (across disease stages), which have been outlined as effective for the visualisation of data in mixed methods research (Guetterman et al., 2015). A fuller description of the integrated analysis results is provided in ROADMAP consortium D2.3 & D2.4 (2018).

Ultimately, WP2 produced a list of priority outcomes for incorporation into ROADMAP's integrated data environment, named the data cube (described below) and highlighted which of these outcomes were priority at the various stages of the disease (see ROADMAP consortium D4.2, 2018). This list of outcomes was refined in teleconferences, and a final, consensus-based list of outcomes was developed.



### 1.3. WP3: Potential Sources of Real-World Data in Europe

In order to identify the available data sources for use in ROADMAP, WP3 investigated five knowledge sources:

1. ROADMAP consortium list of accessible data sources (FPP)
2. EMIF AD + EHR catalogue current fingerprinted data sources (<https://emif-catalogue.eu>)
3. DPUK catalogue of data sources (<https://dementiasplatform.uk>)
4. EU Dementia Mapping project results
5. ROADMAP partner data source landscaping project.

Interrogation of these sources uncovered 300 European data sources, including cohorts, patient registries and EHRs, clinical trial placebo data and patient reported outcomes (ROADMAP consortium D3.3, 2018).

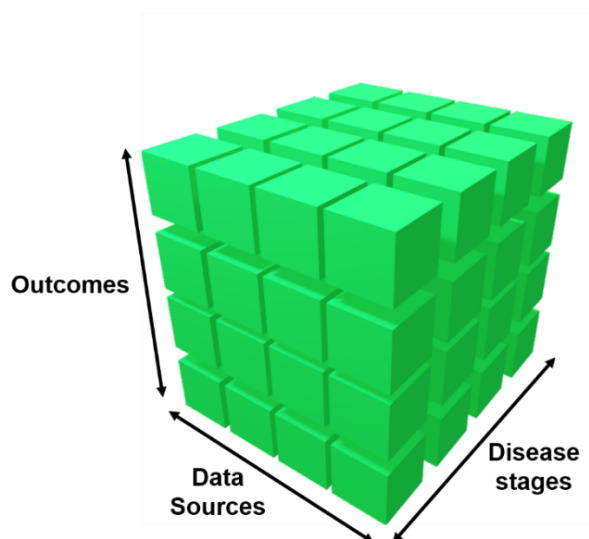
### 1.4. WP4: Content of Real-World Data Sources

WP3 and WP4 subsequently developed an inventory-style questionnaire in accordance with the outcomes list developed by WP2. The questionnaire was sent to the data custodians or researchers with active knowledge of the sources identified by WP3. WP4 compiled the responses, which indicate whether or not each outcome is assessed in each data source, with information supplied on the methods used to measure these outcomes, if it is available only on a sub-group, or via a secondary source.

### 1.5. Integration of WPs 2, 3 and 4 into the Data Cube

WP2, 3 and 4 have aligned the work described above towards the completion of the data cube, the present deliverable (D2.5), and the production of D3.3 (ROADMAP consortium, D3.3, 2018). As a result, the data cube will include information for dementia relevant outcomes, the outcomes of priority for the various stages of the disease, and the availability of data from the data sources outlined by WP3 (Figure 3). The data cube serves as an integrated data environment, which will improve ease of data access, so that intervention trials can conduct research that is more meaningful and relevant to those impacted most by the disease.

**Figure 2: 3D depiction of the data cube, showing the three axes developed by Work Packages 2, 3 & 4**



## 2. Methods

The inventory-style questionnaire circulated by WP3 & WP4 to RWD custodians ranked the availability of data on a 5-point scale based on the question ‘are the following outcomes of AD reflected by any of the measures available in your database? (including tests, measurements, parameters, etc.)’. Participants answered ‘yes, directly’, ‘yes, indirectly’, ‘yes, partially’, ‘we can access this information via other sources’ or ‘no’ for each outcome.

‘Yes, directly’ indicated that the outcome is assessed in the related data source. ‘Yes, indirectly’ refers to data that was not directly recorded but could be extracted or estimated with other information available in the data source. ‘Yes, partially’ indicated that data was only available for a subgroup within the related data source. ‘We can access this information via other sources’ indicates that data was not available in the data source, but could be reached by interacting with other departments or institutions. ‘No’ indicated that the outcome was not captured in the data source.

For the purposes of this analysis, and to give an indication of potential gaps, data for ‘yes, directly’, ‘yes, indirectly’, and ‘yes, partially’ were combined to indicate that the outcome was available, at some level, in the related data source. ‘We can access this information via other sources’ and ‘no’ were combined to indicate that the outcome was not assessed in the represented data source.

The percentage of data sources which contained information on each outcome were calculated, with ‘yes’ indicating that partial or complete data is available and ‘no’ indicating that data was not available directly from that source. There was some variety in questionnaire responses, with some respondents appearing to interpret the questions in slightly different ways.

It is important to note that this report aims to give a broad overview of the types of outcomes assessed in the included data sources as reported in the questionnaire. This does not go into detail about the types of data source included or assess the veracity of questionnaire responses, which might influence interpretations about what is actually measured in each data source and the availability of data (e.g. the difference between population-based and patient-based cohorts). A fuller description of the implications of similar issues, such as data availability and suitability, combining different data source types (e.g. RCT, cohorts and EHRs) and guidelines for the use of data were outlined in ROADMAP consortium D3.6 (2018).

## 3. Results

Questionnaire data on the availability of information on outcomes were collected for four clinical trials, four EHR / disease registries, and 69 cohorts. It is important to note the over representation of cohorts in the following results. This data does not give a representative sample of all EHR and clinical trial practices.

### 3.1. Clinical Diagnosis

Figure 4 shows the percentage of data sources available for outcomes related to clinical diagnosis.

Of the included cohorts, most data sources measured subjective memory complaint, subjective cognitive complaint, mild cognitive impairment, Alzheimer's disease, and dementia. The less common forms of dementia, such as vascular, frontotemporal dementia and dementia with Lewy bodies were captured in fewer cohorts. Preclinical measurements and amnesic or non-amnesic MCI were measured in a smaller number of cohorts. Despite this, there was cohort data available for all outcomes related to clinical diagnosis.

