D8.4 Landscaping paper on ethics of outcome prioritisation in AD treatment

116020 - ROADMAP

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

WP8 – Ethical, Legal and Social Implications

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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.

Publishable Summary

Health outcome prioritisation is the ranking in order of desirability or importance of a set of medical objectives and their associated cost or risk, obtained collaboratively *with* patients and their carers, or *from* patients and their carers. In this review, we summarise and provide an overview of the complex ethical landscape in which the prioritisation of health outcomes in Alzheimer's disease (AD) takes place. Dementia has been described as the 'greatest global challenge for health and social care in the 21st century', on account of worldwide improvements in longevity that drive an increasing number of people affected, and therefore increasing costs for health and social care systems. These pressures throw into sharp relief ethical, social and political challenges around how healthcare resources are allocated, what kinds of health improvements matter to patients and how they are measured. In this review we outline eight areas where such challenges for outcome prioritisation are raised: (1) Public health and distributive justice, (2) Scarcity of resources, (3) Heterogeneity and changing circumstances, (4) Conditions of equitable prioritisation, (5) Conflicting priorities, (6) Communication, autonomy and coercion, (7) Caregiver issues, (8) Disclosure of risk. In illustrating the complexity of the ethical landscape, these areas cover the difficult balances that need to be struck when allocating resources, when measuring and prioritising outcomes, and when individual preferences are sought. We conclude by reflecting on how the tools of the social sciences and ethics can help address challenges posed by resource allocation, measuring and prioritising outcomes, and eliciting stakeholder preferences.

1. Introduction

Health outcome prioritisation is the ranking in order of desirability or importance, of a set of medical objectives and their associated cost or risk, obtained collaboratively *with* patients and their carers, or *from* patients and their carers. The situations in which outcome prioritisation is necessary include: i) regulatory scenarios, for the accurate assessment of the benefit to risk ratio, and hence to establish whether it is feasible to provide a treatment to patients. In these cases, patients and carers are asked for their perspective on, for example, which endpoints would be the most relevant to measure in a Randomised Controlled Trial (RCT); ii) economic scenarios when considering 'value for money', as the finitude of resources precludes being able to achieve every desired outcome; iii) questions of individual benefit-to-risk ratios to establish what kind of care a particular patient wishes to receive. In this review, we summarise and provide an overview of the complex ethical landscape within which these scenarios for the prioritisation of health outcomes in Alzheimer's disease (AD) take place. For reasons relating to changing contemporary approaches to AD management and treatment, an analysis of the ethical issues associated without prioritising outcomes in the disease course is timely and necessary.

In 2017 the World Health Organisation recognised AD as a *'global public health priority'*[1]. This is because AD is the most common type of dementia and, as the 2017 Lancet Commission[2] has stated, *'Dementia is the greatest global challenge for health and social care in the 21st century: around 50 million people worldwide have dementia and this number is predicted to triple by 2050*'. As such the condition imposes a significant and growing health and economic cost, and these costs constitute the reason to reconfigure AD as a public health priority rather than one of only standard individual remedial clinical medicine. This transformation changes the way it is approached and managed (Solomon et al, 2014). In general, the aim to make society-level judgements about resource allocation decisions entails basing those decisions on judgements of utility (Dolan and Kahneman, 2008), as the normative goal of public health decision-making must be directed towards improving the wellbeing of *populations* rather than particular individuals therein. This is not ethically uncontroversial, however unavoidable a strategy it may be at a population level. Identifying the right course of action as that which produces the greatest aggregate benefit risks de-prioritising the interests of the remaining minority of individuals, or subjecting whole populations to interventions to prevent relatively few cases of disease.

When assessing the value of a new therapy an important component is understanding patients' perspectives about what it would mean to them to improve their health; which aspects of health improvement are the most important to them; and how they weigh the risks and opportunities of receiving the treatment in question (Robinson et al, 2008; Fleurence et al, 2013). For example, individuals may have divergent feelings about whether length or quality of life is more important to them; about what type or level of risk they are willing to undertake; or what opportunities they are willing to forgo in order to achieve medical objectives (Fried et al, 2008; Barry and Edgman-Levitan, 2012). Multiple possibilities with different probabilities of success and failure must therefore be weighed against each other.

[1] http://www.who.int/news-room/fact-sheets/detail/dementia
[2] https://www.thelancet.com/commissions/dementia2017

Moreover, there is considerable uncertainty in predicting AD outcomes (Castellani and Smith, 2011), since normal and pathological cognitive decline are not clearly delineated, symptom expression and disease progression are heterogeneous, and health and social care systems are not always sufficiently integrated to ensure the best support for patients. Additionally, 'priority' is likely to be understood differently by different stakeholders. For example, in the scenarios outlined in the first paragraph, i) is a population-level concern based on calculations of aggregate benefit, whereas iii) is a matter of individual-level concern pertaining to benefits and risks for specific patients. These are primarily of interest to epidemiologists and clinicians respectively and the different professional perspectives of these and other stakeholders may give rise to commensurately diverse assessments of how competing outcomes should be weighed and balanced. These are also difficult calculations because whether a treatment ought to be provided is both an evidential and an ethical question. Evidential questions of whether a treatment 'works', does more good than harm, and delivers value for money crucially depend on ethical questions about what one believes it is important to measure and what aspects of personal health one should aim to modify.

