WW - ADNI Meeting

Friday, July 17, 2015 Washington, D.C.
Marriott Marquis, Catholic University Rm.

Summary Notes AAIC 2015

Welcome and Announcements – Jim Hendrix, Alzheimer's Association
The July issue of *Alzheimer's & Dementia* will be entirely devoted to ADNI (released 7/17/15)
July 2015 Volume 11; Issue 7; pages 727-886
ADNI Special Issue pub – Foreword http://www.ncbi.nlm.nih.gov/pubmed/26194307

ADNI Overview & ADNI 3 Plans – Michael Weiner
ADNI Special Issue pub – ADNI Overview http://www.ncbi.nlm.nih.gov/pubmed/26194308
ADNI Special Issue pub – Impact of ADNI 2004-2014 http://www.ncbi.nlm.nih.gov/pubmed/26194320

News and Updates:

- ADNI-2 has about 15 months left
- Two tau Pet studies were funded in the last year
    - DoD Tau PET, includes ADNI subjects
    - ADNI Competitive Supplement – will fund Tau PET on all ADNI and DoD ADNI participants – scanning to begin this Summer
- CogState Add-on Project to examine at home neuropsych testing; subjects to begin testing soon
- Paul Aisen has moved to Alzheimer's Therapeutic Research Institute (ATRI) as USC

Plans for ADNI-3

- Expect to submit ADNI-3 proposal in October 2015 – pending NIA release of RFA
- Overall goal: Validation of biomarkers for AD
- Specific aims:
    - Longitudinal change of cognition and biomarkers: measures that capture longitudinal change with highest statistical power
    - Prediction of cognitive decline:
    - Clinical trial design: Optimum outcome measures, predictors, and inclusion/exclusion criteria for clinical trials
    - Discovery: new markers, new targets

ADNI-3 Study Design

- 900 participants; 40% CN, 40% MCI, 20% dementia (from converted AD)
- Most subjects will be rollovers but this will depend on how many go into treatment trials – they cannot be in both
- Annual collection of data from ADNI participants includes clinical, cognitive, amyloid PET, tau PET, FDG-PET (?), LP/CSF, genetic, and omics data

New Features in ADNI-3

- Brain Health Registry (BHR) for recruitment, assessment and longitudinal monitoring – includes

online cog testing for screening and follow up
- Tau PET – AVID 1451, others are being considered
- Amyloid PET – Centiloid project, AVID, Pirimal, unsure if GE will commit to supplying tracer
- Advanced, connectome, multi-modal MRI for centers that have capabilities
- New platform for CSF analysis, Mass Spec (right now AB, could add others)
- Increased focus on systems biology, omics and data mining

Disclosing results to patients

- Some clinicians want to disclose results (amyloid status) to patients; have had requests to change ADNI policy
    - Advantages: patients have right to know, could facilitate enrollment and retention
    - Disadvantages: could change study outcomes; alter behavior of clinicians and patients
- Current plan is to not include disclosure in ADNI-3 grants

Competitive Space

- Selection for ADNI-3 biomarker platform for CSF – in consultation with Private Partner Scientific Board (PPSB)
- Selection of tau tracer by PET Core
    - Currently AVID 1451 is the only one widely available
    - All possible tau tracers will be considered
- Need to focus on writing a compelling grant proposal that will be funded by NIA; keep it clean and simple
- ADNI-3 begins 9 months after grant submission and enrollment will be competing with many treatment trials

Collaborations

- ADNI grant is submitted, reviewed and funded by NIA; requires close NIA oversight, NIA decides on sample release
- ADNI investigators are responsible for scientific conduct
- Industry support 30% of funding
- The overall goal is to facilitate industry and academic trials; input and collaboration with PPSB is greatly valued (see section on PPSP for updates, progress and perspective)
- ADNI also collaborates with DIAN, PPMI and SAGE

Long-term Future of ADNI

What will happen after ADNI-3?