Among the four included EHRs, there was no available data for prodromal, preclinical AD, and non-amnesic MCI. Most data were available for AD and other dementia subtypes, with less for subjective memory complaint, subjective cognitive complaint, and amnesic MCI.

The four included clinical trials involved people with AD only.

**Figure 3: Percentage of data sources with data for 'clinical diagnosis' outcomes**



### 3.2. Disease Severity and Progression

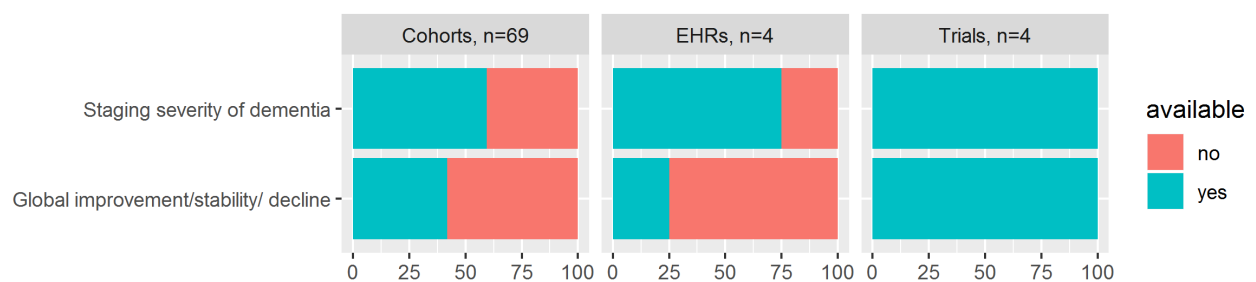
Figure 5 shows the percentage of sources with information on outcomes related to disease severity and progression.

For the cohort data, it was evident that the majority assessed the stage and severity of the condition and roughly 40% measured global improvement or decline.

Three of the four included EHRs assessed stage and severity of dementia, with one assessing global improvement or decline.

All four clinical trials assessed these outcomes.

**Figure 4: Percentage of data sources with data for 'disease severity & progression' outcomes**



### 3.3. Cognitive Abilities

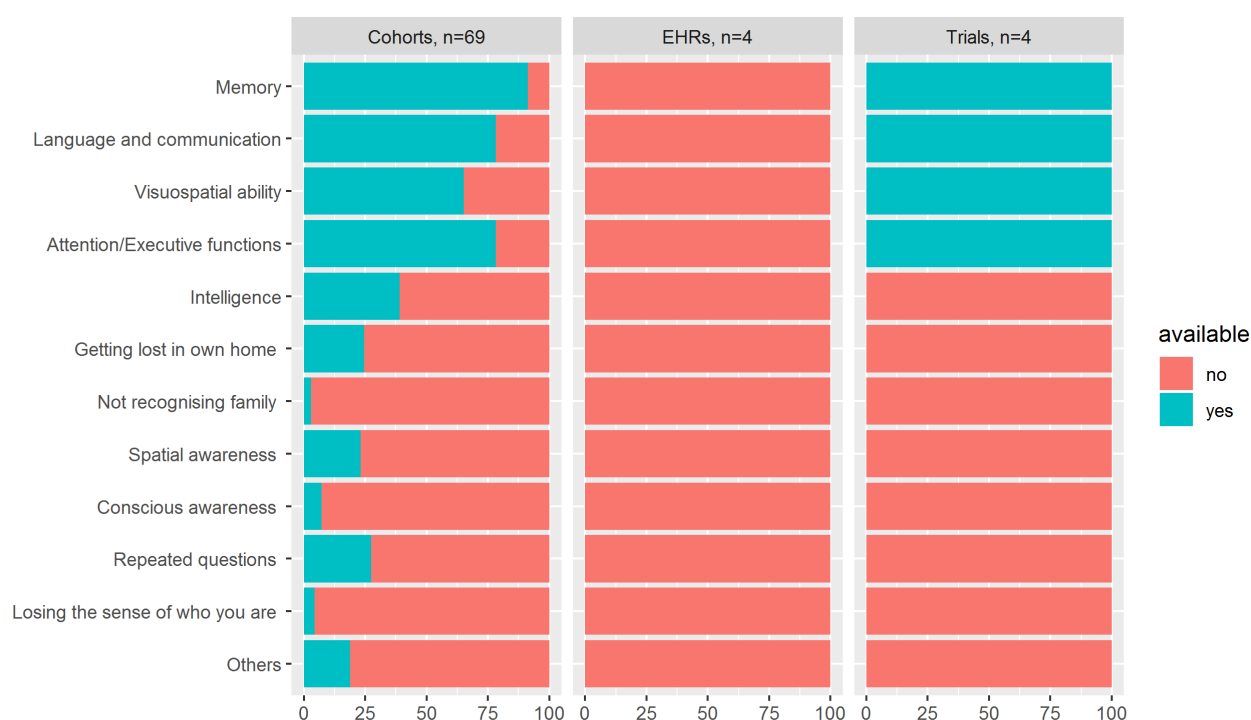
Figure 6 shows the percentage of data sources capturing information on outcomes related to cognitive abilities. This was a priority domain highlighted by WP2 by all stakeholders (ROADMAP consortium, D2.3 & 2.4, 2018).

In the cohort data, memory, language and communication, attention or executive functions, and visuospatial abilities were frequently measured. Outcomes represented less frequently included intelligence, repeated questions, getting lost in own home, and spatial awareness, followed by conscious awareness, not recognising family, and losing the sense of who you are.

Cognitive abilities were not captured in any of the included EHR data sources.

All four clinical trial data sources measured memory, language and communication, attention / executive functions, and visuospatial abilities only.

**Figure 5: Percentage of data sources with data for ‘cognitive abilities’ outcomes**



### 3.4. Functional Ability and Independence

Figure 7 shows the percentage of data sources which included information on outcomes related to functional ability and independence. This was a priority domain highlighted by WP2 by all stakeholders (ROADMAP consortium, D2.3 & 2.4, 2018).