Against this complicated ethical backdrop, outcome prioritisation attempts to ensure that the finite resources available are deployed so as to ensure that they achieve the greatest aggregate benefit. It is important to not here, therefore, that outcome prioritisation is an inherently utility-driven process to the extent that it must attempt to resolve resource allocation dilemmas. As such it may be subject to the criticism that the experiences of patients and carers are irrelevant to this process, since the relevant data pertaining to this is largely qualitative and not amenable to being captured by cost-effectiveness tools such as QALYs. However, this objection can be met by pointing out that that the *aggregated* preferences of patients and carers can still play a legitimate role in determining how to rank the desirability of outcomes. Furthermore, although much data about preferences is qualitative and based on subjective experiences of care and its outcomes, there are tools available in social science research methods such as surveys that can be designed in such a way that they elicit the ranking of preferences for different outcomes.

Connected to outcome prioritisation is the related process of priority setting, which is the *procedure by which the ranking is carried out*. This review focuses on outcome prioritisation, but since questions about health outcomes that are prioritised invokes related questions about how the prioritisation is done, we will touch on this related process occasionally where necessary.

2. Methods

Data collection was carried out in two stages. First, a systematic search was carried out using key words to yield an initial sample. Second, a combination of snowball sampling and input from authors in key areas yielded further documents of relevance. Since this is a landscaping paper of ethical issues in the specified context it was appropriate to combine these methods rather than restrict our methodology to a systematic review approach alone.

One reviewer collated the data from the included studies. Any disagreements were resolved by co-authors and other contributors when circulated during the drafting phase. The following information was extracted: the aim of the study; the objective of the study; the type of participant; the type of dementia; the level of severity; and the outcomes desired and prioritised.

The structured literature review was conducted in December 2017 and January 2018. Data sources included EMBASE, MEDLINE, SCOPUS, Web of Science, and Google Scholar databases. We searched articles titles using the following terms of relevance to the review, in the case of Google Scholar only selecting articles for potential inclusion from the first 100 results returned: ((ethic*[Title]) AND outcome*[Title]) AND priorit*[Title]; ((ethic*[Title]) AND outcome*[Title]) AND health*[Title]; ((ethic*[Title]) AND priorit*[Title]) AND health*[Title]; ((ethic*[Title]) AND outcome*[Title]) AND alzheimer*[Title]; ((ethic*[Title]) AND outcome*[Title]) AND dementia*[Title]; ((ethic*[Title]) AND priorit*[Title]) AND alzheimer*[Title]; ((ethic*[Title]) AND priorit*[Title]) AND dementia*[Title].

In the interests of ensuring a manageable and contemporarily relevant sample, we restricted our search only to literature published in the ten years prior to beginning this review in 2017, and as such the sample extends from 2007 to 2018 in line with this inclusion criterion. Articles were rejected for full text review either because they were in languages other than English, or because on reading the abstract they in fact were insufficiently relevant to the subject matter under analysis. The abstracts and full texts were reviewed by a single reviewer. Following the systematic search we employed snowballing sampling to seek out further relevant material and documents were provided by co-authors to augment the body of literature reviewed.

We will now move on to presenting the findings of this review, firstly with those pertaining to ethical aspects of outcome prioritisation or priority setting in the general context of healthcare, and secondly in relation to the particular context of AD, with some ancillary findings relating to dementia more widely.

3. Results

The search yielded 77 articles which were retrieved having been deemed sufficiently relevant for full text review. From this, 21 articles were rejected after full text review, leaving 56 articles included and reviewed here. Snowball sampling and input from co-authors yielded a further 74 documents, giving a total of 130 documents used in this review.

Below we outline eight areas where authors raise ethical issues in outcome prioritisation. In illustrating the complexity of the ethical landscape, these areas cover the difficult balances that need to be struck when allocating resources, when measuring and prioritising outcomes, and when individual preferences are sought.