- Excitement about Biogen data, but this will create problems for ADNI and ADNI-like trials as they compete for subject enrollment
- We could shift to younger cohort of amyloid negative at long term risk – focus on primary prevention trials to prevent amyloid/tau formation, another option is studies of normal aging
- ADNI-3 can better inform clinical trial design

ADNI 3 Clinical Core – Paul Aisen & Ron Petersen

ADNI Special Issue pub – Clinical Core http://www.ncbi.nlm.nih.gov/pubmed/26194309

ADNI-2 Updates

- ADNI-2 Enrollment is over 900 subjects in 5 groups (CN, SMC, EMCI, LMCI, AD)
    - Cognitive characterization of these groups is what we expected – we should be able to interpret biomarkers appropriately with this data in mind
    - The dropout rate is manageable and expected; rates are not exceeding what was projected in proposal; sites are doing well at retention

- Have data looking at transitions from NL to MCI and NL to Dementia
    - Transition from NL to MCI is very important group; continue to look earlier
    - Transition from MCI to AD – see slides for rates
    - Transition from de novo MCI to incident MCI to dementia – this is a small but very important cohort; they have gone through the entire transition

<u>ADNI-3 Clinical Core Plans</u>

Aims of Clinical Core (see slide for details)

- Aims will focus on shifting earlier to more people in early cohort (CN w/ SMC and early/late MCI)
- Assess genetic, biomarkers and clinical predictors of cognitive decline
- Refine clinical trial designs; including secondary prevention trials, cognitive/behavioral management

<u>ADNI-3 Cohorts</u>

- ADNI-3 will carry forward ~300 CN (with and without SMC) and ~300 MCI (early and late)
- Shift in focus to normal/early stages, but will follow MCI participants that progress to dementia
- There will be some new enrollment but strength is in carrying over people who have been enrolled and followed for 8+ years

<u>Key Hypotheses</u>

- All, or almost all CN participants with brain amyloidosis will show cognitive decline and will progress to MCI when compared to those without amyloidosis
    - It will be essential to confirm this hypothesis for early stage trial design
- MCI participants who are amyloid/tau biomarker positive will progress more rapidly than MCI biomarker-negative
- Amyloid-related cognitive decline involves decline in memory domains across spectrum
- AD-related cognitive decline can be captured with web-based testing
- Early-stage AD cognitive decline predicts later functional and clinical decline
- Web-based registries will facilitate recruitment for ADNI and therapeutic trials

<u>Possible adjustment to assessments</u>

- There may be some changes to the cognitive assessments; in continued discussion with PPSB
- Could drop some tests that seem less informative in tracking progress (RAVLT, Boston Naming, Clock Drawing?)
- Could add web-based cognitive testing
- Should use CFI instead of eCOG? CFI is being used in preclinical AD trials
- We will be conservative in changes so we can continue to compare to older ADNI data
- It is likely most (and possibly all) existing measures will be preserved

ADNI 3 PET Core – Bill Jagust

ADNI Special Issue pub – PET Core http://www.ncbi.nlm.nih.gov/pubmed/26194311

ADNI-2 Updates

- Have many subjects with multiple FDG-PET scans; but have recently stopped collecting these
- Amyloid PET – florbetapir; many subjects have had 2 scans, will have subjects with 3 scans soon
- ADNI florbetapir stratified by ApoE4 status across 5 groups (NC, SMC, EMCI, LMCI, AD)
    - Rates of positivity are dramatic – 99% of ApoE4+ are florbetapir+ in AD; if ApoE4-neg then also negative for florbetapir (see slide for details)

Centiloid Project – standardizing quantitative amyloid plaque estimation by PET (http://www.ncbi.nlm.nih.gov/pubmed/25443857)

- Centiloid will be used for ADNI-3
- Have been doing centiloid with existing ADNI data and reference database from GAAIN

Tau Imaging

- They have been looking at Tau by age and AD – not a simple relationship
    - Can see tau accumulate by age; there is high variation on normal - not whether you have tau but more where it is distributed that is important
- We will need to think about how best to quantify tau, may implement Braak stages to help do this by brain regions, cold help with staging of individuals

ADNI-3 Specific Aims

- Continue amyloid imaging every 2 years; all subjects
- Use multiple amyloid imaging agents
- Tau imaging – frequency to be stratified by amyloid load
- Continue to do FDG-PET at baseline

ADNI-3 Major Hypotheses

- Tau accumulation will conform to Braak staging
- Tau accumulation will occur in MTL in Aβ-negative controls
- The presence of Aβ in controls and MCI will be associated with neocortical tau; longitudinal accumulation will be more rapid
- Tau imaging will be related to cognition - cross-section and longitudinal

Amyloid PET in ADNI-3

- Multiple amyloid imaging agents are planned: florbetapir, florbetaben, flutemetamol (?)
- Companies will do centiloid studies and data will be publicly available (compound vs PiB)

