Design of Clinical Studies of Pharmacologic Therapies for Alzheimer’s Disease

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Description

The Green Park Collaborative (GPC) is an international initiative that is exploring the scientific and procedural feasibility of developing guidance for the life science industry on the design of clinical studies to meet the needs of HTA and coverage bodies. One of its aims is to produce “evidence guidance documents” that provide therapeutic area-specific trial design recommendations. This document is the output of a pilot project directed towards this aim. The purpose of this guidance is to reduce the uncertainty currently faced by the life sciences industry regarding the evidentiary preferences of HTA and coverage bodies, to improve the relevance of clinical research, and to improve patient access to useful innovations. This prototype guidance document is not intended to represent consensus statements on the part of its participants, but rather demonstrate the feasibility of and inform the subsequent development of guidance beyond the pilot phase. The guidance provides recommendations regarding the selection criteria, interventions, comparators, outcomes, and follow-up employed in phase 3 and 4 trials of pharmaceutical therapies intended for use in patients with mild or moderate AD dementia.
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I. ACKNOWLEDGEMENTS

The following pages list the individuals who participated in the development of this Evidence Guidance Document (EGD). The present prototype guidance document is not intended to be a consensus statement that represents the views of all participating organizations, and participation of an individual in the GPC does not imply the endorsement of the EGD recommendations. The recommendations reflect the best effort to integrate the knowledge and perspective of all participants in the process, and are not to be viewed as formal policy statements from any of the organizations with which these participants are affiliated.

Steering Group: The Green Park Collaborative (GPC) operates under the direction of a multi-disciplinary, international steering group of individuals with backgrounds in HTA, reimbursement, regulatory policy, patient engagement, clinical care, research design and drug/device development. The Steering Group is co-chaired by the Center for Medical Technology Policy (CMTP – represented by Sean Tunis, President and CEO) and Health Technology Assessment International (HTAi – represented by Berit Mørland, Past President). Together, CMTP and HTAi lead a management group, which convenes and facilitates collaboration among GPC participants, provides operational oversight, and reports to the organizations’ respective Boards as relevant.

Technical Working Group: The development of this evidence guidance document was led by a Technical Working Group (TWG) of international Alzheimer’s disease (AD) experts that included researchers, patient representatives, and individuals from health technology assessment (HTA) and coverage bodies, and regulatory agencies.

Life Sciences Advisory Group: This group outlined the questions that an EGD on treatments for Alzheimer’s disease should answer, and provided technical, methodological and logistical input to ensure applicability of guidance on drug development.

As described in the Appendix, a team of researchers from the Institute for Clinical and Economic Review (ICER) catalogued the gaps noted in documents prepared by a wide range of stakeholders¹, which served as the basis for this document’s appendices and other contextual information regarding current evidence on Alzheimer’s disease, and informed discussions of draft recommendations.

¹ Available at http://www.greenparkcollaborative.org/background-documents/
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III. PREFACE

There is increasing recognition that health technology assessment and coverage bodies—including payers—have an impact on the development and adoption of drugs, devices and diagnostics. Historically, the clinical development process in the life sciences industry focused mainly on fulfilling regulatory requirements, with the expectation that positive reimbursement decisions would generally follow. Therefore, clinical studies have been primarily designed to address the information needs of regulators with less attention to generating evidence targeted to coverage bodies and the health technology assessment (HTA) bodies that support them. As a result, a number of important questions were inconsistently addressed: Is a new product better or safer than an existing product? How does its value compare to existing products? Could benefits be achieved outside of an academic or research setting and sustained over time? What are the impacts on patient-reported outcomes, quality of life, and on ethical, legal and social issues? Life sciences companies are now keenly aware that they must rethink their approach to the design of clinical studies to provide this missing information.

As it has become clear that more and different evidence is needed by coverage and HTA bodies, these organizations have begun to recognize the importance of clearly communicating to trial designers the information that they expect to see in clinical trials. Regulatory bodies have been providing such guidance to product developers for many years; in the absence of specific guidance from HTA and coverage bodies, pre-approval trial designs may suffer from significant methodological limitations from the perspective of these groups. Recently, several coverage and HTA bodies have recognized the need to provide “scientific advice” to product developers on trial design, including several pilot initiatives that provide joint advice from coverage bodies and regulators. Improved communication of these expectations is anticipated to lead to greater efficiency in clinical development. These efforts have been constructive and well-received, and highlight the potential value of exploring other forms of methodological guidance from coverage and HTA bodies to product developers, with particular emphasis on complementing scientific advice on individual products and building upon guidance provided by regulators.