In the cohort data, it was evident that functional outcomes, often classified into basic activities of daily living (toileting, bathing, eating, dressing, and basic mobility) and instrumental activities of daily living (transportation, transferring, shopping capacity, responsibility for own medications, housekeeping, laundry, food preparation, financial capacity, management of everyday technology, and ability to use the telephone) were assessed frequently. Clinical judgement of independence and social engagement were measured less frequently, with supervision and communication measured least often. Hence, there was cohort data available for all outcomes related to ‘functional ability and independence’.

Two of the four EHR data sources measured functional abilities, with no data collected for walking, supervision, social engagement, management of everyday technology and communication.

The four clinical trials assessed typical instrumental and basic activities of daily living as listed above, but did not measure other outcomes like clinical judgement on independence or financial capacity.

**Figure 6: Percentage of data sources with data for ‘functional abilities/independence’ outcomes**



### 3.5. Behavioural and Neuropsychiatric Symptoms

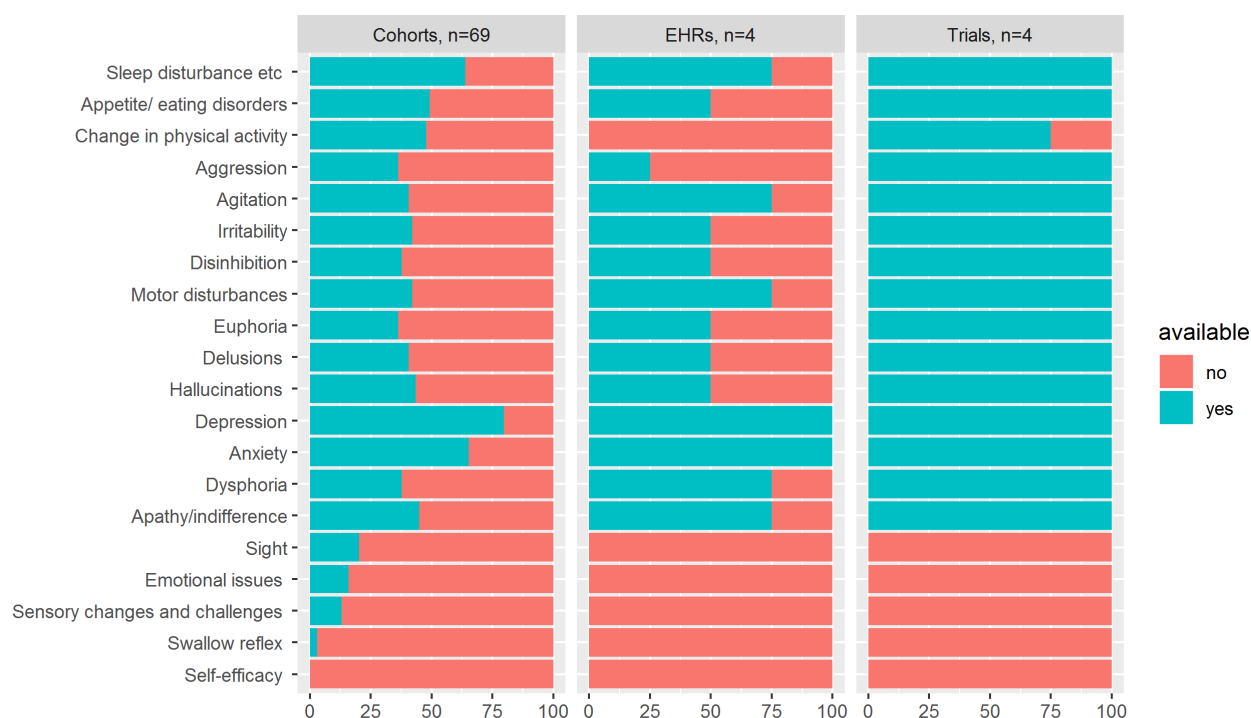
Figure 8 shows the percentage of data sources that capture behavioural and neuropsychiatric symptoms. This was a priority domain highlighted by WP2 (ROADMAP consortium, D2.3 & 2.4, 2018).

In the cohort data, the most commonly measured outcomes were anxiety and depression. A large portion of the cohorts (~40 – 50%) captured the majority of other behavioural and neuropsychiatric outcomes, however swallow reflex, sight, sensory changes and challenges, and emotional issues were measured less frequently.

In the EHR data, depression and anxiety were most frequently measured. The majority of other outcomes were captured in two or three of the EHR sources, however no data was available for swallow reflex, sight, sensory changes and challenges, self-efficacy, emotional issues and change in physical activity.

The included clinical trials assessed most of the behavioural and neuropsychiatric outcomes, however no data was available for swallow reflex, sight, sensory changes and challenges, self-efficacy, and emotional issues.