3.1. Public Health and Distributive Justice

We will begin by considering outcome prioritisation in AD at the macro-scale, from the perspective of health policy rather than treatment options for the individual patient. A vital aspect of contemporary ethical relevance in AD is the current policy-level drive to reconfigure the disease as a target of public health prevention (Livingston et al, 2017), not only one of standard, remedial, clinical medicine (Yaffe, 2018). As we have seen, AD is being reconceptualised as a public health priority and a target for preventive measures because of the increasing cost of supporting an expanding and ageing population in which AD will increase in prevalence (Dartigues, 2009; Kuljis, 2010; Naylor et al, 2012; Winblad et al, 2016). It is important, however, not to overstate the benefits of a preventive approach

(Leschner et al, 2017; Yaffe 2018) since, as Yaffe (2018, p. 281) notes, *"There are no specific interventions that have sufficient evidence to warrant a public health campaign for the prevention of dementia"*, rather the benefits of promoting general health advice may extend to dementia. For example, Livingston et al (2017, p. 2673) identify many risk factors that it is independently beneficial for individuals to seek to modify, such as *"more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity"*. This is significant in terms of determining an ethical prioritisation of outcomes in two important respects.

First, the provision of information to the public about how they can reduce their risk of a developing a condition such as AD through sustainable lifestyle and consumption choices from early life onwards affects the relationship between the state and its citizens (Buchanan, 2008). Pressure to make certain choices may be viewed as an infringement of liberty (Jennings, 2009; Radoilska, 2009) and, even if one does not object to the provision of health-promoting information as such, the residual questions remain of: a) whether the state has the right to expect that individuals modify their behaviour accordingly; and b) whether it is acceptable to prioritise treatment for people if they develop AD and have not followed the preventative information.

Second, critiques of QALYs (Quality Adjusted Life Year) are relevant here (Kind et al, 2009). QALYs are quantitative tools widely used for making distributive decisions in public health. The ethical challenge of using QALYs in relation to the priorities of individuals is whether a calculation can adequately capture the subjectively bound nature of 'quality of life', given that evaluations will differ between individuals (Hagell et al, 2009). As such, this fundamental difficulty inherent to making aggregate, population-level, distribution decisions must be taken into account when considering the ethical landscape regarding the allocation of resources to reduce and manage the societal and individual burden of a common and debilitating disease such as AD. Moreover, the concepts of 'benefit' and 'value' may be interpreted and defined differently. For example, it is essential, at least from a health economic perspective, to know how to attach a particular price to a particular level of benefit (Rabins and Black, 2007; Tinetti and Studenski, 2011) and this is a complex matter. Furthermore, different views about these will be held by different stakeholders, such as patients, their carers, health care professionals, providers, and payers of medical treatments.

3.2. Scarcity of Resources

Resources are finite and outcome prioritisation therefore requires making distributive decisions about who will receive what and in what proportion to realise the particular outcomes that are desired. How these prioritisation decisions are made, however, differs geographically. For example, in the UK, the National Institute for Clinical and Care Excellence (NICE) prioritises cost-effectiveness, whereas cost-effectiveness does not inform decision-making in Germany, and in the Netherlands it does inform decision-making but only above a certain price threshold, such that drugs that become very cheap do not attract scrutiny in this way (Bauer et al, 2018).

Irrespective of the particular metrics used for making distributive decisions, as Khayatzadeh-Mahaini et al (2009) point out, the finitude of resources means that some people are denied access to certain interventions that might otherwise be able to benefit them. A gap between a population's health needs and what it is possible for its government to provide is inevitable (Norheim 2016), and this raises clear ethical challenges as the gap will necessarily contain some proportion of the population. The needs

of some proportion of the population will be de-prioritised in favour of the needs of others, and the resulting gap may conflict with the clinical duty of care. This is the case both for people with the same condition and prioritisation between people with different conditions. How these priorities are weighed is normatively significant since, as Hermeren (2009) summarises baldly, to prioritise is inevitably to say 'no' to somebody. In this regard the principle of prioritisation according to the resources available is contentious and ethically challenging (Steinbrook, 2008), since some individuals will not be able to benefit or derive any value from the treatment on offer.

3.3. Heterogeneity and Changing Circumstances

Not only is the amount of resources limited, but it is also not necessarily constant. Budget constraints may increase or decrease and are products of political choices and decisions (Geneau et al, 2010). As such it is important to treat considerations of outcome prioritisation as an ongoing process requiring revision according to changing circumstances. Prioritisation is additionally challenging in this regard because advances in medical science expand the range of what is therapeutically possible. Given that the global trend is towards population growth and increasing life expectancy, it is not clear that the therapeutically possible and the economically or politically possible remain in step with each other (Kenny and Jofres, 2007). Decisions about what resources to deploy, when, and to whom, require ongoing deliberation as needs and options change.