Objectives of the Green Park Collaborative

The Green Park Collaborative (GPC) is an international initiative that is exploring the scientific and procedural feasibility of developing guidance for the life science industry on the design of clinical studies to meet the needs of HTA and coverage bodies. One of its aims is to produce “evidence guidance documents” (EGDs) that provide therapeutic area-specific trial design recommendations. This document is the output of a pilot project directed towards this aim. The purpose of this guidance is to reduce the uncertainty currently faced by the life sciences industry regarding the evidentiary preferences of HTA and coverage bodies, to improve the relevance of clinical research, and to improve patient access to useful innovations. This prototype guidance document is not intended to represent consensus statements on the part of its participants, but rather demonstrate the feasibility of and inform the subsequent development of guidance beyond the pilot phase. Additional technical work in consultation with experts and stakeholders would be required to produce a document at the level of technical sophistication necessary to be relied upon by HTA organizations, coverage bodies, product developers and others to guide the design and/or assessment of clinical research in Alzheimer’s disease. Even so, experts and other key stakeholders devoted a substantial amount of effort and care to the development of this pilot EGD, enabling it to be informative in its current form.

EGDs are mindful of the need for trialists to have flexibility in design, both to meet local requirements and to allow for testing different hypotheses, as well as advances in methodology, clinical care and scientific understanding of disease. As such, EGDs do not provide recommendations that govern all aspects of trial
design, conduct, and analysis, and are intended to be “living documents” that will be updated as knowledge evolves.

**Scope of This Document**

This EGD is intended to address the major aspects of Alzheimer’s disease (AD) research that are relevant to review by HTA agencies and decisions by coverage bodies. This document is not intended to comprehensively describe all aspects of research on AD, and it is not intended to provide basic advice on the design, conduct, or analysis of randomized clinical trials, all of which are well-known to trialists. The present document limits its considerations to evidence requirements in AD, while a separate work product of the GPC describes the principles underlying the decisions that HTA and coverage bodies make.¹

This document pertains to phase 3 and 4 trials of pharmaceutical therapies intended for use in patients with mild or moderate AD dementia. Special considerations for studies of patients who do not meet criteria for the diagnosis of dementia, but who might develop it (for example, mild cognitive impairment) are also addressed. Studies of therapies targeting patients with severe AD are not addressed because such studies are likely to require a different set of outcomes, different considerations regarding enrollment, and other unique aspects of study design. Wherever relevant, the present document compares its guidance to guidance issued by regulatory agencies, and particularly the 2008 guidance issued by the European Medicines Agency (EMA).

While the EGD was in its final stages of review, the United States Food and Drug Administration (FDA) released draft guidance on developing drugs for the treatment of early stage AD.² Because of the timing of the FDA draft guidance’s release, the EGD could not incorporate direct comparisons. However, many similarities exist among this draft guidance, draft guidance from the FDA, and guidance from the EMA.

**Evidence Guidance Documents**

Evidence Guidance Documents are developed through a consultative process involving a broad range of experts and stakeholders (the process of this EGD’s production is described in the Appendix). The documents’ primary audience is the community of clinical researchers who develop research protocols for studies that are intended to be helpful to patients, clinicians and payers who make clinical or health policy decisions. This includes researchers from life sciences companies with clinical development responsibilities, or other clinical researchers receiving funding from public sources, foundations, etc. EGDs are intended to be analogous to regulatory guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision making. They are intended to reflect the expressed evidence preferences of Health Technology Assessment (HTA) and coverage bodies.

EGDs seek to provide study design recommendations that achieve an acceptable balance across a number of desirable dimensions, including internal validity, relevance, feasibility and timeliness. Overall, the objective is to describe the characteristics of studies that would give decision makers a reasonable level of confidence that an intervention would improve net health outcomes.

There are a number of potential benefits to creating and using EGDs. First and foremost, they could help increase the degree to which the body of clinical research reflects the information needs articulated by HTA and coverage bodies. In addition, EGDs could contribute to greater consistency of trial design across studies of related treatments within specific clinical conditions, allowing for higher quality systematic reviews and meta-analyses due to reduced heterogeneity across multiple studies. By considering existing regulatory guidance in the EGD process, it is hoped that EGDs will help to achieve optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and coverage decision making.
At the same time, we recognize that regulators tend to emphasize the value of well-controlled explanatory trials whereas HTA bodies emphasize the value of trials that reflect actual clinical practice. Therefore, resolution of these two perspectives will not always be possible.

There are three primary features that distinguish EGDs from other methods guidance documents. First, EGDs focus on a specific clinical area or category of interventions. Second, a number of other documents provide guidance on reviewing the quality of existing studies, while EGDs provide guidance for the design of the clinical studies themselves. Finally, we are not aware of any other document production processes that have actively engaged multiple coverage and HTA bodies as well as patients and clinicians to develop publicly available guidance.
IV. ALZHEIMER’S DISEASE

The Condition

Dementia is a persistent and growing problem, currently affecting an estimated 35 million persons worldwide. As the population ages, this number is expected to grow to 65 million by 2030 and over 115 million by 2050. Alzheimer’s disease (AD) is by far the most common form of dementia, representing approximately 60-80% of cases. A patient is diagnosed with AD on the basis of clinical assessment and when other forms of dementia have been ruled out. Late onset (after age 65) of AD is much more common than early onset, and AD is slightly more common in women than in men. First-degree relatives of those with early onset AD are more likely to develop the disorder.

AD and other dementias are also associated with great individual and societal burden. Worldwide, the total annual costs of dementia are estimated to exceed $600 billion, or approximately 1% of the world’s gross domestic product.