**Figure 7: Percentage of data sources with data for 'behavioural/neuropsychiatric' outcomes**



### 3.6. Medical Investigations

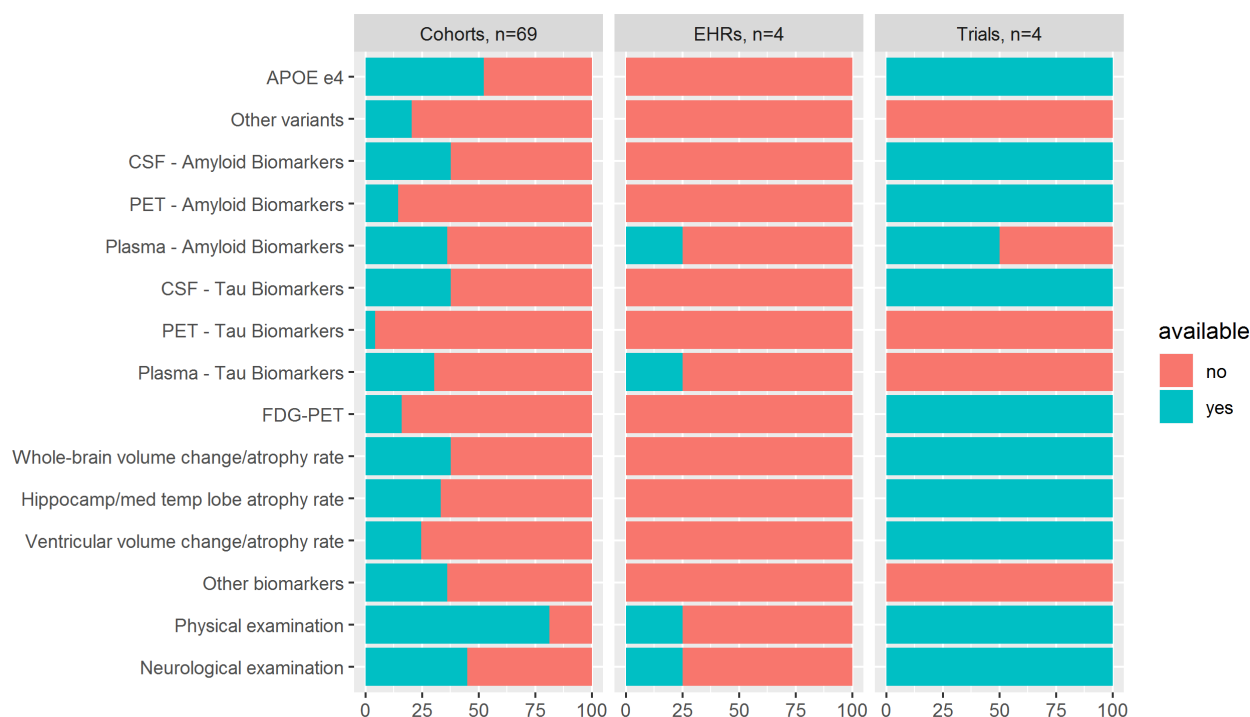
Figure 9 shows the percentage of data sources that collect data for medical investigations.

In the cohorts, most data were available for physical examinations, followed by APOE e4 and neurological examination. Data for biomarkers were less frequently collected, with the most common being CSF tau and amyloid. Plasma tau, PET amyloid & tau were captured least frequently. Despite this, there was cohort data available for all outcomes relating to medical investigations.

One of the four EHR data sources collected plasma tau & amyloid, physical examination and neurological examination data, with no other data for other medical investigations available.

In the clinical trials, data was not available for plasma tau, PET tau, and other variants / biomarkers, though all others were captured.

**Figure 8: Percentage of data sources with data for ‘medical investigations’ outcomes**



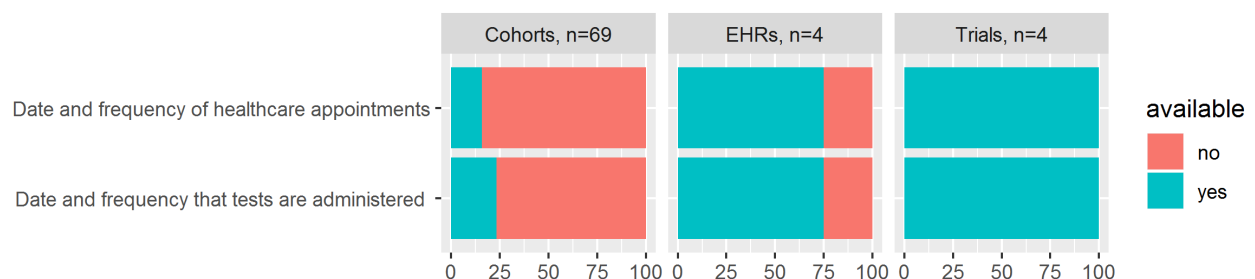
### 3.7. Assessments by Health Professionals

Figure 10 shows the percentage of data sources which collect data for assessments by health professionals.



In the cohorts, data were collected for the date and frequency that tests were administered in approximately 25% of available data sources, with less data collected for date and frequency of healthcare appointments, three of the four EHRs and all four clinical trials collected data for both outcomes.

**Figure 9: Percentage of data sources with to data for ‘assessments by health professionals’ outcomes**



### 3.8. Use of Health Care and Social Services

Figure 11 shows the percentage of data sources which capture information on the use of health care and social services.

In the cohorts, most data were collected for patient health care resource use and living accommodation. There were limited or no data for all other outcomes, with fewest data available for caregiver-oriented outcomes like caregiver work status and caregiver sleep.

All four EHRs measured patient health care resource use, with two of four assessing living accommodation, and one assessing health service costs and co-payment patient. No other outcomes were measured.

All clinical trials assessed patient health care resource use, living accommodation, informal caregiver time, health services costs, and caregiver work status, but did not measure the remaining outcomes.

**Figure 10: Percentage of data sources with data for ‘use of health care and social services’ outcomes**



### 3.9. Therapeutic Treatment

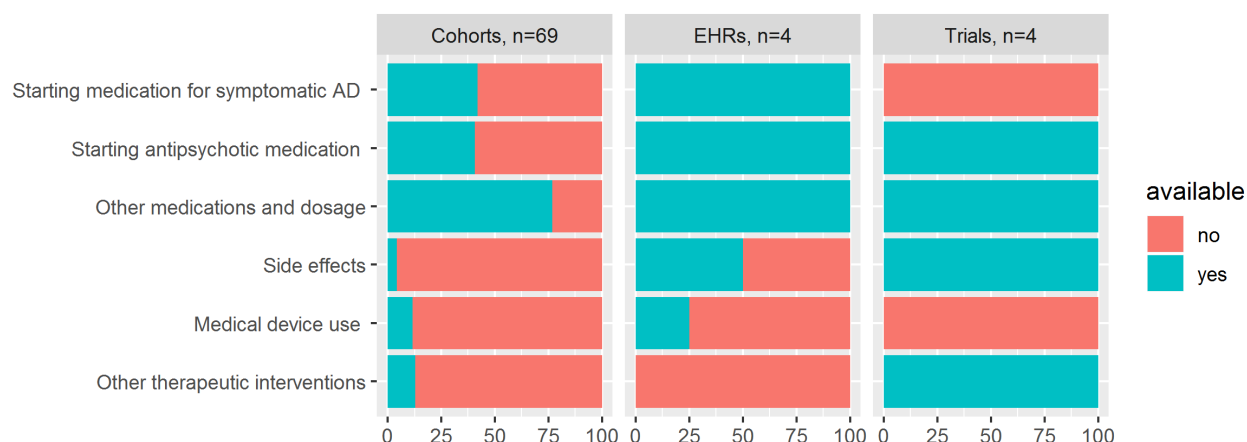
Figure 12 shows the percentage of data sources that collect data for outcomes related to therapeutic treatment.

