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Prevention trials in Alzheimer's disease: An EU-US task force report☆

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ABSTRACT

Despite enormous financial and scientific efforts, still no approved disease-modifying therapies exist for Alzheimer's disease (AD). During the last decade all Phase III clinical trials on disease modifiers in AD have failed. The dementia stage of AD being probably too late in order to allow for successful disease modification has been identified as a possible culprit that could explain the failure of so many clinical trials. In parallel, a major development in the diagnostic research field of AD was achieved by the recent proposal of new diagnostic criteria for AD, which also specifically incorporate the use of biomarkers as defining criteria for preclinical stages of AD, thus extending the traditional definition of disease to very early stages that may be a more feasible target for various disease modifying therapeutic interventions. This ongoing paradigm shift in AD definition and diagnosis represents a fundamental basis for redefinition of interventional trials in AD, allowing to specifically focus on preventative measures during very early pathophysiologically confirmed stages of disease. This consensus paper reflects the outcome from a European Union and North American Task Force meeting comprised of experts from academia,

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Abbreviations: Aβ42, amyloid beta 1–42 peptide; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; ApoE, apolipoprotein E; CDR, clinical dementia rating; CRO, clinical research organization; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; EMA, European Medicines Agency; FCSRT, free and cued selective reminding test; GCP, good clinical practice; GEM, Ginkgo Evaluation of Memory Study; MCI, mild cognitive impairment; MMSE, mini mental state examination; MRI, magnetic resonance imaging; NIA, National Institute of Aging; PI, principal investigator; PET, positron emission tomography; PiB, Pittsburgh substance B; p*tau, phospho-tau; t*tau, total-tau.

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industry, private foundations, and regulatory agencies that was convened in Toulouse, France on November 5, 2010 and that focused on prevention trials in AD. This position paper thoroughly analyzes prerequisites for successful preventative trials in AD and concludes with concrete recommendations on biomarkers, statistical tools and other variables important for improved study designs suitable for preventative as well as for early therapeutic interventional trials in AD.

Contents

1. Introduction

Recent disappointments in therapeutic clinical trials in mild–moderate Alzheimer's disease (AD) have forced researchers and clinicians to re-examine the manner in which trials are designed and conducted. Recognizing that the field must improve the confidence that Phase II clinical trials will translate into successful Phase III trials, and that this is a world-wide problem requiring multi-national solutions, a European Union and North American Task Force of experts from academia, industry, private foundations, and regulatory agencies was convened in Toulouse, France on November 5, 2010 to focus on prevention trials in AD. In addition to reviewing and learning from recent negative and inconclusive trials, the task force explored the role of biomarkers in prevention trials and new trial designs that would maximize the likelihood of demonstrating a therapeutic signal while minimizing the duration and number of subjects required.

There has been growing concern that the timing of therapeutic trials, i.e., treating those with established mild–moderate AD, may be too late in the disease process to substantively improve the outcome. This may be especially true for anti-amyloid approaches, as it is now clear that amyloid deposition is one of the earliest, if not the initial feature of the disease. Thus, there is an emerging consensus that AD modification programs should focus on the earliest stages of the disease, before the underlying pathophysiologic mechanisms have advanced to a stage that corresponds to dementia (Aisen, 2009). While earlier task force meetings focused on reaching consensus on issues related to disease modifying trials (Vellas et al., 2007, 2008), the focus has now shifted to prevention rather than treatment of dementia, with the prevention paradigm encompassing both primary prevention—preventing the pathology, and secondary prevention—preventing symptoms (Aisen et al., 2011). Many important issues concerning how the field will move forward in a coordinated way to identify prevention strategies are still to be considered.

2. The future of multi-national clinical trials

In both the United States and Europe, large cultural, educational, and socio-economic differences present challenges in designing clinical trials. There are additional challenges in world-wide trials due to the many diverse countries and many languages spoken as well as large differences between countries in terms of the organization and governance of health care systems. Specifically with regard to clinical trials, many countries differ considerably in terms of their experience, reimbursement issues, types of clinical institutions at which trials can be conducted (academic vs. private), availability of clinical trial expertise and technologies, and other differences regarding regulatory processes, coordination, and ethical considerations. Variability in expertise between academic and non-academic sites, for example, continues to plague U.S. trials. In one study on subjects with mild cognitive impairment (MCI), for example, academic sites were found to be twice as effective as non-academic sites in terms of subject retention and AD conversion (Edland et al., 2010). Regardless of where the trial is being conducted, trials require high quality scientific and clinical expertise, combined with correct implementation of good clinical practices (GCP), compliance with regulatory guidelines, and adequate training. Possible solutions include:

- Ensuring study-wide certification of clinical trial raters with re-certification of these raters on a 6–12-month schedule. This could possibly be accomplished through web-based training and certification.
- Limiting the number of raters at a given site and ensuring that a particular subject is always seen by the same rater, to the extent that this is possible.
- Limiting the number of countries and sites.
- Selecting PIs based on their proven track record in AD research and particularly, in the conduct of clinical trials.
- Selecting a national PI to be responsible for the trial conduct within each country.
- Using only highly qualified CROs and limiting their ability to select sites.
- Requiring independent monitoring of CROs to maintain consistent quality.
- Requiring a minimum number of patients for a site to be eligible in order to assure balance.
- Making payment dependent on reaching that minimum number of appropriate subjects.
- Focusing more research on recruitment issues that will enable increasing the number of patients per center, decreasing center variability, and establishing strong, manageable networks.

The problems experienced in clinical treatment trials are compounded in prevention trials, where the goal is to enroll subjects with minimal or no symptoms with the hope of stopping the disease before the neurodegenerative process adversely effects quality-of-life. Considering the recent failures and serious adverse effects of some disease modifying drugs in AD patients (e.g., severe

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neuroinflammation, accelerated cognitive deterioration, etc.) the preventative application of pharmaceutical agents in healthy subjects needs a thorough consideration of the potential benefit-to-risk ratio. Another challenge in the development of preventative AD compounds are economic issues, which may influence the approval of drugs within the state health systems of some countries. Cost-to-benefit considerations are an ongoing issue even with already approved symptomatic drugs for AD. Exemplary, the U.K. based guidelines of the National Institute for Health and Clinical Excellence (NICE) have repeatedly re-evaluated and re-formulated their official recommendations with regards to the application of cholinesterase inhibitors in AD with special respect to their anticipated benefit to cost ratio. This issue will potentially be of even higher relevance for preventative compounds which will have to demonstrate a convincing long-term cost benefit, even more so as some of those preventative compounds may have to be applied chronically.

Two recent prevention trials—the GEM (Ginkgo Evaluation of Memory) (Snitz et al., 2009) and GuidAge studies (Andrieu et al., 2008)—both failed to demonstrate significant effects on the primary endpoint, prevention or slowing of cognitive decline. However, secondary analyses in GuidAge hinted that there may have been some potential benefit in conversion to dementia from long-term (4 year) exposure to treatment. Both of these studies were randomized double-blind trials of EGb 761®, an extract of Gingko biloba. GEM was conducted at 6 academic medical centers in the United States, GuidAge at a network of general practitioners and memory clinics throughout France.

There is much to learn from these trials that may guide future prevention studies. A positive lesson from GuidAge involved the use of family physicians to lower the barrier for recruitment. These physicians received training from the GuidAge team on identifying appropriate subjects, and then referred those subjects to the memory clinics to be enrolled in the trial. The family physicians also saw the subjects every three months to give them the study medication and assess side effects, which helped increase drug compliance.

GuidAge targeted people over the age of 70 who had complained of memory problems to their physicians. Subjects with depression or anxiety were excluded, as were those with mini-mental state (MMSE) scores below 25 (on the basis that they were more likely to have prodromal AD). These criteria may have contributed to the low rate of conversion seen in the study population. There are various possible strategies that could be considered for improving the likelihood of conversion to dementia:

- Screen for the inclusion of appropriate biomarkers (see Section 4). For example, confirming a central amyloid burden either by including a positive baseline amyloid imaging scan (e.g., with PIB or AV-45, florbetapir) or by demonstrating a CSF Aβ42 level below a lower threshold (this could also be achieved using a combination of T-tau and Aβ42/P-tau181). This is especially critical as about one-third of individuals with a clinical picture of prodromal AD do not have an amyloid burden.
- Select candidates on the basis of ApoE4 genotype.
- Select subjects with a global Clinical Dementia Rating (CDR) of 0.5. Whether this will indeed increase the chance for a trial to be successful is questionable unless combined with a trial of longer duration, however. Moreover, it must be acknowledged that the rate of conversion of CDR 0.5 subjects recruited for prevention trials through advertising differs from those with CDR 0.5 recruited from memory clinics.
- Limit enrollment to subjects greater than 80 years of age with subjective memory complaint
- Exclude those with high MMSEs at baseline (>28) could also enrich the cohort with subjects more likely to decline during the study time frame.