This process of deliberation is ultimately concerned with both outcomes and endpoints, which are related but distinct parameters. Outcomes denote measured effects of treatment, whereas endpoints are pre-identified targets of a study that are built into its design. It is important to note here from an international perspective that what outcomes and endpoints are considered important is contentious and dependent on the characteristics of particular markets (Vellas et al, 2008). Moreover, there are numerous ways in which outcomes and endpoints can be measured, and the difficulty of determining preferences for these is compounded by the plethora of assessment tools that are available. Moreover, one of the main challenges in AD is that assessment tools are not ideally sensitive or specific and as such do not yield ideal validity, neither in earlier and preclinical stages of the disease (Ritchie et al, 2017), nor in more severe stages (Robert et al, 2010; Voisin and Vellas, 2009).

In spite of recent population-wide gains in healthy longevity, ageing is nevertheless associated with decline in health and an increase in comorbidities, a consequence of which is that determining treatment priorities becomes more difficult as health needs become more complex (Mangin et al, 2015). Naturally, this complexity is multiplied significantly as the number of ageing people grows, and questions of distributions involve increasingly numerous factors. In particular, as van Summeren et al (2017) report, the evaluative dilemma faced by patients, carers, and clinicians, is frequently how to balance factors such as the benefit of palliation of symptoms and maintenance of life or independence against the discomfort caused by the side effects of a potentially complicated drug regime.

3.4. Conditions of Equitable Prioritisation

3.4.1. Evidence

Determining what counts as fair prioritisation of outcomes depends partly on what needs to be known to make a prioritisation decision. As Janssen et al (2014) note, whether an intervention is or is not

desirable can only be judged according to its outcome, and since interventions - pharmaceutical ones in particular - may have trade-offs between desirable effects and undesirable side-effects, the weighing of these is less straightforward where comorbidities requiring different types of treatment are present (Bunn et al, 2014).

Randomised Controlled Trials (RCTs) of new drug products may investigate drug-drug interactions to some degree, but this is not comprehensive in all cases. As such, data about these may be inadequate due to a lack of statistical power following from inadequate sample sizes, or they may be unavailable with regard to all possible drug-drug combinations. Trials usually assess the efficacy, or in the case of pragmatic trials the effectiveness, of a single experimental drug; however, the expense and length of time required for doing so are constraints that make it impossible to determine optimal clinical practice in as heterogeneous a context as AD. This is problematic because in a real-world context the health needs of people with a condition such as AD, who are typically older and more likely to have comorbidities, are usually complex (Duthy et al, 2011; Buchman et al, 2007; Mrak, 2009). This means that in some instances a cocktail of drugs is prescribed without clinicians fully knowing the risk of harm due to lack of evidence. As such, ensuring an optimal balance of outcomes in the context of old age is particularly challenging.

A further complication associated with RCTs, and one for which they are sometimes criticised, is that although they yield high internal validity, their results are limited in their generalizability (Pearce et al, 2015; Nordon et al, 2016) and are prone to bias (Krauss, 2018). There is in addition the challenge of attrition compromising the validity and / or generalisability of results (Dumville et al, 2006; Dettori, 2011). There is evidence that older, sicker individuals in particular are more likely to drop out of studies (Matthews et al, 2004; Matthews et al, 2006; Bhamra et al, 2008; Tinker et al, 2009), since the average age the older patients are and the more comorbidities they have, the less likely they are to participate in an RCT, as they are more likely to die before the trial is concluded or to discontinue the study treatment due to adverse effects. As such, if drugs are to be brought to market for as heterogeneous a group as AD patients, these drugs may in fact be ineffective or toxic for some or many of them. This uncertainty in turn poses a challenge for being able to realise certain prioritised outcomes if these are ones which depend on the effectiveness of a particular drug.

Having said this, in mitigation it is not impossible for clinicians to be reliably informed about likely drug-drug interactions. Although RCTs cannot test all conceivable combinations, they do nevertheless report any adverse drug events or reactions (ADEs or ADRs)3 (Pocock, 2013). Indeed, separate studies are designed to address these issues (Lewis, 2010), and knowledge of the mechanism of action of certain drugs contributes usefully to decision-making. Notwithstanding the challenges outlined above, therefore, it is not the case that clinicians do not know what they are doing in prescribing certain drugs. Rather, the biggest challenge arises when patients have multiple comorbidities all of which require treatment (Maher et al, 2014), since it may then become necessary to prioritise the treatment of some rather than other in order to realise an all-things-considered desirable outcome.