In the cohorts, most data were collected for other medications and dosage, followed by starting medications for symptomatic AD and starting antipsychotic medication. There was less data available for medical device use and other therapeutic interventions, and least for side effects of medications. Hence, there was cohort data measured for all outcomes relating to therapeutic treatment.

All four EHRs measured other medications and dosage, starting medication for symptomatic AD, and starting antipsychotic medication. Two of the four assessed side effects, with one assessing medical device use. No data were collected for information on other therapeutic interventions.

All clinical trials assessed side effects of medications, other therapeutic interventions, other medications and dosage and starting antipsychotic medications. No data were collected for starting medication for symptomatic AD and medical device use.

**Figure 11: Percentage of data sources with data for ‘therapeutic treatment’ outcomes**



### 3.10. Significant Disease-Related Life Events

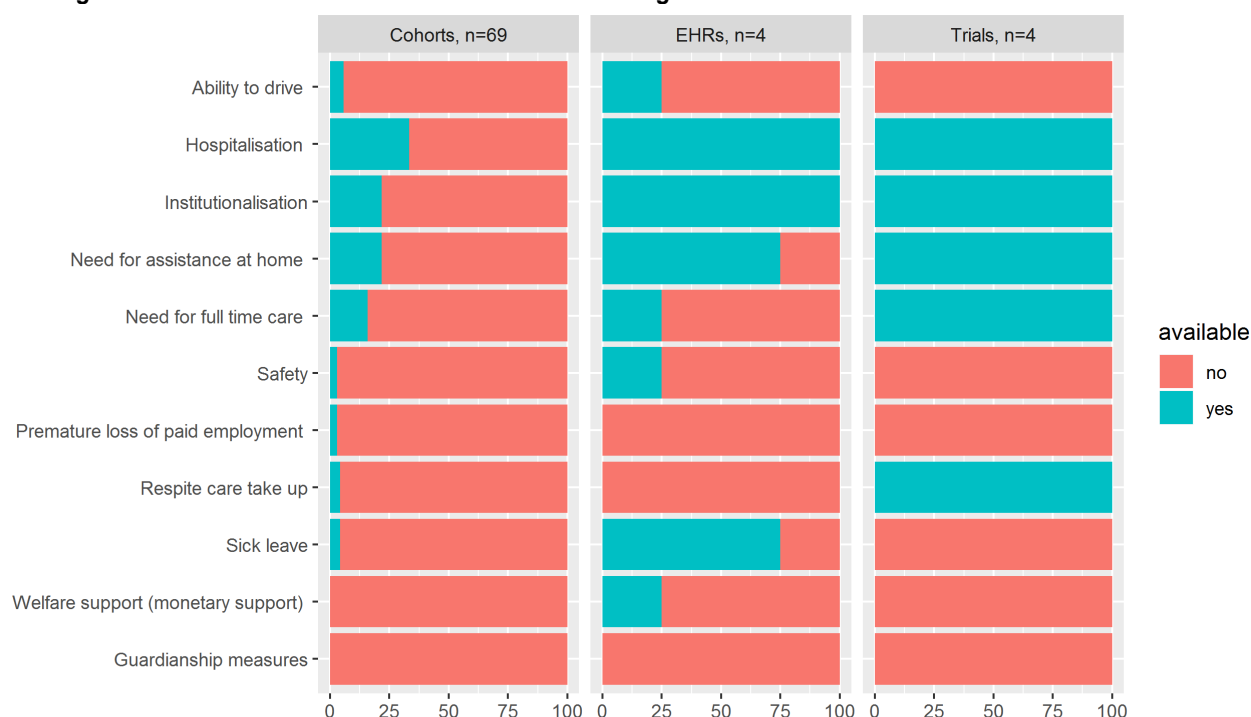
Figure 13 shows the percentage of sources with data on significant disease-related life-events.

In the available cohorts, the largest number of data sources collect data for hospitalisation. Institutionalisation, need for assistance at home and need for full time care were measured less frequently, and fewer cohorts assessed sick leave, safety, respite care take-up, premature loss of paid employment, and ability to drive. No cohorts measured the need for welfare (monetary) support or guardianship measures.

Of the four EHRs, all measured institutionalisation and hospitalisation, with three of the cohorts assessing need for sick leave. Data for welfare (monetary) support, safety, need for full-time care and ability to drive were assessed in one EHR data source.

All four clinical trials assessed respite care take-up, need for full-time care, need for assistance at home, institutionalisation, and hospitalisation, with no data collected for the remaining outcomes.

**Figure 13: outcomes of data sources with data for 'significant disease-related life-events' outcomes**



### 3.11. Patient Quality of Life

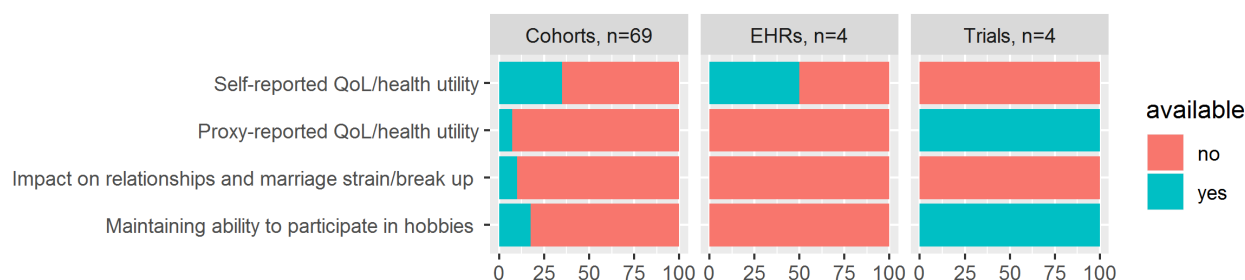
Figure 14 shows the percentage of data sources with information on patient quality of life. This was a priority domain highlighted by WP2 by all stakeholders (ROADMAP consortium, D2.3 & 2.4, 2018).