Another factor affecting the outcome of the trial were the many dropouts, particularly in the first 2 years (most of the dropouts occurred early in the trial). Because the trial used an intention-to-treat analysis, some of the effect of the drug may have been masked by this high dropout rate.

The primary endpoint for GuidAge was conversion to dementia based on neuropsychological, cognitive, and activities of daily living assessments. An alternate method would have been to utilize CDR Sum of Boxes (CDR-SOB) score, which, in comparison to the CDR global score, provides additional information helpful in making a diagnosis in the earliest stages of dementia (Lynch et al., 2006). There were also concerns about learning effects with the FCSRT (Free and Cued Selective Reminding Test); to optimize long-term follow up of memory function, another cognitive assay with a sufficient number of versions may be needed.

3. Selecting the appropriate statistical tools

Another study design decision that can dramatically affect the results of a trial is the statistical tool or tools chosen to analyze the data. The most commonly used statistical approach to assess time to conversion is the non-parametric Log-rank test or the proportional hazards model (Cox model). The Log-rank test is particularly powerful if the hazards ratio is constant over time, and is the safest alternative when no prior information is available. However, other statistical methods are more efficient when the effect of the drug is not constant over time. When the protective effect is early, the Gehan–Wilcoxon is most powerful, whereas if the protective effect is only seen at the end of the trial, the Fleming–Harrington test is more powerful. The Renyi test is particularly useful when the hazard ratio can vary substantially over time including an inversion of effect. The Renyi test therefore covers a broad class of alternatives. A broad class of alternatives also results in smaller power, but a far smaller risk of power collapse due to a true effect outside the retained narrow class of alternatives, such as a late effect analyzed with a planned Gehan–Wilcoxon test (Klein and Moeschberger, 1997; Salsburg, 1992; Scherrer, 2009).

Thus, selecting the appropriate statistical test is crucial in designing a trial, and may require simulations to determine power under various plausible scenarios. Because post hoc selection of the statistical test is generally frowned upon by regulatory agencies, the retained primary test is often the Log-rank test due to its good efficiency in a relatively broad class of alternatives. Proportionality of hazards or constant effect over time may be tested and, if rejected, another planned test may be used in a sensitivity analysis, although the credibility of latter one is not as good as the primary analysis. It might be possible to have a co-primary test, with adjustment of the type-one error because you are performing two tests, but this practice is not frequent. The European Medicines Agency (EMA) has established a new group on statistics and methodology, which has proposed that it may be possible to redefine the statistical plan to an adaptive design as long as it is done while the data are still blinded and other characteristics of the trial have been pre-specified. Unfortunately it is not possible to test proportionality of risk and to deduce the most efficient test without unblinding. The cleanest solution remains to carry out an initial trial with the Log-rank test, to assess the constancy of the hazard ratio over time and to plan the optimal test in a confirmatory trial.

4. Biomarkers in prevention trials

One possible solution to ensure the selection of appropriate (informative) candidates for prevention trials would be to screen candidates using biomarkers that predict disease progression. Just recently, new criteria have been proposed for biomarker-based

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preclinical stages of AD (Sperling et al., 2011). Although meant to be used strictly for research purposes, the definition of such preclinical diagnostic entities is an important prerequisite for planning and conducting primary preventative interventional trials in AD. Such markers can enhance power and enable trials with substantially reduced sample sizes. Some of these biomarkers may also be used to monitor progression and/or to monitor the effectiveness of disease modifying therapies.

Recent studies suggest that analysis of CSF biomarkers may be useful in prevention trials to identify asymptomatic candidates who are likely to progress (De Meyer et al., 2010). There are also a number of other novel CSF biomarkers, such as BACE1 and other Aβ species that may be useful in identifying prodromal AD (Hampel et al., 2010).

