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Editorial

What Is Reasonable and Necessary for Alzheimer Patients from Randomized Clinical Trials to Clinical Practice?

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The question of "what is reasonable and necessary" is not foreign to clinical practice. Considering what is reasonable and doing what is necessary are the next steps, once a diagnosis is made. In most cases there are no one-size-fits-all solutions, and decisions typically have to be adapted to the individual's clinical status and medical history, among the available therapeutic options, based on a personalized medicine approach. This is somewhat distinct from the precision medicine model, which pre-requires tools and technologies for a precise qualification of the clinical status of patients such as, in the case of Alzheimer's disease (AD), establishing the presence of an abnormal cerebral burden of Amyloid and Tau, in addition to evidence of Neurodegeneration, based on the AT[N] biomarker signature. There is a vast diversity in the availability of such technologies in different countries around the globe, or among hospitals within a given region. At a macro level, "what is reasonable and necessary" is also an essential dilemma for governmental and other healthcare providers and payers. In this issue, Linus Jönsson and Anders Wimo discuss the range of issues and considerations regarding reimbursement, as they attempt to address the question of "what is reasonable and necessary" from a health economic perspective.

On the other hand, randomized clinical trials (RCTs) typically aim at selecting the best targeted population for efficacy and defining the optimal primary and secondary outcomes, as well as employing the most appropriate tools in evaluating outcomes and safety, with good sensitivity and specificity. The translation of larger scale phase III RCTs to clinical practice, in different clinical settings, has its own challenges, particularly in diseases such as AD and related dementias (ADRD). What is necessary in RCTs, in terms of clinical and other investigations to evaluate outcomes and safety, may not be easily applicable in clinical practice or acceptable to patients or payers. For instance, repetitive investigations, such as structural magnetic resonance imaging (MRI) or amyloid and tau positron emission tomography (PET) may be acceptable to volunteers in RCTs but will add considerable burden to patients, in clinical practice, as well as exponentially escalating costs that may be variably feasible and acceptable to healthcare payers, notwithstanding the limited availability of required technologies, even in developed countries, worldwide. These discrepancies represent a significant translational gap from RCTs to the clinic that will need to be addressed in the design of future trials, in the field.

These and other challenges in the translation of the results of the Aducanumab, Lecanemab and Donanemab RCTs to clinical practice are addressed by all the authors of this issue. David Scrase and colleagues (1), from a clinical geriatrics perspective, point out that physicians and patients are likely to carefully consider the potential benefit vs their real costs in their particular circumstances. Lon Schneider (2) notes the divergence between the US Government and insurance companies and consumers (physicians, patients and their families, advocacy groups and charities) regarding "what is reasonable and necessary". Whilst this may be a legal term for the former, the question is interpreted quite differently by the wider consumer community, at least in the US. This viewpoint is shared by Rachelle Doody and Simona Skerjanec (3) who conclude with a recommendation for pharmaceutical companies to work closely with payers to define the patients who should be treated, and who should then be able to count on their payers to cover the medication costs. Gauthier et al (4) underline the conceptual shift of AD, from a perception of a terminal illness to a chronic disease, with pre-clinical, mild and end-organ phases. The authors argue that health systems are unprepared to accommodate this shift, as also highlighted in a recent Lancet Neurology editorial (5), and make practical recommendations on a way forward. Monica Moreno and Maria Carillo (6) outline the efforts of the US Alzheimer's Association to formulate an evidence-based policy on "what is reasonable and necessary" and conclude that, as AD is a chronic disease, doctors and patients should be allowed to have access to FDA-approved treatments. Finally, in the context of RCTs for AD (using the example of Lecanemab), Christina Sampaio addresses the challenges of specifying the "minimum clinically important difference" (MCID), which is at the heart of the discussion on "what is reasonable and necessary", after

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only 18 months (7). The author argues that to adequately measure and qualify the drug effect in terms of clinical meaningfulness, it would be essential to accrue further data on rates of progression and of adverse events, over a longer period of time and in a real-world setting.

In conclusion, following 25 years of failures in efforts towards disease modifying therapies for AD and ADRD, mainly focusing on the amyloid hypothesis (8), positive results from three RCTs of monoclonal anti-amyloid therapies are re-invigorating the field, albeit with significant challenges in their translation to clinical practice and in terms of their clinical meaningfulness. Alzheimer's disease is defined by the triad biomarker AT[N] signature, but its commonest late onset form is multifactorial, and its aetiological "puzzle" is not yet well understood. Whilst research and development efforts for anti-tau compounds are on-going, recent evidence suggests that modifiable risk factors account for 40% of cases of dementia (9). The two-year multi-domain lifestyle FINGER RCT showed positive results both at two years (10) and for up to eight years, in terms of incidence rates for dementia and multi-morbidity (11). The recently initiated MetFINGER RCT (NCT05109169), combining multi-domain lifestyle intervention and a repurposed antidiabetic drug (Metformin) may provide a model for future combination therapies targeting different disease mechanisms. Combination therapies have proven their value in other chronic multifactorial diseases, such as hypertension, HIV-AIDS and several cancer forms. As our knowledge of the mechanisms underpinning the development of AD and ADRD continues to expand, combination therapies may prove to be the future of disease modifying, precision medicine therapies for AD and ADRD, tailored to the clinical profiles of individual patients.

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