In the cohort data sources, most data was collected for self-reported QoL / health utility, followed by maintaining ability to participate in hobbies. Fewer cohorts measured the impact on relationships and marriage strain / break up, with least data relating to proxy-reported QoL / health utility.

Two of the four EHRs assessed self-reported QoL / health utility, with no data collected for the remaining outcomes.

All four clinical trials assessed proxy-reported QoL / health utility and maintaining the ability to participate in hobbies; however, no data were collected for self-reported QoL / health utility or impact on relationships and marriage strain / break up.

**Figure 14: Percentage of data sources with data for ‘patient quality of life’ outcomes**



### 3.12. Quality of the Carer's and Family's Lives

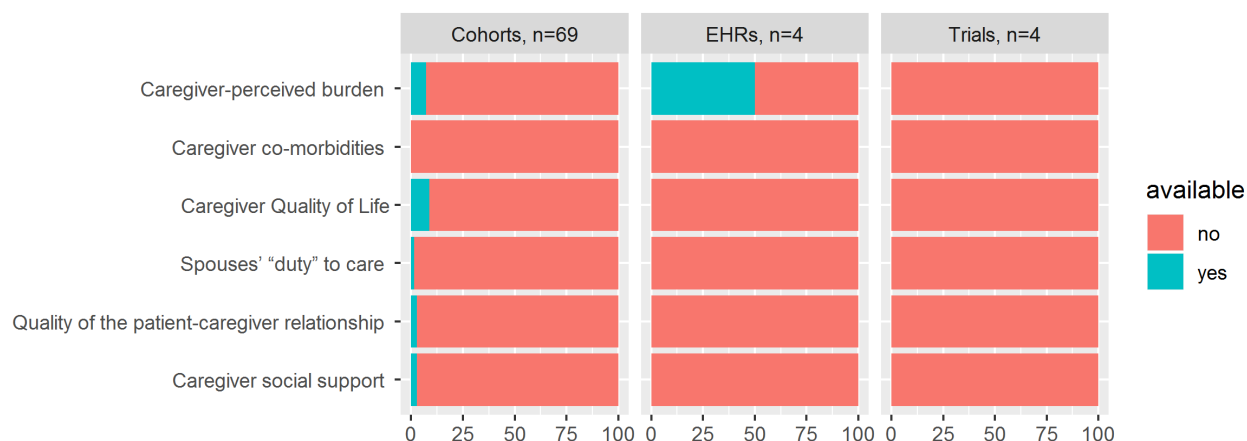
Figure 15 shows the percentage of data sources with information on outcomes related to quality of the carer's and family's lives. This was a priority domain highlighted by WP2 (ROADMAP consortium, D2.3 & 2.4, 2018).

For the cohort data sources, there was most data collected for caregiver quality of life, with fewer data sources assessing caregiver-perceived burden, and a small number of cohorts assessing spouses' duty to care, quality of the patient-caregiver relationship, and caregiver social support. There was no data collected for caregiver co-morbidities.

Data for caregiver perceived burden was assessed in two EHR data sources, with no data available for the remaining outcomes.

None of the four clinical trials measured any outcomes relating to the quality of the carer's and family's lives.

**Figure 15: Percentage of data sources with data for ‘quality of the carer's and family's lives’ outcomes**



### 3.13. Mortality and Comorbidities

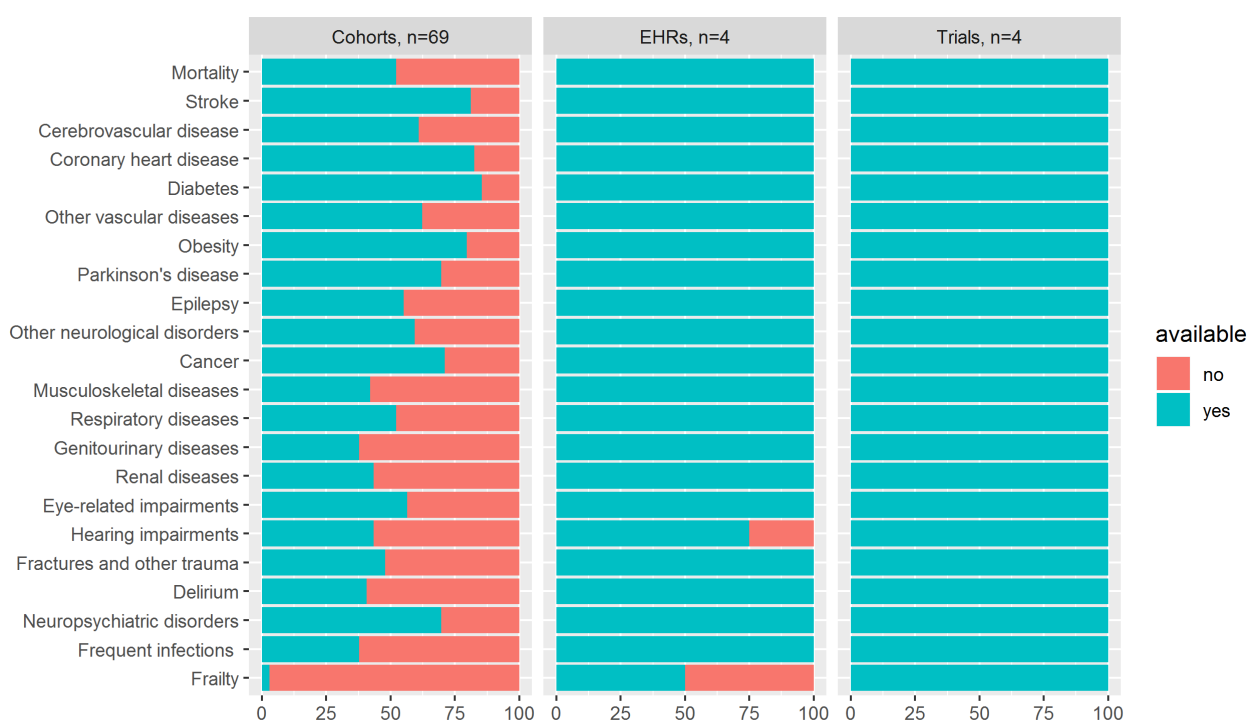
Figure 16 shows the percentage of data sources with information for outcomes related to mortality and comorbidities.