The disease is characterized by the development of “plaques” in the brain containing beta-amyloid protein as well as “tangles” containing tau protein. These plaques and tangles accumulate over time, and are associated with significant loss of neurons and synaptic activity in the brain. Patients with clinical AD typically first present with impaired memory and language dysfunction, but other effects, including visuospatial dysfunction, impaired ability with calculations and complex tasks, may also be present. Behavioral and/or psychiatric symptoms may also develop as the disease progresses. Because the average duration of the illness, from onset of symptoms to death, is 8–10 years, mortality is rarely used as a primary study endpoint in this area.

The Interventions

There is no cure for AD. The current mainstays of drug treatment are pharmaceuticals intended to address the cognitive symptoms of AD, in combination with supportive medical and behavioral intervention. Two major classes of drugs are currently available to treat the symptoms of AD:

Marketed Drugs

Acetylcholinesterase inhibitors (AChEIs): These include donepezil, rivastigmine, and galantamine. An older AChEI, tacrine, is rarely used due to concerns about liver toxicity. AChEIs boost the amount of acetylcholine, an important neurotransmitter in the areas of the brain that control learning and memory. These drugs have been approved for use in patients with mild-to-moderate AD on the basis of short-term (i.e., 6 months or less) improvements in memory and cognition in clinical trials. There are no data suggesting that use of AChEIs modifies or delays disease progression.

N-methyl-D-aspartate (NMDA) receptor antagonists: A single NMDA receptor antagonist, memantine, is currently approved for the treatment of symptoms of moderate-to-severe AD. Memantine binds to NMDA receptors that are associated with excessive stimulation and eventual death of neurons. Findings from clinical trials suggest small positive effects of memantine on cognition, activities of daily living, and behavior. Memantine is not thought to affect disease trajectory or progression.

Disease-Modifying Therapy

In addition to the symptomatic treatments currently marketed, a host of potentially disease-modifying therapies have been studied, and numerous others are in development. These include treatments that
modulate inflammation and oxidative damage, as well as treatments that interfere with Aβ deposition such as anti-amyloid aggregation agents, anti-amyloid antibodies, selective Aβ42-lowering agents, γ-secretase inhibitors, α-secretase potentiators, and β-site APP cleaving enzyme inhibitors.⁸
V. GUIDANCE

A. Population

i. Representativeness

There are two related but distinct factors to consider when planning which patients to enroll in a clinical trial of AD: 1) causes of dementia other than AD, and 2) co-morbid conditions that could make a response to treatment difficult to detect. AD trials that aim to examine the effectiveness of a therapy with established efficacy should exclude patients with causes of dementia other than AD, but should enroll patients who reflect, as closely as feasible, the range of co-morbidities seen in clinical practice, including those who have treated, stable co-morbid conditions that could contribute to impaired cognition, and who are frequently excluded from clinical trials. Specifically, if a therapy is expected to be provided to patients with co-morbidities such as stable thyroid disease, anemia, depression, cerebrovascular disease, history of head injury, stable congestive heart failure, atrial fibrillation, coronary artery disease, osteoarthritis, or diabetes, trials on that therapy should not exclude patients with those co-morbidities as long as these conditions are not contraindications to drugs of the same class as the experimental drug. Because individual trials may not be able to enroll the entire range of co-morbidities seen in clinical practice, evidence on a therapy’s effectiveness and safety in patients with co-morbidities may also be developed across a series of trials. As described in the preface, the scope of this guidance is limited to mild-to-moderate AD, and different considerations may apply at different levels of disease severity.

In section 4.1.4 of its guidance on dementia, the EMA suggests that trials exclude “treatable causes of dementia as infections of the CNS (e.g. HIV, syphilis) or Creutzfeld-Jakob disease,” also noting that “subdural haematoma, communicating hydrocephalus, brain tumours, drug intoxication, alcohol intoxication, thyroid disease, parathyroid disease, and vitamin or other deficiencies also need to be excluded when appropriate.” In contrast, this EGD recommends that patients with stable thyroid disease and anemia are appropriate to include in trials meant to inform HTA and coverage bodies. Still, for amyloid-targeting therapies in particular, AD studies should exclude patients with vascular dementia, along with those with rapid cognitive decline that occurs over weeks or months.

Additionally, in section 4.3.5 of its guidance on dementia, the EMA notes that “it is desirable, particularly in exploratory trials to avoid any treatment likely to impair alertness, intellectual function and behaviour. These include hypnotic, anxiolytic, antidepressant, antipsychotic, anticholinergic and memory enhancing drugs.” HTA and coverage bodies do not disagree with this position on exploratory trials, but recognize that many patients with AD will be taking such therapies, and it is therefore recommended that such patients be considered for inclusion in AD trials. Alternatively additional studies (phase 3b and 4) could include patients receiving these other treatments unless there is a medical justification (e.g., the other treatments are contraindicated to the AD treatment under study) for their exclusion.