[3] https://health.gov/hcq/ade.asp

3.4.2. Values and Circumstances

Fairness also consists in part in patients being able to make their own decisions on the basis of the information given to them by their doctors. This ideal has become increasingly salient in recent decades via the notion of 'patient-centred care' (Sandman and Munthe, 2009; Richards et al, 2015). The previously dominant 'doctor knows best' approach to healthcare decision-making is normatively inadequate for properly respecting the values and circumstances of patients. It is important to note here that this should not mean swapping a paternalistic approach for an equally polar norm of practice in which patients have complete autonomy (Badger et al, 2009; Lantos et al, 2011). Respecting autonomy and self-determination is of vital ethical importance, but to the extent that doctors nevertheless possess expertise and knowledge that the patient does not, there is a point at which assenting to a patient's wishes may be harmful – possibly without their knowing that this is the case. There is, for instance, an in-built imbalance between the clinical expertise of the doctor who is aware of the parameters of knowledge regarding the predictability of outcomes, but who is not the one who must experience the disease and its treatment; and the patient whose clinical expertise may be relatively deficient, but who is an expert at least in the context of their own experience and who is the subject of the disease and its treatment. This imbalance is inevitable (Joseph-Williams et al, 2014; Koeck, 2014; Ters and Yima, 2014). As such, patient-centred care and the prioritisation of outcomes should be conceived as a collaboration between clinical experts (namely, doctors) and experts in their own lives (namely, patients), both drawing on the available body of expert knowledge available from the work of HTAs, clinical studies and approved clinical guidelines, in a process that is known as 'shared decision-making' (Elwyn et al, 2012; Barry and Edgman-Levitan, 2012).

3.5. Conflicting Priorities

There are methodological complications when determining and combining preferences. For example, the radical difference between qualitative and quantitative research provides a challenge when pooling and attempting to appropriately weigh different forms of evidence (Bryman, 2007; Polit and Beck, 2010). Nevertheless, there are methods and techniques, including preference elicitation techniques (Danner et al, 2011; Llewellyn-Thomas and Crump, 2013; Weernink et al, 2014), that are used to help patients to arrive at a decision or ranking of the various outcomes and permutations thereof. The ordering of outcomes according to their desirability may not be straightforward, however, given the different ways in which a disease and its symptoms may affect daily living and wellbeing. For example, in patients with multiple conditions or comorbidities – as is frequently the case for older people with AD – there will be a range of countervailing factors that need to be taken into account (Fried et al, 2014) to arrive at what is, overall, the best balance between benefits and risks of one particular approach to treatment rather than another (Maust et al, 2015; Buckley and Salpeter, 2015). The ordering of outcomes is also complex because the 'best' balance of risks and benefits may be plural, insofar as there may be equally desirable prioritisation outcomes depending on the value one places on different priorities. As such there may be more than one 'right' decision in any given scenario.

Ethical challenges in outcome prioritisation emerge when priorities conflict. For example, the value of shorter and longer term goals in AD prevention and treatment must be balanced in making treatment decisions. Although research may yield better treatments in the long term, the development of drugs and tests is slow and resource intensive (Law et al, 2011) and there may also be conflicts of priorities

between different individuals or groups. Moreover, there may also be antecedent challenges in involving all relevant stakeholders in the prioritisation process. For example, minority ethnic groups are often excluded from research due to cultural factors such as linguistic barriers and different values that are not taken into account by the majority ethnic group in which they exist and who are more likely to be conducting the research (Woodall et al, 2010; Uybico et al, 2007; Dilworth-Anderson et al, 2008; Grill and Galvin, 2014).

As Hunter (2006) notes, the ranking of outcomes in order of their priority is also ethically contentious to the extent that there may be disputes about whose responsibility it is to engage in this process. This creates a further set of practical ethical complexities around the balance of duties and responsibilities between patients, their carers, society at large, clinicians, policy makers, health economists, and any other bodies who have a stake in ensuring the optimality of care. For instance, prioritisation may be complex when making choices regarding prevention or disease progression. Given two groups of people with AD, defined as groups by virtue of sharing the same clinical indication or subtype of severity thereof, where group A has a lower quality of life and group B has a higher quality of life with respect to that indication, if resource constraints are such that only one group may receive intervention X which will contribute meaningfully to delaying onset or the worsening of symptoms, it is not obvious which of A or B should receive it.

It may be argued that group A's needs should be prioritised above group B's because they have more to gain from receiving treatment and the outcome is in this respect more substantial than if B were to receive it. In response, however, it is arguable that those in group B should receive it because they have more to lose than those in group A and since at least part of the justification for treatment is the importance of preserving normal activities of daily living, so B's needs should take priority in the allocation decision. There is no straightforward way to resolve dilemmas such as this and they remind us that we cannot assume that priorities and evaluation of the various outcomes will be uniform and agreed between patients, their carers, clinicians, and the wider general public (McBrien et al, 2007; Werner, 2009; Lejman et al, 2013). As Hunter (2006) notes, the ranking of outcomes in order of their priority is ethically contentious to the extent that there may be disputes about whose responsibility it is to engage in this process. Indeed, it may be that such dilemmas are fundamentally unresolvable insofar as it may not be possible to reach a consensus. In these cases what counts as a successful decision and legitimate prioritisation of outcomes will consist in the fastidiousness of the process by which the decision was reached in terms of considering the views of as wide a range of stakeholders as possible, rather than the decision itself.

