

Perspectives

Priorities for research consortia on Alzheimer's disease

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**Abstract**

Coordination and harmonization of efforts between five major research consortia on Alzheimer's disease may increase our understanding of this condition and improve our therapeutic approaches. Specific opportunities include a registry for families with early onset dementia, a study registry, minimal data sets, validation of assessment tools and outcomes, update on ethical issues, resolution of methodological issues, new investigators training, longitudinal observation studies, prevention studies, and liaison with stakeholders such as Alzheimer Disease International.

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**1. Introduction**

Worldwide, there are currently five research consortia with special interest in the prevention and treatment of Alzheimer's disease (AD) and related disorders. A meeting of representatives of these consortia during the 14<sup>th</sup> International Congress of the International Psychogeriatric Association in Montreal on September 3<sup>rd</sup> 2009 provided an opportunity to share an update on their structure and mode of operation. More importantly, there was sharing of ideas on how to increase our capacity to perform randomized clinical trials (RCTs) to test treatment hypothesis against AD and related disorders. This text is a summary of our discussion, offering a template for international collaboration, particularly towards primary and secondary prevention. The information provided has been updated during the full meeting of the European Alzheimer's Disease Consortium that took place in Geneva, Switzerland, March 23–24, 2010.

**2. Structure and mode of operation of research consortia on AD**

The five research consortia are the Alzheimer Disease Cooperative Study (ADCS) in the United States of America

(USA), the Consortium of Canadian Centers for Clinical Cognitive Research (C5R), the Australasian Consortium of Centers for Clinical Cognitive Research (AC4R), the European Alzheimer Disease Consortium (EADC), and the Asian Society Against Dementia (ASAD). They are listed in chronological order, based on their year of creation (Table 1). The number of participating sites in each consortium ranges from 12 to 57. Some sites are core participants, others only for specific RCTs.

The ADCS was conceived and first funded in 1991 by Zaven Khachaturian while at the National Institute on Aging and under the leadership of Leon Thal, MD, at the University of California, San Diego. The project's core mission was to conduct investigator-initiated clinical trials in AD that were unlikely to be conducted by industry and to develop new designs, instruments, and technologies for the use in clinical trials for AD [1]. Of particular interest are trial designs demonstrating the slowing of progression, halting of neurodegeneration, and treatment of troublesome behaviors. Now under the direction of Paul Aisen, MD, the most recent efforts have included developing instruments and technologies for trial designs aimed at disease prevention. The ADCS was initially formed from the Alzheimer Disease Centers, another NIA-funded program designed to focus research resources on AD. Today, the ADCS has expanded to include other major centers in the US with 35 Steering Committee member sites. Additional performance sites are added for specific trials. Studies conducted by

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Table 1  
Research consortia on Alzheimer's disease

	ADCS	C5R	AC4R	EADC	ASAD
Starting year	1991	1991	1997	2001	2006
No of sites core+occasionnal	35+50	35	8+4	57	13
Peer-reviewed funding	1			2	
RCT funding		*	*		*

1. From National Institute on Aging, 5-year renewals

2. Initially funded by the European Community, but not currently

the ADCS include investigator-initiated projects that are submitted with the ADCS Consortium application, as well as clinical trials funded by investigator-initiated grants, such as the RO-1 mechanisms. Industry-initiated projects may be done by members of the ADCS but are not typically considered ADCS studies. The steering committee of the ADCS meets three times a year and, in addition to reviewing progress on funded initiatives, it sets the scientific mission for the organization, insuring representative recruitment, and maximum opportunity to publish secondary results from the available data. New proposals are brought to the committee for evaluation for scientific interest and feasibility. The Data Coordinating Center for the ADCS has become an important resource for other collaborative initiatives including the Alzheimer Disease Neuroimaging Initiative (ADNI) study and for Dominantly Inherited Alzheimer Network (DIAN) which are described below. Funding of the consortia's infrastructure is from peer-reviewed national or international (European) sources for the ADCS and the EADC. The three other consortia depend on revenues from RCTs, generally with pharmaceutical companies. Funding may improve because of current national priorities for funding research on AD in different countries.

### 3. Areas of possible collaboration between consortia

#### 3.1. An international registry of early onset familial AD

Since these subjects have pure amyloid pathology, compared to older persons with mixed pathology associated with dementia, prospective studies are possible on the correlation between amyloid deposition and clinical manifestations. Furthermore, they offer a unique opportunity for proof-of-concept RCTs in pre-symptomatic or early symptomatic stages of AD using amyloid-specific therapies.

This collaboration can be built on the current Dominantly Inherited Alzheimer Network (DIAN) established by John Morris in the USA, which include sites in the United Kingdom (London) and Australia (Perth). Furthermore, an initiative for the diagnosis of early onset dementia led by Florence Pasquier has been funded in France.