The steps recommended for achieving a more representative patient population while excluding those with untreated or un-stable co-morbidities are:

1. Screen for co-morbid conditions listed above.

2. Create an opportunity for those conditions to be treated.

3. Re-screen for trial eligibility, and exclude those with untreated or unstable co-morbidities.
4. Enroll patients if their co-morbidities are stable, and even if the co-morbidities have not been entirely reversed.

This is best accomplished when a patient’s practicing physician—not the investigator—performs an appropriate medical history and evaluation and diagnostic laboratory tests intended to identify contributing conditions (as opposed to alternative causes). This evaluation and subsequent intervention should occur before randomization.

In comparison with trials that enroll a narrow population, trials that include patients with typical co-morbidities and co-medications will generally require larger sample sizes to ensure that these participants are adequately distributed across trial arms, and to account for the impact that co-morbidities may have on the rate of change in outcomes. Intention-to-treat analyses that include all patients enrolled should accompany per protocol analyses. Subgroup analyses that exclude co-morbidities and co-medications should be kept to a minimum, and should be pre-specified in an analysis plan with a rationale predicting how the treatment effect might vary.

While investigators should seek to include participants whose co-morbidities and co-medications represent the population of patients with AD, it is reasonable to exclude those with life-threatening diseases, and those who have unstable conditions or co-morbidities.

B. Interventions and Comparators

i. Combination Therapy

HTA and coverage bodies value trials of a new therapy given in combination with already-employed therapies that target different physiological processes than the new drug. For example, putative disease-modifying therapies should be assessed in combination with symptomatic therapies such as cholinesterase inhibitors or NMDA receptor antagonists. Add-on studies are one strategy to accomplish this assessment. Other strategies include limited placebo period studies, randomized withdrawal, factorial designs, and three-arm trials. The EMA’s Note for Guidance on Choice of Control Group in Clinical Trials describes the strengths and weaknesses of these approaches. The specific goals of the trial should determine the relative timing of the combination of drugs, but will typically involve adding the investigational drug to a stable dose of a commonly prescribed drug with regulatory approval.

Our recommendation is similar to that of the EMA which, in section 4.2.2 of its guidance on dementia, states:

“In many countries symptomatic treatment of dementia with cholinesterase-inhibitors is considered as standard of care, particularly in mild to moderate Alzheimer’s disease. Therefore in the future new treatments for dementia may be evaluated more and more by using add-on-designs, particularly in long term studies the “pure” use of placebo control for demonstration of efficacy may be difficult to justify. However, substantial differences between placebo patients in the different trials and distinct subtypes of dementia have been shown, therefore placebo controlled studies are still necessary.”

We note that our present suggestion should be viewed with our suggestions on non-pharmacological therapy, which are discussed in section B.iii below.

ii. Superiority Trials
When a new pharmaceutical will compete with an existing one, compare the two in the same study. HTA and coverage bodies are interested in the incremental effectiveness of new interventions. This requires comparing competing pharmaceuticals. Direct comparisons provide more reliable data for relative effectiveness assessments and economic models than data derived from indirect comparisons, and are therefore recommended in the context of AD drugs. Indirect effectiveness and economic comparisons can be problematic for many reasons, including the fact that different studies may enroll different patient populations, have different rates of enrollee withdrawal, and use different protocols. A guideline in development by the European network for HTA (EUnetHTA), although not specific to AD, emphasizes that health technology assessments should employ indirect comparisons if, and only if, direct comparisons are unavailable, and the studies to be combined include sufficiently similar participants, interventions, and outcomes measured.11

Designing trials with active controls requires ensuring the use of optimal and comparable doses and administration for all pharmaceuticals under study. Also, using active control groups is likely to increase the number of patients that need to be enrolled in a trial. This number can be minimized by implementing measures to reduce withdrawals, and/or by using repeated measures designs.

In section 4.2.2 of its guidance on dementia, the EMA stated that:

“Active control parallel group trials comparing the new treatment to an already approved treatment are needed in order to give the comparative benefit/risk ratio of the new treatment, at least in those treatments intended for symptomatic improvement. However, due to concerns over assay sensitivity, the use of a non-inferiority design versus active control only will not be accepted as proof of efficacy. Therefore three-arm studies with placebo, test product and active control or a superiority trial are the preferred design options. As feasibility of long term placebo controlled studies have become seriously limited due to the evidence of efficacy of available treatments, a second option is to compare the new treatment to placebo in a trial of shorter duration (e.g. 6 or 12 months depending on the dementia subtype) and thereafter to switch placebo patients to a predefined active treatment or randomise them to the experimental product or a predefined active treatment.”

While HTA and coverage bodies recognize the value of placebo-controlled studies, they especially value studies with active control groups. Therefore, this EGD supports the use of three-arm or superiority trial designs to inform coverage decisions.

iii. Non-Pharmacologic Background Therapy

In addition to the preceding considerations, patients in the intervention and control groups of a trial should receive the non-pharmacologic care recommended by regional or national clinical guidelines. Specifically: trial protocols should reflect the non-pharmacologic care recommended by regional or national guidelines, but, in order to improve trials' external validity, trialists should avoid tight controls on adherence to these guidelines, and instead report divergence from the study protocol.