Any strategy for achieving a distribution of resources for realising a particular hierarchy of outcomes that can be judged as ethical must take account of the stake that all citizens have in how prioritisation decisions will affect them. Given the multiplicity of complex challenges raised by this, the preceding analysis reminds us that although new developments and choices for treatments and outcomes thereof will continue to emerge, this dynamism requires ongoing reflection about what means are justified and necessary and for whom in meeting the challenges of the disease (Gillain et al, 2016; Pistollato et al, 2016; Ritchie et al, 2017)

3.6. Communication, Autonomy, and Coercion

AD impedes communication (Brannelly, 2011), cognition (Cubit, 2010), autonomous decision-making (Smebye et al, 2016), social participation (Brannelly, 2011), independence (Shoval et al, 2008) and

has a psychological and emotional impact affecting relationships and perceptions of self and personhood (O'Connor et al, 2007; Edvardsson et al, 2008) as the disease progresses from Mild Cognitive Impairment (MCI) onwards (Barrios et al, 2016; Werner and Korczyn, 2008). This becomes an increasingly acute ethical issue as the disease advances and compromises more aspects of life.

The review so far communicates why effective prioritisation of outcomes depends on understanding patient preferences. As we have seen, prioritisation is not a straightforward question of maximising the good in a narrowly statistical sense, but one that must also take into account disease heterogeneity, patient heterogeneity, conflicting patient needs and clinical endpoints, and advancing but uneven progression in scientific understanding.

As we have seen, the way to do this is to ensure ongoing reflection and deliberation and this needs to include the diverse perspectives, values, and preferences of patients, which in turn involves seeking out their views (Street et al, 2009). Doing so makes it possible to take into account not only the effectiveness of a particular drug in clinical trials, but the qualitative, subjective, hermeneutic aspects of the patient's overall experience of living with a given health problem (Crites et al, 2016). Questions of self-determination are of immediate relevance in this context. Seeking out the preferences of people with AD and other dementias is crucial as far as it is possible to do so (Roger, 2008) and it is important not to assume that people with dementia are necessarily unable to speak for or represent themselves. For example, at the end of life it is of the upmost importance that the dying person's wishes are understood as explicitly as possible in advance (Burla et al, 2014; Lawrence et al, 2011; Van der Steen et al, 2013; Weidemann, 2012; Goodman et al, 2013). Indeed, in its ethical guidelines for assisting people with AD at the end of life, Alzheimer Europe (2008)4 emphasises the primacy of the autonomy of the person with the disease and recommends that capacity, rather than a lack of it, should always be assumed before ceding priority to the wishes of caregivers or other proxy decision makers (assuming that such are present, as some people with dementia live on their own).

In relation to outcome prioritisation we should not assume that people will be unable to express their preferences in some form, even at later stages of the disease or at the end of life (Batsch and Mittelman, 2012). This is key when considering who has a say in determining which outcomes matter, firstly to ensure that those who can contribute do so, and secondly to ensure that first-hand experiences of different disease stages are represented. This is an issue of both fairness (in that there should be no systematic exclusion based on assumptions about capacity at particular stages) and validity (in that the actual priorities of patients are heard above the hypothetical priorities of those imagining being in such circumstances).

3.7. Caregiver Issues

Given the progressive, degenerative nature of dementias such as AD it becomes increasingly difficult to know what the priorities and preferences are of the person affected. Often, caregivers, whether

[4] http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/2008-End-of-Life-care-for-people-with-dementia

professional (Egede-Niessen et al, 2012) or family members (Elliott et al, 2009; Flores et al, 2009; Barnes and Henwood, 2015; Landau and Werner, 2012) understand what the affected person's wishes are as their ability to communicate their own preferences diminishes (Barnes and Brannelly, 2008). However, the challenge arises of how we can be sure that carers properly represent the affected person's interests and, crucially, that carers respect and protect the dignity of the person with dementia (Tranvag et al, 2013; Tranvag et al, 2014). This is a considerable ethical challenge, as knowing what we ought to do for people with AD if their preferences are only indirectly discernible or require interpretation creates a risk of making erroneous decisions.

People affected by AD are vulnerable if they cannot communicate effectively, and as such they may be more reliant on their carers to represent their interests and wishes. While most carers will do this, it cannot be assumed that all risks of misrepresentation or mistreatment are eliminated (Robinson and Crawford, 2010). For example, carers' evaluations of the quality of life of people with AD are typically negative (Conde-Sala et al, 2009; Zucchella et al, 2015), and yet we cannot verify that this is the case precisely because of the impaired communication that the disease brings about. Similarly, there is evidence to suggest that carers wish patients to remain in the milder stages for as long as possible and decline rapidly towards the end to avoid the suffering and impact that it will have on them, but we cannot assume that this is what the person being cared for would also wish (Nelson et al, 2018). One reason for this may be that the utility of carers decreases as the patient's disease progresses, and as such a carer's judgement of the patient's quality of life is negatively influenced by the deterioration in their own quality of life (Vellone et al, 2008; Rosness et al, 2011). Nevertheless, it is also important in this situation to consider carers as stakeholders with a legitimate voice of their own regarding outcome prioritisation, separate from the extent to which they can reliably interpret the wishes of those for whom they are caring (Van der Vorm et al, 2008; Van der Vorm, 2008).