The majority of cohorts assessed comorbidities, with most data collected for stroke, diabetes and coronary heart disease. Frailty was captured in the smallest amount of data sources.

Hearing impairments were captured by three EHR data sources and frailty by two. Four assessed all other comorbidities.

All mortality and comorbidity outcomes were assessed in all four clinical trials.

**Figure 16: Percentage of data sources with data for ‘mortality and comorbidities’ outcomes**



## 4. Discussion

### 4.1. Which Outcomes can be Obtained at Scale from the RWD Sources Identified by WP3?

Regarding clinical diagnosis (Figure 4), Alzheimer's disease, dementia, mild cognitive impairment and subjective cognitive / memory complaints were assessed in most cohort and EHR data sources, with Alzheimer's disease being captured in all clinical trial data sources. This might be indicative of the prevalence of AD as the most common cause of dementia (Scheltens et al., 2016). There was also a substantial amount of cohort and EHR data for the less common dementia subtypes, such as vascular, frontotemporal, and dementia and dementia with Lewy bodies.

For outcomes relating to disease severity and progression (Figure 5), the majority of data sources collected data for staging the severity of dementia and global improvement / decline. This might be expected, given that the included cohorts often involve repeated measures over time. In clinical trials, assessing disease severity and improvement over time are key to understanding the effectiveness of an intervention (Eichler et al., 2011).

Memory, language and communication, attention / executive functions, and visuospatial abilities were assessed at scale in the cohort and clinical trial data sources (Figure 6). This could be explained by the relevancy of these cognitive outcomes to the pathology and diagnosis of dementia and related diseases (World Health Organisation, 1992; American Psychiatric Association, 2000). Additionally, these outcomes were captured in common dementia measurements like the Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the Alzheimer's Disease Assessment Scale (ADAS-Cog; Rosen et al., 1984), which were applied in many of the included data sources. In terms of priority outcomes identified by WP2, cognitive abilities, such as memory, attention and executive functions, and language and communication, were deemed priority by all stakeholders in all workstreams (ROADMAP consortium, D2.3 & 2.4, 2018). This is reassuring, and highlights there was a large amount of data available for some of the outcomes of greatest importance to those affected most by the disease.

Similarly, functional outcomes like basic activities of daily living (toileting, bathing, eating, dressing and basic mobility) and instrumental activities of daily living (transportation, transferring, shopping capacity, responsibility for own medications, housekeeping, laundry, food preparation, financial capacity, management of everyday technology and ability to use telephone) were assessed frequently across data sources (Figure 7). Again, functional decline is central to dementia diagnosis and

pathology (World Health Organisation, 1992; American Psychiatric Association, 2000), and common measures of functional abilities, such as the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL; Galasko et al., 1997), capture many of the functional outcomes listed. These were used in the majority of included data sources. Functional abilities were deemed priority by all stakeholders included in WP2 (ROADMAP consortium, D2.3 & 2.4, 2018), in particular instrumental and basic activities of daily living.

Additionally, behavioural and neuropsychiatric symptoms, such as anxiety, depression, hallucinations, agitation and delusions were frequently assessed in the included data sources (Figure 8). Again, this finding is expected given the centrality of behavioural and neuropsychiatric symptoms to the pathology and diagnosis of dementia and AD (World Health Organisation, 1992; American Psychiatric Association, 2000). In WP2, behavioural and neuropsychiatric outcomes like anxiety, depression and other mental health issues were priority to key stakeholders (ROADMAP consortium, D2.3 & 2.4, 2018).

For medical investigations (Figure 9), physical examinations and APOE e4 data were available in the majority of cohorts and all clinical trials. APOE e4 can be assessed with a blood test (as opposed to scanning or CSF collection), and is often used when diagnosing AD (Sadigh-Eteghad et al., 2012), which might explain why it was commonly assessed. Amyloid and tau biomarkers were measured in all included clinical trials, in addition to 40 – 50% of cohorts assessing whole brain volume and hippocampal / temporal lobe atrophy, conducting neurological examinations, and assessing CSF – tau and amyloid biomarkers.

For outcomes relating to therapeutic treatment (Figure 11), details of other medications used, and the starting date of antipsychotic medication use are available in the majority of data sources. The starting date of medications for symptomatic AD was also available in the majority of cohort and EHR data sources.

It is evident that information for mortality and comorbidities was available across the majority of data sources (Figure 16), in particular for illnesses with strong links to dementia (stroke, cardiovascular diseases, diabetes, etc.; Scheltens et al., 2016).

## **4.2. Which Outcomes are Challenging to Obtain from any of the Data Sources Identified in WP3?**

Despite the availability of data for all outcomes related to clinical diagnosis (Figure 4), there were fewer data sources available for preclinical and prodromal AD and amnesic / non-amnesic MCI.



Preclinical and prodromal patients are harder to access in the general population, given the silent nature of the disease in these early stages (Dubois et al., 2016). To illustrate, AD is characterised by a long preclinical phase, and in the subsequent prodromal phase, symptoms are mild (Scheltens et al., 2016). As a result, diagnosis is often made in the dementia phase of the disease (Scheltens et al., 2016), which might explain the smaller number of data sources.