#### 3.2. An international registry for observational studies and RCTs in AD and related disorders

Modeled on the current clinical trial registry in the USA, such an international registry would allow for comparison

and sharing of interest, experience, and resources, and avoid unnecessary duplications. For instance, a longitudinal observational study named Canadian Outcomes Study in Dementia (COSID) has been running in Canada [2], followed by a similar study named PRIME in Australia [3]. Knowledge of ongoing or planned studies would facilitate inter-consortia collaboration and allow comparisons between subjects of different genetic, environmental, and cultural backgrounds.

#### 3.3. Minimal data sets for subjects studied in the different consortia

The experience of the ADCS and the EADC in establishing a minimal data set or comparable measures across most studies within their consortia has demonstrated the feasibility and high value of minimal data sets for subjects involved in observational studies and RCTs [4]. Observational studies on the natural history of mild cognitive impairment and of different types of dementia would greatly benefit from the comparisons between subjects of different genetic, environmental, and cultural backgrounds. The positive results of ADNI [5] in the USA, Canada, and Europe, as well as the equivalent AIBL project in Australia, demonstrate the value of common clinical and imaging data sets.

#### 3.4. Validation of assessment tools and outcomes across languages and cultures

Instruments for global measurement of disease stage or change over time, or for specific domains of cognition, activities of daily living and behavior, require translation to multiple languages and adaptation to local cultures. A structured approach between consortia towards a registry of current translations of core instruments for the purpose of diagnosis, clinical follow-up, and RCTs outcomes would facilitate international studies. The validated scales could be posted on a dedicated website and available for free download, as was done successfully for the Montreal Cognitive Assessment (MoCA) available on [www.mocatest.org](http://www.mocatest.org).

#### 3.5. Developing training procedures for clinical trial procedures and outcomes

An important effort that can be accomplished through international collaborations would be the standardization of training methods for clinicians and study staff. While GCP is a recognized standard for collection of data and delivery of care, there is a need for an equivalent set of guidelines to insure comparable skill for diagnosis, administration of evaluations, and data collection at all levels. This standardization would be important for evaluation of biomarkers as well as clinical measures. This could include guidelines for minimal education, training, and experience for all aspects of evaluations. Harmonization of the criteria and methods of clinical trial procedures to insure a universal skill set, a common language and globally-recognized quantification

of outcomes, would provide a basis for conducting comparable studies internationally.

### 3.6. Updates on ethical issues

The available symptomatic treatments may be recognized as “standard therapy” in mild-to-severe AD, but they achieve an effect size far less than that observed in Parkinson’s disease using levodopa. The use of placebo-controlled trials is fraught with controversy for Institutional Review Boards and Ethics committee with no clear decision over the past decade [6]. The acceptance of placebo-controlled RCTs in AD for six months duration or longer to test the efficacy and tolerability of new compounds is limited unless the investigational drug or placebo is added to a cholinesterase inhibitor  $\pm$  memantine or the population has sufficient capacity to make such decisions. Hopefully, the involvement of participating subjects themselves will change this attitude [7].

Other issues of international interest include tissue banking with transfer of specimens across borders, registry of data from participants in different countries, and reporting of serious adverse events.

### 3.7. Methodological issues related to RCTs

The Clinical Trial Against Dementia (CTAD) Meetings in Toulouse (2008) and Las Vegas (2009), and the biannual Springfield meetings over the past 20 years illustrate the need for discussions between industry and investigators on how to better conduct RCTs for AD and related disorders. Issues of specific interest to consortia include budget planning, review of adverse events, design, and utility of open-labeled studies.

### 3.8. New investigators training

The first generation of investigators in the diverse consortia is concerned that a cadre of new investigators is required for the future, particularly if observational and interventional studies towards primary and secondary prevention (*vide infra*) are being planned. Global training and support mechanism include research-specific training awards such as the NIH K awards system. The Paul B. Beeson Career Development Awards in Aging Research Program has supported 162 Beeson Scholars in the USA and Ireland and offer a mechanism to support clinical research and the development of clinical trial skills ([www.beeson.org](http://www.beeson.org)). The Fogarty’s Research Training Grants—which provide funding to train researchers and builds sustainable research capacity in low- and middle-income countries ([www.fic.nih.gov](http://www.fic.nih.gov))—provide a model for insuring that training is available across the globe. Possibly, an approach modeled on the Lundbeck Institute, with regular meetings of clinicians from different countries aiming at education on the management of different neurologic and psychiatric disorders, will be successful, with emphasis on RCT methodology and ethics. Coordination of training across trials

is also required to avoid duplication and could be facilitated by the collaboration between the consortia.