Implementing guidelines from different countries is likely to affect the variance in a trial and, hence, its statistical power. An increase in variance that is caused by conducting trials in multiple countries and, therefore, with heterogeneous guidelines, might be offset by employing standardized case management strategies across trial sites.12 Randomization will help trials avoid systematic differences in non-pharmacologic care across trial arms.
Guideline-recommended care often includes social and professional support. Examples include guidelines by the UK’s National Institute of Health and Clinical Excellence\textsuperscript{13}, the California Workgroup on Guidelines for Alzheimer’s Disease Management\textsuperscript{14}, and the American Psychiatric Association.\textsuperscript{15}

Trial enrollees often become unable to provide meaningful reports of their status, necessitating that proxy reports be provided by the care partner. **Trials should provide support to care partners.** Such support can include, as proposed by the California Workgroup on Guidelines for Alzheimer’s Disease Management, connecting care partners to “support organizations for linguistically and culturally appropriate educational materials, and referrals to community resources, support groups, legal counseling, respite care, consultation on care needs and options, and financial resources.”\textsuperscript{14} Additionally, NICE guidelines have suggested that support include training courses about dementia, services and benefits, and communication and problem solving in the care of people with dementia.\textsuperscript{13} Trials that rely on care partner involvement should also develop contingency plans for what to do if there must be a change to a new care partner (for example, in the event of a care partner’s death) during a trial.

Providing care partners with support may enhance the accuracy of their responses, thereby providing more accurate information about the effectiveness of the treatment being studied. To facilitate interpretation of results, trialists should report the types of support that patients and care partners receive.

Care partners would also benefit from support with activities that surround a trial. Enrollment is facilitated when trial centers proactively inform them, as well as new enrollees, about the status of a trial and give them sufficient notice about when patients are to first report for it. Employing predictable schedules and providing advanced notice of appointments, additional or more convenient trial locations, and additional assistance with trial-related activities is also helpful to care partners, many of whom encounter financial and productivity burdens associated with missing work, taking patients to and from trial sites, and waiting for them while they are there. Such support may also serve to reduce rates of withdrawals from a trial.

**C. Outcomes**

1. **Objective Cognitive Tests; Self-care and Activities of Daily Living**

In section 4.2.1 of its guidance on AD, the EMA requires that objective cognitive tests and functional measures (activities of daily living) be co-primary endpoints (i.e. that studies be powered to detect changes in both of these domains). Although they find other outcome domains highly valuable, **HTA and coverage bodies also recommend that a cognitive endpoint and a functional endpoint be co-primary.**

EMA guidance requires that the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) be used to assess cognition.\textsuperscript{2} For functional endpoints, the EMA notes the promising linearity of the Alzheimer’s Disease Cooperative Study ADL (ADCS-ADL) scale and Disability Assessment for Dementia (DAD) in those with mild-to-moderate AD. Similarly, we recommend the use of the ADAS-cog to assess cognition, and the ADCS-ADL, DAD, or BADL to assess activities of daily living. The mini-mental state examination (MMSE) has substantial limitations as an outcome measure, and should not be employed as a primary outcome, but including the MMSE as a secondary outcome can help make trials more relevant to clinical practice.

\textsuperscript{2} The EMA also notes that the Neuropsychological Test Battery for use in Alzheimer’s disease (NTB) may be used to assess cognition, but requests that, if the ADAS-cog is not included as a primary endpoint, “estimations with the ADAS-cog should supplement the results for consistency of interpretation.”
The scope of this guidance is limited to mild and moderate AD, and the ADAS-cog should be used in studies of this population. However, HTA and coverage bodies are best served when a single instrument is used in studies across disease states, and, given the floor and ceiling effects of the ADAS-cog, those decision-makers encourage the development and use of alternative instruments with validity and reliability across the AD spectrum.

EMA guidance requires that trials “aimed at demonstrating short term improvement in AD should last at least 6 months” but notes that "longer study durations are required to establish the maintenance of efficacy." Since maintenance of efficacy is of paramount importance to HTA and coverage bodies, **trials intended to inform their decisions should be at least 1 year in duration**. Doing so will give HTA and coverage bodies greater confidence that observed effects will persist, and will permit more robust extrapolation beyond the duration of the trial.

Furthermore, because declines in activities of daily living (ADL) and cognition can follow multiple trajectories, and several AD trials have been criticized by HTA and coverage bodies for assessing changes in cognition too infrequently, **HTA and coverage bodies recommend assessment of these outcomes every six months at a minimum, while also recognizing that most trials, particularly shorter ones, will benefit from more frequent measurement intervals**. More frequent measurement can improve statistical power, though practice effects may be of concern when care partners are involved in completing the instruments used to measure an outcome, which is often the case as the disease progresses.

Citing uncertainty that the course of AD approximates a linear model over time in the presence of a (potentially disease-modifying) treatment effect, the EMA does not specify a statistical model for slope analysis. For the same technical reasons, we do not give guidance on the appropriate statistical model for slope analysis in the context of a potentially disease-modifying therapy for mild or moderate AD dementia, but note that such analyses are not a preferred measure of effectiveness, and therefore we recommend against their use. The difference between group means and the proportion of patients reaching a target criterion provides a more direct measure of the effect of a treatment.