Imaging biomarkers, both structural and functional, also show promise in identifying subjects likely to convert to AD. Whole brain, hippocampal, or entorhinal cortex atrophy assessed using MRI (Vemuri et al., 2010; Frisoni et al., 2009); deposition of amyloid in the brain as shown using ^{11}C-PIB (Pittsburgh Compound B) or fluorinated ligands with positron emission tomography (PET) (Morris et al., 2009); regional hypometabolism assessed with fluorodeoxyglucose (FDG)-PET (Reiman et al., 2010); abnormalities in cortical regions shown with functional MRI (fMRI); and microstructural white matter lesions shown using diffusion tensor imaging (DTI) (Teipel et al., 2010) all may be probably capable of identifying structural and functional changes long before cognitive symptoms appear and thus could be useful in selecting candidates for prevention trials. However more studies are still needed to confirm this potential. There are also network changes, particularly in the default mode network, that appear to be among the first maladaptive functional alterations in the brain and that can be assessed using fMRI techniques (Pihlajamäki and Sperling, 2009; Hampel et al., in press). It may be that combinations of biomarkers, rather than a single biomarker, will provide the highest predictive value for future dementia.

It should be noted that the current conceptualization of the progression of markers from normal to abnormal over the course of the disease implies that amyloid markers may be abnormal in the earliest stages, followed by functional/metabolic, and finally structural markers. The corollary is that either amyloid or functional/metabolic markers should be preferred to select patients and monitor disease activity in primary prevention, while structural measures might be preferred in a secondary prevention trial. However, this framework is largely hypothetical and more evidence needs to be accumulated before it can soundly inform operational decisions. Moreover, cost and feasibility considerations will need to be done in the choice between markers providing similar information (e.g., Aβ42 in the CSF and amyloid imaging, or fMRI and EEG).

Genetic variations have been instrumental in delineating the earliest detectable markers of disease (Ridha et al., 2006). In elderly populations, non-symptomatic ApoEε4carriers (especially homozygous) have a higher risk of having high amyloid burden as measured by amyloid imaging or low CSF Aβ42, which is typical for AD (Vemuri et al., 2009). The risk of developing AD in these ApoEε4carriers is thus several-fold higher than in the general population, with slightly varying risk dependent on the genetic background. Familial AD mutations (e.g., presenilin 1 and amyloid precursor protein mutations) show an autosomal dominant pattern of inheritance and often the age of onset can be predicted in one respective family. Both of these populations are useful for studying biomarkers in presymptomatic subjects, with ApoEε4 being a means of enriching for subjects at high risk and familial mutation carrier status a means selecting individuals that are predictably on the way to developing AD. However, it needs to be considered that genotype-based enrichment will narrow down the at-risk or clinical study population to specific genetic endophenotypes, which represent only a fraction of the total AD population. Both approaches are currently followed by different consortia (e.g., the Alzheimer's Prevention Initiative, API, and the Dominantly Inherited Alzheimer Network, DIAN), as well as individual investigators. Potentially new markers could be developed in these observational studies, but there are still insufficient data to conclude that these markers can identify asymptomatic individuals who are likely to develop sporadic AD. More studies are needed, particularly multicenter initiatives such as the worldwide Alzheimer's disease Neuroimaging Initiative (ADNI) studies. There are also concerns regarding the reliability and stability of CSF Aβ measurements and the reproducibility and standardization of imaging measures, although efforts are currently ongoing to standardize the collection and measurement of CSF markers and hippocampal volumetry on MR (Mattsson et al., 2011; Boccardi et al., 2011). Fully automated measures would help, but these need to be validated versus the gold standard of manual segmentation in large multi-center studies. Another concern about using biomarkers to select subjects for trials is that the treatment as well could be limited to this group of biomarker positive individuals, but not the general AD population, as described in the labeling of the drug. This would also necessitate that the biomarker is at least qualified (fit for purpose), if not fully validated for its intended use.

While ADNI and other studies suggest that the demonstration of a central amyloid burden, either by CSF Aβ42 measurement or amyloid PET imaging, may be useful in screening individuals for inclusion in clinical trials, there are still issues to be resolved regarding the acceptability of the two methods by regulators, clinicians, and volunteers. This includes standardization and generally accepted reference and/or cut-off values. The cost of amyloid imaging has come down significantly in recent years, at least in the United States, and is less invasive than lumbar puncture. However, there remain questions about the diagnostic utility of amyloid imaging, given that many people show significant amyloid deposits despite having no signs of cognitive impairment. One problem in comparing the two methods is that the data are different, with more longitudinal data available regarding CSF biomarker studies and more cross-sectional data available regarding amyloid imaging.