### 3.9. Longitudinal observation studies

Already successfully done in countries such as France, longitudinal observation studies in the geographic areas subserved by the different consortia with coordination through common objectives and minimal data set will greatly increase the relevance of findings for populations at large, at different levels of risk towards AD and related disorders.

### 3.10. Prevention studies

Challenges to designing trials to assess prevention of AD include the large sample size, the long observation period and tolerance for a low risk to benefit ratio [8]. Multinational collaborative efforts can provide a valuable opportunity to conduct such trials. The coordinated planning underway through the former Lou Ruvo Institute—based in Las Vegas, and now being headed by the Campaign to Prevent Alzheimer’s Disease 2020 ([www.pad2020.org](http://www.pad2020.org)) for a three countries (USA, France, Canada)—approach to a non-pharmacologic multi-domain intervention (structured cognitive training and physical exercise) in persons at risk of AD is a good example of what can be achieved through international collaboration [9–11]. Such a joint approach to primary and secondary prevention could be done among the five consortia.

### 3.11. Link with Alzheimer Disease International, national Alzheimer associations, and the Campaign to Prevent Alzheimer’s Disease by 2020 (PAD2020)

Scientific research will be much more effective if conducted in liaison with persons at higher risk or in early stages of AD, represented by Alzheimer Disease International (ADI), national Alzheimer associations and PAD2020. Such a link will increase interest in participation in longitudinal studies and RCTs, help in retention, foster international collaboration and facilitate dissemination of findings applicable to populations.

## 4. Conclusions

We are at a turning point in the history of research on AD therapy and prevention, with testable hypothesis in populations at different levels of risk for AD. Coordination and harmonization between the five research consortia dedicated to AD treatment will have a positive influence on our understanding of AD and related disorders, and help provide for a significant reduction of the prevalence of dementia with one generation.

## References

- [1] Thal LJ. The Alzheimer’s Disease Cooperative Study in 2004. *Alzheimer Dis Assoc Disord* 2004;18:183–5.

- [2] Sambrook R, Herrmann N, Hébert R, McCracken P, Robillard A, Luong D, et al. Canadian Outcomes Study in Dementia: study methods and patient characteristics. *Can J Psychiatry* 2004;49:417–27.
- [3] Ames D, Woodward M, Boundy K, Brodaty H. Baseline demographics of dementia patients seen at Australian clinics: preliminary data from PRIME. Australian and New Zealand Conference. Gold Coast, Australia April 2007.
- [4] Morris JC, Weintraub S, Chui HC, Cummings J, DeCarli C, Ferris S, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. *Alzheimer Dis Assoc Disord* 2006;20:210–6.
- [5] Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI). Clinical characterization. *Neurology* 2010;74:201–9.
- [6] Kawas CH, Clark CM, Farlow MR, Knopman DS, Marson D, Morris JC, et al. Clinical trials in Alzheimer disease: debate on the use of placebo control. *Alzheimer Dis Assoc Disord* 1999; 13:124–9.
- [7] Gauthier S, Leuzy A. Diagnosis of prodromal Alzheimer's disease: do you really want to know? *Can J Neurol Sci* 2010;37:2.
- [8] Thal LJ. Prevention of Alzheimer disease. *Alzheimer Dis Assoc Disord* 2006;20:S97–9.
- [9] Khachaturian ZS, Petersen RC, Gauthier S, Buckholtz N, Corey-Bloom JP, Evans B, et al. A roadmap for the prevention of dementia: the inaugural Leon Thal Symposium. *Alzheimers Dement* 2008; 4:156–63.
- [10] Khachaturian ZS, Snyder PJ, Doody D, Aisen P, Comer M, Dwyer J, et al. A roadmap for the prevention of dementia II: Leon Thal symposium 2008. *Alzheimers Dement* 2009;5:85–92.
- [11] Khachaturian ZS, Camí J, Andrieu S, Avila J, Rovira MB, Bretelet M, et al. Creating a transatlantic research enterprise for preventing Alzheimer's disease. *Alzheimers Dement* 2009;5:361–6.

# Did you know?

The screenshot shows the website for *Alzheimer's & Dementia*, the journal of the Alzheimer's Association. The page features a navigation menu on the left, a search bar at the top right, and a main content area. In the 'JOURNAL ACCESS' section, there is a text block stating: 'Full-text articles are available from July 2008 to the present. Access to abstracts is complimentary. Access to full-text is limited to print subscribers. Nonsubscribers may purchase individual articles or Register or log in to:'. Below this text, there are three options: 'Activate Online Access', 'Buy a Subscription Now', and 'Access Neurobiology of Aging'. An arrow points from the 'Full-text articles...' text to the 'Email Alert' option in the 'FEATURES' section.

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