3.8. Disclosure of Risk

Risk of dementia or AD may be an important outcome for people at early stages of the disease, however the uncertainty around such predictions, as well as the limited ability to act on it, make knowledge of one's risk ethically important. For instance, although preclinical testing for AD is advancing in accuracy and scope (Dubois et al, 2016), understanding the wishes of all those to whom such testing may be relevant is ethically important in terms of harm reduction (Kelly et al, 2015). People identified as being at high risk for developing AD, such as some MCI patients, will already feature in such considerations, since, as Rose (2001) points out, the best indicator of major disease in future is often the existing presence of minor disease. Indeed, in the context of AD, the current diagnostic guidelines state that AD dementia is preceded by MCI, and MCI is preceded by an asymptomatic preclinical AD phase (Jack et al, 2011). However, as algorithms become better at predicting risk in asymptomatic individuals, namely those who have biomarkers of the disease but who show no signs of having the disease, the groups of people to whom this will become relevant will increase in line with the increasing accuracy of predicting AD at the asymptomatic stage.

In each group of people deemed at risk, the ethical ramifications of testing centre on questions of how individuals, and those close to them, should respond to knowledge about individual risk as well as what responsibilities fall on those disclosing the risk status. For example, this will extend to family members, as knowledge that an individual will or is likely to develop AD will affect their lives, not least because some of those family members may have to become carers (Brodaty and Donkin, 2009;

Bunn et al, 2012). Moreover, in the case of genetic risk factors for AD which can be identified at any age such as APOE, genetically related relatives may be faced with a decision about whether they too wish to undergo testing for presence of such markers (Genin et al, 2011).

These testing and screening scenarios are ethically challenging as long as AD remains incurable. For example, while cognitively normal, asymptomatic, individuals may be able to reduce their risk of developing MCI or AD by making lifestyle changes in mid-life to reduce or eliminate amyloid and tau accretion, these changes do not guarantee to do so (Flicker, 2010; Qui, 2012; Lovden et al, 2013). As such it cannot be assumed that receiving knowledge that one is at risk in the absence of a guarantee of being able to prevent it is an outcome that individuals will necessarily prioritise. Nevertheless, there may be some benefits to early risk assessment and diagnosis, since patients can in these cases more capably make legal and care arrangements and change their lifestyle so that they can maximise the time they have with significant others (Weimer et al, 2009; Mattson et al, 2010; Prince et al, 2011).

To the extent that a foundational duty of healthcare professionals is to avoid or prevent harm, it is necessary to keep in mind a broad conception of harm that encompasses not only the physical and cognitive impairment caused by the progression of AD, but the psychological and emotional damage that may come to people by knowing their risk5. As such, it should not be assumed that, for example, individuals who have positive amyloid scans but are cognitively normal (Lingler and Clunk, 2013) should automatically be informed of the results of their scan, as this may cause significant distress, even if the information is sought. Indeed, there are cases in which amyloid positive individuals can live to old age (Aizenstein et al, 2008) or die before developing notable symptoms, either because of another condition or an accident, even though there is a consensus among clinicians that these individuals would have developed dementia had death not intervened first. In these cases, it is important to elicit what an individual's preferences are with respect to AD relative to other health risks that they face, also taking into account how legal rights to the disclosure of information to individuals are framed in different jurisdictions.

Aside from the harms of the disease, therefore, disclosure may pose a risk of psychological and emotional harm to both affected individuals (Draper et al, 2010) and their carers and families as well as the interpersonal relationships between them (Porteri et al, 2017). Finally, for individuals with private health cover rather than the majority in the European context who depend on state health provision, known information relating to the risk of disease may affect individuals' insurance premiums and coverage and cover if they are obliged to disclose this to insurers (Davis, 2017), and as such the risk of harm that may come from the exploitation of this information by insurers should be taken into account and anticipated when balancing the priority of potential outcomes. The kinds of risks outlined here are some of those adduced in arguments against dementia screening (Brayne et al, 2007; Le Couteur et al, 2013) and help to demonstrate that while the assumption that diagnosis and knowledge of one's condition would and should always be one's priority may look reasonable prima facie, when subjected to scrutiny the situation may reveal itself too complex for the assumption to be applicable or necessarily beneficial.