**ii. Global Assessment of Change**

Section 4.2.2 of the EMA’s guidance on dementia describes the potential usefulness, as well as the limitations, of these assessments, and notes that “although such a global assessment of patients’ benefit is less reliable than objective measurements of response and often appears insufficient to demonstrate by itself an improvement, it should be part of clinical trials in dementia as it represents a way to validate results obtained in comprehensive scales or objective tests, particularly when it is applied by an independent rater.”

HTA and coverage bodies’ needs with respect to global assessments of change do not substantially differ from those expressed by the EMA. We therefore **recommend that a global assessment of change be included as a secondary outcome measure**, and recommend the Alzheimer’s Disease Cooperative Study Unit Clinician’s Global Impression of Change (ADCS-CGIC) – a well-validated and frequently-used measure—for this purpose.

**iii. Health-Related Quality of Life**

Measurements of health-related quality of life (HRQoL) are frequently an important consideration for reimbursement. **HTA and coverage bodies prefer that studies include both a disease-specific and a generic HRQoL measure**. The Dementia Quality of Life measure (DEMQOL) is a suitable disease-specific measure.
and the EuroQol measure of quality of life (EQ-5D) and Health Utilities Index (HUI) are suitable generic measures. However, the relevance of such measures depends on the purpose of the study. A guideline in development by EUnetHTA summarizes 22 countries’ recommendations regarding HRQoL measurement, and describes the considerations that should determine the relevance of generic and disease-specific measures to a given study. Measurements from generic instruments are valuable to HTA and coverage bodies because they permit comparisons of treatments across multiple disease areas. Countries that require economic evaluation to support product reimbursement decisions in particular find generic instruments—and especially multi-attribute utility instruments such as the EQ-5D, or the HUI—highly useful. However, generic instruments may not measure all of the constructs that are targeted by AD therapies, and may be limited in their responsiveness to the effects of these therapies. Therefore, disease-specific instruments such as the DEMQOL are also valuable for HTA and coverage bodies. Such instruments measure patient-relevant outcomes that are not captured by cognitive measures, and are not attributable to behavioral symptoms.

Patients with AD dementia may be limited in their ability to appreciate the concepts that HRQoL instruments measure, and memory losses might mean that patients with AD dementia lack the context needed to gauge their status. Therefore, information on their HRQoL may be obtained from a care partner using an instrument validated for that purpose. However, trials should present a justification for the use of proxy reports, and should consider the inherent limitations of such reports.

In section 4.2.2 of its guidance, the EMA does not require that HRQoL measures be primary study outcomes and, citing insufficient validation, does not make specific recommendations regarding the measurement of quality of life. Similarly, we do not require that HRQoL be included as a primary study outcome. However, we recommend the inclusion of HRQoL measures at least as secondary outcomes. Doing so will facilitate meta-analyses.

**iv. Behavioral Signs and Symptoms**

While behavioral signs and symptoms are important outcomes for HTA and coverage bodies, and should be strongly considered for inclusion in trials, HTA and coverage bodies do not require that they be included as primary outcomes. The EMA notes common scales like the Neuropsychiatric Inventory (NPI), the Behavioural Pathology in Alzheimer’s disease Rating Scale (BEHAVE-AD), and the Behavioural Rating Scale for Dementia (BRSD).

**v. Minimum Clinically Important Difference**

Many HTA and coverage bodies are interested in having information about the clinical importance of the effects of an intervention. This information is obtained by comparing the effect of an intervention to an established minimum clinically important difference (MCID), which is the smallest difference in an outcome measurement that matters to patients.

MCIDs are best defined by empirically determining them in the target population. This is particularly difficult in the case of AD because the magnitude of the MCID could shift as the disease progresses, and because responses to interventions are often determined by care partners and/or clinicians which, in turn, necessitates validating the MCID with them as well as patients. Participants in the development of this guidance did not achieve consensus regarding the optimal way to overcome these challenges. One approach proposes that, in the absence of data on clinical relevance, trialists employ a between-groups effect size of 0.4 – 0.6 standard deviations of change from baseline as the MCID. This approach was employed in the DOMINO trial, and the effect size appears to be appropriate across a wide range of medical conditions.
We recognize that the specific effect size chosen will vary with the outcome being measured and the instrument used to measure it. We also understand the need for further research into the MCIDs that are most appropriate for the study of AD, and that such empirically derived Alzheimer’s-specific MCIDs will supersede the values proposed here. However, investigators must power their studies around some value, and using these values could lead to greater consistency in interpreting study results. Assuming appropriate randomization and comparable baseline values, the MCID can be expressed in terms of the difference between groups in their change from baseline, or as the difference between groups at a given time point. In order to make the MCID easier to interpret, trials that take this approach should specify the point change (for continuous scales) or the change in odds ratio that is equivalent to 0.4 – 0.6 SD. They should also report the proportion of patients who experienced an MCID (i.e. a dichotomous measure) to facilitate modeling and to provide additional information on the heterogeneity of the treatment effect.