The use of biomarkers in prevention trials will also vary depending on whether the goal is primary or secondary prevention. In a primary prevention trial, where the goal is to prevent the target pathology (e.g., Aβ deposition) from developing, PIB-PET imaging might be a useful screen. If the aim is to prevent neurodegeneration, it may be reasonable to select individuals with positive amyloid PET scans. But if the aim is to prevent amyloid deposition it might be necessary to select individuals with negative amyloid PET scans, but perhaps with some other marker of risk (e.g., abnormal FDG-PET). In secondary prevention trials where the goal is to prevent the emergence of symptoms, functional biomarkers might be more relevant. Moreover, selecting presymptomatic subjects for drug trials on the basis of a biomarker such as Aβ deposition may also expose many people to a drug even though they would not go on to develop AD or would develop it many years in the future. The exposure of so many people to a drug raises questions not only about increased likelihood of adverse events, but also poses a potentially huge cost to society. At the very least, the safety profile of the drug would need to be appropriate to the risk–benefit profile.

Biomarker selection in drug trials may also vary depending on the presumed mechanism of action of the drug being tested, since different biomarkers are likely to be differentially affected by different types of drugs.

5. Subject selection and study design for prevention trials

New criteria have been proposed for defining the different stages of AD, and validation of these criteria across geographical

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boundaries could help engage clinicians in identifying candidates for prevention trials. In the United States, three working groups convened by the NIA and the Alzheimer's Association proposed three diagnostic categories: a pre-symptomatic phase; a symptomatic phase (currently MCI), which is further subdivided into three groups—low, moderate, and high probability; and Alzheimer's dementia. The clinical and biomarker criteria for these stages all need to be validated before they will be accepted by both the research and clinical communities. Meanwhile, the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) is in progress and the American Academy of Neurology is conducting an evidence-based medicine review of the literature. How much of an effect these efforts to better define the disease will have on clinical practice may depend on whether the criteria are well validated, their ease of use, and the expense to conduct them; but in terms of designing clinical trials, these definitions may turn out to be important and they will most certainly have regulatory/labeling implications.

There are already numerous trials underway and planned around the world with different recruitment strategies (including enrichment strategies), outcome measures, and trial designs. Globally accepted diagnostic criteria would increase the compatibility of various trials; and with regard to subject recruitment, core requirements for inclusion and exclusion criteria and designs that shorten trial duration could be established. Worldwide methodological standards for various technologies, such as those being established by worldwide ADNI studies will also facilitate harmonization of studies. One recruitment tool recently established in the United States is the Alzheimer's Association TrialMatch, a free service that matches potential candidates with trials that are recruiting. Individuals with a diagnosis, family members or other carers, and physicians can all access TrialMatch; and the Association would also like to extend the system internationally.

Attention must also be paid to the factors that determine participation and adherence to preventive trials. According to a study conducted by Sandrine Andrieu and colleagues, people agree to take part in studies (Multi Domain Alzheimer Preventive Trial, M.A.P.T., unpublished preliminary results) for both altruistic and non-altruistic reasons; for example, the hope that participation will result in improved health or memory and that they will get better information and have more frequent contact with clinicians. Reasons people may refuse to participate include the duration of the trial, transportation issues, burden in terms of time required to participate and/or the nature of the testing, anxiety about potential adverse effects, an unwillingness to be randomized, or lack of trust in the investigator or sponsoring agency (Papp et al., 2009). Many of these issues could be addressed with shorter and more selective trials, and better provision of information to general practitioners, the general public, and potential trial participants.

6. Recommendations for prevention and early intervention trials

Potential reasons why recent therapeutic clinical trials have failed include ineffective drugs, i.e., the drug mechanism of action does not substantively contribute to a clinical effect; suboptimal study designs (including endpoint selection); inadequate Phase II studies, e.g., failure to demonstrate target engagement prior to launching late stage clinical trials; inclusion of subjects who did not truly have AD pathology; and selection of study populations at a disease stage too late for effective intervention.

With a consensus that disease modification can be more readily demonstrated with early intervention, the movement now is toward prodromal stages of the disease, that is, subjects who are symptomatic and who have biomarker evidence of AD pathology (e.g., Dubois criteria). However, more longitudinal data are needed regarding how best to identify people at this stage. While ADNI 1 recruited individuals with mild dementia, amnestic MCI, and no cognitive impairment, and followed them for several years, ADNI 2 will follow these cohorts for an additional 5 years. ADNI 2 (as well as the run-in ADNI GO study) will also enroll an additional cohort of less impaired, early MCI individuals. An alternative approach to this neuropsychologically based selection could be selection based on the combination of amyloid imaging and subjective memory impairment. Early results with the 18F PET amyloid ligand, AV-45 in M.A.P.T. show an important prevalence of amyloid deposits in those age 70 or older with subjective memory complaint, twice that seen in individuals without subjective memory complaints in ADNI.