[5] https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme#implementation-criteria

4. Conclusions

On the basis of our analysis we conclude that there are three significant groups of ethical issues in outcome prioritisation, which we will now summarise. We will also make some remarks about what normative approaches it might be appropriate to adopt in relation to these ethical issues. For example, philosophical tools such as differing theoretical accounts of justice may help to inform debate and decision-making in arriving at conclusions about how resources should be distributed; and at the micro level, tools of social science such as qualitative research methodologies can help to elicit the personal perspectives that are required for understanding what outcomes are important to whom, and why. There are instances of research consortia which draw together and integrate these expertise towards developing fair and equitable methods of outcome prioritisation in AD, such as the IMI EU EFPIA ROADMAP[6] initiative.

The first group of issues relates to the importance of ensuring the adequacy of the procedures according to which finite resources are to be allocated. For example, if it is the case that the needs of a certain group of people cannot be met because meeting these needs does not reach the appropriate threshold of cost-effectiveness, then it is important: first, that relevant professionals are trained to give individuals difficult and potentially distressing news; and second, that the commissioning process is thorough and comprehensively justified, with efforts made to ensure that geographical disparities, or 'postcode lotteries' in provision do not arise. Similarly, procedures for prioritising outcomes must also be able to respond effectively to advances in therapy and the consideration of these under whatever protocol for allocation is being applied. If it is important to realise maximum benefit from all available treatments, then it is a vital ethical priority to ensure that potentially beneficial new developments can be incorporated into resource allocation decision procedures. It is in these kinds of considerations that we adopt the most general, macro-level perspective. Given that due consideration for the correct balance of rights and responsibilities between the state and the individual falls squarely within the purview of ethics, it is here that the philosophical tools derived from understanding competing theories of justice are instructive for negotiating resource allocation and prioritisation dilemmas.

The second set of issues relates to the specific outcomes to be measured and prioritised, and how it is possible to ensure that those being measured are most important and meaningful to relevant stakeholders. Prioritisation can only be carried out in a way that meets the needs and wishes of the affected parties if there is an understanding of what outcomes are valued by the people to whom allocation decisions pertain. This may differ at different stages of the disease and for this reason it is important also to have valid and reliable outcome assessment tools to measure the priority outcomes that are appropriate to these different stages. This obviates the need to elicit the preferences of people with AD and their carers, rather than assuming what outcomes are desired and in what order of preference. Moreover, and as we have pointed out earlier, understanding what outcomes are prioritised and in what order is also complicated in view of the complexity of a disease such as AD. Medications may have side-effects and / or drug-drug interactions that may affect the overall outcome for a patient, and since AD is largely a disease of old age it is frequently important to take comorbidities

[6] https://roadmap-alzheimer.org/

into account when attempting to attach a value to a particular outcome and course of action (Clague et al, 2016). To the extent that an ethical duty of prioritisation decisions is to optimise outcomes for people with AD, understanding what the preferences of these people happen to be is a necessary step in discharging that duty. Meeting these micro-level demands is amenable to qualitative and quantitative research methods in the form of interviews, focus groups, surveys, and questionnaires. As such, the tools of social science research can be usefully employed for seeking out and understanding individual preferences and the reasons behind them.

The careful application of these tools is also valuable for negotiating the third group of ethical challenges, which, much like the issue of age-related comorbidities, is also AD-specific, and concerns the way in which individual preferences are sought. Dementias such as AD can impair the ability of affected people to clearly make and convey their preferences and wishes, and as such there is a potential ethical risk in not prioritising outcomes in a way that meets the needs and wishes of those people. Furthermore, given that AD can impair communication it can be the case that carers need to make decisions on their behalf, and in view of this there may be conflicting accounts of the patient's best interests. Adequate and ethically robust outcome prioritisation processes depend in part on first having identified what is needed by and important to people with AD, and as such the procedures used to elicit this information must be capable of doing so. Since cost-effectiveness decisions are necessarily utility-driven, unless preferences and wishes for outcomes are successfully elicited, there is a risk that these important and qualitative aspects of AD are lost against the background of the aggregative method by which prioritisation is directed.

Finally, it is important to underline the crucial role that ethical deliberation plays in ensuring the just prioritisation of outcomes. Indeed, given that discussions about how we ‘should’ allocate resources is an irreducibly normative question, expertise in ethical and philosophical reasoning are indispensable for a task such as this, irrespective of the fact that the task is an applied one and these kinds of expertise are theoretical. Of course, the data to which we refer in this review are similarly indispensable, since without empirical information about how and why different stakeholders prioritise outcomes in the way that they do, no rational negotiation of these towards a just outcome can be carried out. Nevertheless, what ought to be done cannot simply be read off these data. For this reason, allied with the compelling need to find new strategies for managing AD in view of the growing societal pressure that it is exerting, we reiterate the central role that ethical reflection can and should contribute in decision-making processes regarding the prioritisation of patient outcomes.

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