**vi. Effects on Care Partners**

Caring for a patient with AD has both psychological and economic effects that can include depression, missed work and loss of productivity. Ultimately, the increasing burden associated with caring for patients whose disease is progressing is linked to the timing of the patient’s institutionalization. Because of this, many HTA and coverage bodies desire measurements of care partner burden.

We recognize that measuring care partners’ outcomes (not to be confused with proxy reports by care partners) is difficult. There is likely to be considerable heterogeneity among care partners and the effects of an intervention on them. This makes it unlikely that a given study will have the statistical power to detect the effects of intervention on care partner outcomes as statistically significant. However, reporting them will facilitate future meta-analysis, and may produce utility scores useful for cost models. A recent systematic review noted the Adult Social Care Outcomes Toolkit (ASCOT) as a promising measure of social care related quality of life. We recognize that instruments for measuring care partners’ outcomes require further development, but we recommend that studies employ ASCOT or a similar measure.

Regardless of which instrument is used, measurements of care partner burden should also assess the time care partners devote to caring for patients with AD and the psychological symptoms of those care partners. Care settings and the relationship of the care partner to the patient should be reported. For example, care partner burden is likely influenced by socioeconomic status, and by the number of individuals who share responsibility for caring for a patient. Finally, it is preferred that care partner burden and AD patient outcomes be assessed in the same trial, so that the relationships between them can be further explored.

**vii. Healthcare Resource Utilization**

Report the effects of intervention on institutionalization, days of hospitalization, office visits, and emergency room visits in phase III trials. These outcomes have substantial impact on the costs associated with treating and caring for patients with AD. As such, the effects of an intervention on them are of great interest to HTA and coverage bodies.

Although it is unlikely that a single trial will be able to enroll enough patients to obtain statistically significant results on hospitalization and office and emergency room visits, reporting them will facilitate future meta-analysis.
When feasible, the unit costs of institutionalization, care from home health aides and respite care should be captured and reported to allow HTA and coverage bodies to identify variability across health systems and assess applicability to the population for which they are responsible.

The effects of an intervention on institutionalization are most likely to be statistically significant in longer-term trials of patients with mild-to-moderate AD. The Resource Utilization in Dementia (RUD) instrument and the RUD lite are commonly used for capturing this information. The point at which patients with AD are institutionalized will, because of different definitions and different healthcare systems, vary across countries. Reporting of results might therefore be stratified accordingly. Similarly, such reports should distinguish between in-home care from health aides, short-term or respite care, and permanent institutionalization.

We also suggest that trialists facilitate data interpretation by reporting cognition, activities of daily living, behavioral symptoms, quality of life, effects on institutionalization, and other healthcare resource utilization in the same trial whenever feasible. It is difficult to interpret results when some outcomes are reported in one trial and others are reported in other trials. Under these circumstances, differences in study population or in the doses or frequency of administration of a drug can render interpretation tenuous. These and other differences add uncertainty about whether the conclusions drawn from diverse data sources, including the conclusions of economic models that use such data, are valid.

In some situations, collecting the cost data relevant to this recommendation may be difficult to obtain within the confines of a clinical trial. This may require conducting additional studies or using administrative and other databases (routinely used in health services research) to obtain this information.\textsuperscript{12}

D. Follow-up

Follow study participants who discontinue treatment, and document the reasons for discontinuation.

Study participants who discontinue treatment are often considered as having withdrawn from a trial, and direct information about them is not available for use when analyzing a trial’s results. Sometimes, information about them is imputed. Simple imputation techniques like last observation carried forward (LOCF) facilitate intention to treat analyses, but they do not account for the progressive deterioration that characterizes AD.\textsuperscript{26} More sophisticated techniques like multiple imputation are rarely appropriate to employ because they rely on the assumption that the data are missing at random. Patients often discontinue treatment due to adverse effects or because they find their treatment ineffective; therefore, their data are not missing at random.

Collecting data from patients who discontinue treatment will also reduce the number of assumptions on which economic models are based, thereby increasing the robustness of these models. We recognize that complete data collection on all patients who have discontinued treatment is frequently infeasible. However, some data collection is nevertheless possible, and at a minimum, should include data on institutionalization, an outcome that is not only costly, but also highly salient to patients and their families. Furthermore, this data should be collected from participants in all arms of a study – not only the experimental arm. Large trials that collect data from a sample of participants who discontinue treatment should obtain data from all or nearly all of that sample, should report information that demonstrates that the sample was representative of the entire cohort of patients that discontinued treatment, and should engage in secondary sensitivity analyses of the data to determine whether obtaining data from all patients would have influenced the results.
HTA and coverage bodies also note that open-label extension trials can provide useful information regarding drug safety and reasons for discontinuation, though these decision-makers expressed varying levels of confidence in such trials’ ability to support conclusions about maintenance of efficacy.