Tau-PET in ADNI-3

- Will propose AV1451 for ADNI-3 but consider other options; review state of field as of mid-2015
- AV1451 ligand is not perfect but we have a good plan for dealing with issues, we have the most data available on this tracer and it can be delivered to sites
- Application will outline features of acceptable tracers and propose plan for selection of final tracer(s) into project

Tau tracer characteristics

- Need to consider both scientific and logistical issues
- Need multisite study – tracer delivery, management of regulatory issues, protocol is simple, well-tolerated and reliable
- Need tracer validation – preclinical data for specificity, affinity, uptake, favorable pharmacokinetics, reasonable clinical data in subjects with diverse diagnosis
- Ideal to have full kinetic models in comparison to SUVR

ADNI 3 MRI Core – Michael Weiner

ADNI Special Issue pub – MRI Core http://www.ncbi.nlm.nih.gov/pubmed/26194310

MRI continues to play a role; need longitudinal MRI for safety monitoring, can also continue to collect more data at the same time; good for proof of concept

ADNI-3 Protocol

All sequences in all subjects

- 3D T1 Volume
- 3D FLAIR
- T2 GRE
- ASL – arterial spin labeling
- TF-fMRI – task-free fMRI – 2-tiered, use capability of advanced systems
- dMRI – Diffusion MRI – 2-tiered, use capability of advanced systems
- Coronal high resolution T2 – hippocampal subfields

ADNI-3 MRI Protocol Rationale

- 3D-T1, FLAIR, T2-GRE
    - Continue to do these in ADNI-3; they provide precise longitudinal measures, associations with tau PET (and other measures), needed for safety standards, clinical reads
- ASL, dMRI, TF-fMRI – promising associations, but not strong enough to recommend for ADNI-2
    - Significant developments since ADNI-2
    - Opportunity to see if advanced methods cross the “value” threshold for use in clinical trials
    - Could potentially be used to provide signal of early treatment response
    - Addition of advanced sequences provides added novelty for grant proposal
    - Do not want to be using outdated methods by the end of ADNI-3

MRI Phantoms

- Phantoms are used to track scanners through upgrades and maintenance cycles and compare new models as they emerge

- We have been using the ADNI Phantom designed by ADNI MRI core in 2004/5 ($6K per unit)
- NIST-ISMRM has developed a quantitative MRI phantom
    - Provides similar geometric fidelity as ADNI phantom WITH resolution and slice thickness assessments
    - More expensive than ADNI Phantom, but may go down with increased production

Plan for ADNI-3 Phantoms

- Keep existing ADNI phantoms in the field until they age out; when supply is exhausted replace with NIST-ISMRM phantoms
- Comparison testing to be done this Summer 2015

ADNI 3 Biomarkers Core – Les Shaw, John Trojanowski

ADNI Special Issue pub – Biomarker Core http://www.ncbi.nlm.nih.gov/pubmed/26194312

Biomarker Core – Aims for ADNI-3

- Continue to collect, store, curate and track all biofluid samples collected from all ADNI subjects
    - The Biomarkers Core continues to review and reconcile sample information with the Clinical Core – a very important, essential, part of the management of biofluid samples
- Implement new test methods for CSF biomarkers
    - Implement newly validated Mass Spec-based assay to identify and measure $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{1-38}$-close to having a reference standard for $A\beta_{1-42}$.
    - Work initiated for mass spec-based method for t-tau and possibly tau isoforms in CSF
    - Implement new automated immunoassay platform for CSF amyloid and tau – following review and validation of all possible systems in conjunction with PPSB
    - Implement other validated and promising new biomarkers immunoassays (eg, plasma biomarkers, exosomes)
- Continue longitudinal studies of ADNI biomarkers that look most informative and propose adding the most promising ones to CSF AD panel
    - Neurogranin, Vilip1 data recently uploaded; α-synuclein, PS129 α-synuclein, YKL40 data available later this year
- Collaborate to find best combinations of biomarkers for prediction of cognitive and functional decline; both within ADNI cores and with FNIH consortium
- Continue to collaborate with GBSC, IFCC to establish certified reference material for Aβ – progress will be presented at GBSC AAIC meeting