For cognitive abilities (Figure 6), outcomes like not recognising family, losing the sense of who you are, getting lost in own home, and conscious awareness were captured less frequently than outcomes like memory or executive functions. These outcomes were defined in participants' own words in WP2 (ROADMAP consortium, D2.3 & 2.4, 2018), which might account for this difference. As a result, it might not be clear to the person completing the questionnaire what was meant by these terms or how they should be measured. Outcomes like memory are also captured in common cognitive measures like the MMSE, hence easier to access. One issue with the use of scales like the MMSE is that scores are combined into a more 'global' representation of cognitive abilities, ranging from 0 – 30 (Folstein et al., 1975). Recent discussion has questioned this approach, as it does not allow for detailed understanding of the individual components of cognition (Scheltens et al., 2016). Future scales and questionnaires might utilise outcomes like 'not recognising family' as items or questions, to give a fuller understanding of cognition using outcomes of priority to key stakeholders.

All functional abilities (Figure 7) were assessed in the included data sources, however, supervision (preventing dangerous events), management of everyday technology, and communication were measured less frequently. Communication might relate more to cognitive abilities, as opposed to everyday functioning (see language & communication, Figure 6), and management of everyday technology appeared to be assessed through other means, such as the ability to use the telephone.

For behavioural and neuropsychiatric outcomes (Figure 8), fewer data sources captured physiological outcomes like maintaining the swallow reflex, sight, and sensory changes / challenges. Emotional issues were also assessed less frequently, as relevant aspects of this term may have not been apparent to the questionnaire respondent, or indeed, how it should be measured. However, related outcomes like anxiety and depression were measured in a large percentage of data sources.

With regards to medical investigations (Figure 9), fewer data sources assessed biomarkers using plasma and PET. This might be indicative of the increased application of biomarkers in recent times, and the need for validation and standardisation of this form of medical investigation before application in clinical practice (Scheltens et al., 2016). For outcomes relating to assessments by health care professionals, fewest data sources measured the data and frequency of medical appointments.

For significant disease related life events (Figure 13), there was limited data available for the need for welfare (monetary) support, sick leave, safety, loss of employment, and losing the ability to drive (i.e. losing licence). Loss of employment and losing the ability to drive were major issues identified in work by WP2 (ROADMAP consortium, D2.3 & 2.4, 2018), highlighted by key stakeholders. These were strong indicators of disease progression, and were identified as abilities that should be preserved.

For patient quality of life (Figure 14), either self-reported or proxy measures were assessed in around half of data sources, however outcomes which impact quality of life, such as losing the ability to participate in hobbies, or marriage strain / break down were measured less frequently. Patient quality of life was identified as priority by all stakeholder groups in WP2 (ROADMAP consortium, D2.3 & 2.4, 2018), highlighting the importance of these outcomes.

Caregiver-oriented outcomes related to the use of health care and social services were measured in a limited number of data sources (Figure 11), and only one cohort (Actifcare) consistently measured caregiver related outcomes. Outcomes such as formal or informal caregiver time, work status, sleep, and healthcare resource use were measured infrequently.

Further, outcomes relating to the quality of the carer's and family's lives (Figure 15) were measured infrequently, and data for quality of the patient / caregiver relationship, caregiver quality of life, caregiver social support, caregiver comorbidities, and the impact of the disease on caregivers (burden) was limited. This domain was identified as priority in WP2 (ROADMAP consortium, D2.3 & 2.4, 2018), highlighting that some priority outcomes are underused in the identified cohorts or are lacking data. As the population of PWD continually increases, with a predicted 135 million people affected by dementia worldwide by 2050 (Prince et al., 2015), the caregiver population will also increase. Given that the disease also affects families, spouses, and close friends, the global caregiver population could far surpass the population of PWD.

### **4.3. Which Outcomes are not Adequately Captured in any Identified Data Source?**

Self-efficacy was not assessed in any of the included data sources. In a study involving people with MCI and their caregivers, self-efficacy was ranked as the second most important outcome from a list of twelve, second only to quality of life (Barrios et al., 2016). This concept relates to the belief in one's ability to achieve goals, or *"how well one can execute courses of action required to deal with prospective situations"* (Bandura, 1982). In terms dementia, an example of self-efficacy would be how

confident an individual is that they can complete errands despite their cognitive difficulties (Barrios et al., 2016).

Additionally, personal financial items (relating to PWD), caregiver comorbidities, and guardianship measures were also not captured in any data source. This lack of data for caregiver-oriented outcomes reiterates the points in the last section.

#### 4.4. Summary and Key Issues

Outcomes relating to cognitive abilities, functional abilities and independence, behavioural and neuropsychiatric symptoms, details of therapeutic treatment, and mortality & comorbidities were captured frequently in the data sources. Fewer data sources measure outcomes regarding significant disease related life events, medical investigations, use of health care and social services, and patient quality of life. A limited number of data sources captured caregiver-oriented outcomes, in particular outcomes related to the quality of the carer's and family's lives. If future research aims to target outcomes of priority to those affected most by the disease, outcomes relating to the caregiver should be assessed.

There are a number of key issues that should be acknowledged when interpreting results. First, the uncertain accuracy of the answers to the questions posed to data custodians (or those answering on behalf of custodians) should be acknowledged, since some of the questions seem to have been interpreted inconsistently. If an outcome was deemed 'not available' in a data source, it might be explained by a study excluding such subjects at the outset. The information (e.g. on whether a subject has vascular dementia) may actually be available, although not recorded per se. Additionally, the large differences in the types of data likely to be available from population-based cohorts, and cohorts that recruit people based on being at high risk of developing dementia or people with established dementia is also important to consider.

The incomplete coverage of all data sources by the questionnaire, at present, should also be acknowledged (information was collected from 77 of 300 identified data sources). Further, assessment scales were not a key focus of this report, however it is important to recognise that there is a lack of harmonisation across data sources in terms of scale selection. The small number of EHRs and clinical trials involved in this exercise means that it is unlikely that this is a representative sample of these data source types.

One should also acknowledge the potential for overlap of outcomes across domains. Collaborative effort in WP2 involved assigning outcomes to domains. In such instances, the outcome was placed

where it appeared to fit best according to clinical nosology (World Health Organisation, 1992), or previous WP2 deliverables. It is an ongoing necessity to ensure that these make sense to key stakeholders in light of new or evolving evidence.

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