VI. SPECIAL CONSIDERATIONS

A. MCI due to AD, Prodromal AD

A significant proportion of research on AD in the near future will likely focus on patients with what the EMA describes as “mild cognitive deficits but without the complete picture of dementia,” along with varying degrees of evidence that these deficits are attributable to the same pathophysiological process as AD dementia. For investigators who choose to pursue treatments in this area, we present here some considerations that pertain to patients with mild cognitive impairment (MCI) due to AD, as defined by the National Institute on Aging and Alzheimer’s Association (NIA-AA) workgroup or for patients with "prodromal AD" or "MCI of the Alzheimer’s type" as defined by Dubois and Albert. We use these terms in place of "mild cognitive impairment" because we are mindful of the concern, noted by the EMA, that “up to now MCI is not considered a homogeneous clinical entity and more work on characterization of meaningful diagnostic criteria is needed, particularly the multiplicity of MCI definitions, the role of aetiological subtypes (e.g., amnestic type of MCI) and the development of appropriate assessment tools has to be refined.”

Trial Duration

While the guidance in section V proposes that trials that include mild or moderate AD dementia and that are intended to demonstrate maintenance of efficacy should be at least 1 year in duration, trials that include patients with MCI due to AD or prodromal AD will demand longer study periods in order to observe their effects on primary and secondary outcomes. Also, since those therapies would be more likely to be prescribed for longer periods of time to patients who may not develop AD dementia with or without therapy, longer study durations are warranted.

Proxy Reports

The guidance in section V notes that trial enrollees with mild or moderate AD dementia may become unable to provide meaningful reports of their status, necessitating that proxy reports be provided by the care partner. Patients who have not progressed to dementia are reasonably assumed to provide meaningful reports of their own status, making the use of proxy reports unnecessary.

Enrichment

HTA and coverage bodies support efforts to direct therapy—both in trials and in clinical practice—towards those who are most likely to benefit from it. Trials that employ biomarkers to define their trial population should reflect the costs of those biomarkers in economic analyses, and should use biomarkers that are widely available to the population for whom they will seek coverage. Trials of anti-amyloid therapies that use biomarkers as part of enrollment criteria should employ amyloid-specific biomarkers. Examples include CSF-AB and PET amyloid imaging, though several investigators have noted the limitations associated with these modalities. In its qualification opinion on AD novel methodologies, the EMA states "Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population," while cautioning that "neither the value of PET (+) or (-) to accurately predict rate of such
progression to dementia in the referred subjects nor the relative value of other biomarkers have been reported.\textsuperscript{32} If blood tests or other less invasive, less expensive biomarkers are developed and validated, those tests would be preferable especially to ensure that the biomarkers that trials use to define their population can be used in clinical practice across many settings and regions.

A trial that uses an amyloid-specific biomarker to define enrollment should also monitor that biomarker at later points in the trial. Those outcomes may not directly inform coverage decisions, but would provide an opportunity to: a) help validate those biomarkers as enrollment criteria by correlating them with other outcomes; b) move towards assessing the validity of those biomarkers as surrogate outcomes; c) provide additional evidence regarding the amyloid hypothesis; and d) improve the certainty that observed clinical effects will persist.\textsuperscript{27}
VII. APPENDIX: METHODS

We began with the identification of the research gaps perceived to exist by numerous stakeholders, including regulators and particularly by HTA and coverage bodies. To accomplish this, the Institute for Clinical and Economic Review (ICER) catalogued the gaps noted in documents prepared by regulatory authorities in different countries, HTA agencies, public and private payers, clinical societies and other organizations that develop clinical practice guidelines, and patient advocacy organizations.

Documents were eligible for review if they were promulgated between January 1996 and 2011. This timeframe was used to coincide with the period that began with the introduction of donepezil, the first acetylcholinesterase inhibitor (AChEI) to be widely used to treat the symptoms of Alzheimer’s disease (AD).

A total of 206 documents were screened. Eighty eight were deemed to have relevant AD-related information and were fully reviewed. Among these were 23 systematic reviews conducted independently by academic groups. Nearly half of the documents we reviewed were from regulatory authorities in five countries, and most of these came from the U.S. Food & Drug Administration (FDA) or the European Medicines Agency (EMA). HealthCanada, the Canadian regulatory agency had no AD-specific documentation. Drug reviews from Canada were available only from the Canadian Agency for Drugs and Technology in Health (CADTH), an HTA agency.

The catalogue of gaps was then presented to a Life Sciences Advisory Group (LSAG) comprised of representatives from 11 companies involved in pharmaceutical research on AD. The LSAG offered comments on the gaps and noted the areas in which they would like to receive guidance.

In response to these discussions, the EGD was produced using an iterative process of review involving a Technical Working Group (TWG), Life Sciences Advisory Group (LSAG), and Steering Group (SG) described in the acknowledgements of the present document, with each group reviewing at least three drafts of the guidance. The TWG had the most direct role in shaping the guidance; the LSAG offered advice on the feasibility of the guidance and its application to drug development; and the SG defined the scope and format of the guidance.
IX. REFERENCES


32. EMA Qualification opinion of Alzheimer’s disease novel methodologies / biomarkers for PET amyloid imaging (positive / negative) as a biomarker for enrichment, for use in regulatory clinical trials in predementia Alzheimer’s disease. 44, (2012).