ADNI 1 showed that among people with amnestic MCI and early AD, neuroimaging measures, including measures of brain atrophy and ventricular volume, were superior to cognitive and clinical measures in detecting disease progression. Neuroimaging was also shown to be an effective enrichment strategy for recruitment into secondary prevention trials, reducing sample sizes by as much as 60% (McEvoy et al., 2010). Although these measures have yet to be fully validated as biomarkers of the disease, the ADNI data support the idea that neuroimaging markers could also serve as continuous outcome measures in clinical trials, which would be superior to the traditional survival-to-dementia type analysis in assessing the effectiveness of a drug in prodromal disease.

The ADNI data also suggest that late MCI, and possibly even early MCI or cognitively normal subjects could be selected for trials based on either CSF Aβ42 measurement or amyloid imaging (Aisen et al., 2010b). ADNI analyses indicate that reasonably sized (group sizes of 200–300) and reasonably short (<2 years) proof of concept trials for secondary prevention could be conducted by screening cognitively normal individuals over the age of 70 with either CSF biomarkers (requiring lumbar puncture) or amyloid PET imaging. Using multiple outcome measures, e.g., volumetric MRI, FDG-PET, amyloid PET, MMSE, and sensitive neuropsychological tests, such a trial could achieve the goal of both validating (or at least qualifying) surrogates and demonstrating efficacy.

Taking this a step further, a true primary prevention trial could be conducted in older individuals with no symptoms and no signs of amyloid deposition. However this would require a very long trial and a very safe treatment. While such a study could be enriched by enrolling mutation carriers or those with a family history of disease, subjective memory complaints (raising the issue of whether the trial would represent true primary prevention), or frailty syndrome, ultimately it will be necessary to test interventions in the general population. What happens in people in the earliest stages of the disorder, before amyloid deposition, is perhaps one of the most critical unexplored areas of research, and one that can only be addressed through longitudinal population-based studies. While substantial data exist indicating that amyloid may an initiating factor in AD, this remains an unproved hypothesis and it is possible that amyloid deposition is merely a marker of normal aging and/or that impacting the central amyloid burden may not affect the disease outcome. Moreover, it will ultimately be necessary to establish a functional relationship between biomarkers and clinical outcome. This relationship will not only be important in defining the natural history, but also in interpreting successful treatment; for example, does reduced CSF-tau correlate with an improved or stabilized clinical syndrome? However, true primary preventative trials in cognitively intact and amyloid (and other core AD-)biomarker negative subjects are challenged by the fact that preventative compounds with their potential adverse effects would inevitably have to be applied to subjects, some of which may never be affected by AD. Therefore, development of novel biomarkers is required that could accurately

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predict the development of AD pathophysiology in otherwise core AD biomarker negative healthy subjects. Different biomarkers may be useful at different stages of disease, and particularly during the earlier stages of disease when compensation may play an important role, markers of decompensation may also be valuable. Only further research investigating multiple markers throughout all stages of the disease can answer these questions, as discussed in previous task force meetings (Schindler, 2010; Schneider, 2010), and with regard to our experience from negative trials (Douillet and Orgogozo, 2009; Hendrix and Wilcock, 2009).

The task force reached consensus on a number of issues related to planning prevention trials in AD.

1. Enriching the study population for subjects likely to decline during the time frame of the study will improve the power and minimize the length of the study, although labeling issues need to be addressed when enriched populations are used.
2. CDR Sum of Boxes scores or a specific cognitive endpoint such as episodic memory, rather than a global score, may offer greater sensitivity to early clinical change, and thus could provide a more sensitive selection criterion or endpoint.
3. Selecting the appropriate statistical tool depends on the characteristics of the drug being tested, such as when the protective effect is expected to be seen and the particular clinical trial design. Simulations of the trial prior to selecting the statistical method can help ensure the most accurate analysis.
4. More study is needed of the various biochemical, imaging, and behavioral biomarkers in the prodromal and early stages of disease, so that biomarkers can be used both to select appropriate subjects for preventive trials and monitor effectiveness of interventions.
5. More education programs are needed for both general practitioners and the public to ensure adequate numbers of volunteers for prevention trials as well as compliance with study parameters and retention within a clinical trial.
6. Globally accepted diagnostic criteria, core requirements for inclusion and exclusion criteria, and designs that shorten trial duration would facilitate international drug development for AD.

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