Selection of new automated immunoassay platform for ADNI-3

- Goal: move from manual immunoassay to fully automated platform for ADNI-3
    - Due diligence started in Q4;2014; selection will be done in consultation with ADNI PPSB/BBWG/DDWG
- Need preliminary validation data for ADNI-3 grant submission
    - Sought after features include precision/accuracy, intra/interlab performance, commitment to ADNI study, on IVD trajectory, commitment to pre-competitive activities and data sharing

ADNI Subjects – CSF Aβ trajectory over 3-4 years

- Recent studies show that in ADNI subjects with baseline normal CSF AB42, some remain stable and some decline
    - We will need to much tighter, precise methods to measure this over time; moving from dichotomous categories (pos/neg) to continuous quantification

Support for CSF Standardization of Efforts

- ADNI long-term commitment to standardization of all methods
- Alzheimer's Association Global Biomarker Standardization Consortium
- CAMD (Coalition Against Major Diseases)

Biomarker Core Aims for ADNI-3 Renewal – AD Heterogeneity

- Need to take into account heterogeneity of AD in Biomarker Core for ADNI-3
    - Most (82%) of ADNI subjects had plaques and tangles in addition to TDP-43 and/or alpha-synuclein as well as hippocampal sclerosis
- We have access to a CSF total alpha-synuclein assay and phospho-alpha-synuclein assay that could be incorporated into ADNI-3
- TDP-43 biomarkers are not yet available; not yet certain if they will be in time for ADNI-3
- We will also need to address co-morbid cerebrovascular disease (CVD) but this may come more from imaging than biomarker studies

New biomarkers in NIA/ADNI/RARC-approved studies (see list on slide)

- It is still being worked on what new biomarkers could be added on
- Could decide what to add-on once platform is confirmed
- Collaboration will be needed; budget is an issue

ADNI-3 Genetics Core – Andy Saykin

ADNI Special Issue pub – Genetics Core http://www.ncbi.nlm.nih.gov/pubmed/26194313

ADNI-2 Progress and Impact

- Have completed a significant amount of data collection, analyses and release
    - 1707 participants with DNA from LCL sample; 1685 participants with DNA from genomic blood sample; 1198 participants with RNA sample (data as of March 2015)
    - Have made significant progress on genotyping, genome-wide association studies (GWAS), whole-exome sequencing (WES), whole genome sequencing (WGS), RNA genome-wide expression profiling (see slide for participant numbers for each)
    - Over 300 publications have used genetics data from ADNI as of Jan 2015

Converging –omics and Systems Biology

- Moving towards convergence of omics to molecular/cellular function to brain structure/function to genetics
    - Beginning to look at "exposome" – exposure to environment, lifestyle, diet, drugs
    - Looking at epigenetics with help from industry – data should be coming in the next few

months
    - Collaboration to look at transcriptome – RNA analysis
    - Exploring new analytics to sort through connectome data against noise of background
- Increased focus on systems biology – including new focus group (Genetics Core, PPSB, EAC, Analytics Organizations, AMP-AD, others)

Genetic Signals to Targeted Therapeutics

Goal is to integrate genomics to inform clinical trial design

- Identify genetic subsets that have different rates of amyloid or tau accumulation
- Genetics can help discover and validate novel targets
- Recent novel target discovery examples using ADNI data
    - FASTKD2
    - REST
    - IL1RAP

Genetics Aims for ADNI-3

Genetics can contribute to all ADNI-3 Specific Aims (see list from ADNI-3 overview section)

- Rationale
    - Genetics informs precision medicine and impacts trial design
    - Genetics contributes to the discovery, validation and prioritization of diagnostic and therapeutic targets
    - Genetics can identify patients most likely to benefit from treatments

- Overview
    - The aims for ADNI-3 are similar but there will be increased focus on the analysis of multi-omics data
    - Continued data collection, QC, sample banking and sharing
    - Comprehensive/integrative genomics and bioinformatics; an increased emphasis on systems biology
    - Determine clinical/biological significance of identified variants
    - Provide organization and leadership for genomic studies of quantitative biomarker phenotypes

ADNI 3 Biostatistics Core – Laurel Beckett

ADNI Special Issue pub – Biostatistics Core http://www.ncbi.nlm.nih.gov/pubmed/26194315

ADNI-2 Progress and Accomplishments

- More participants, more diagnostic categories and new measures – the wealth of data has expanded and this presents corresponding challenges but also draws new insights
- This data sheds light on where we are going for ADNI-3; both ADNI-2 and ADNI-3 will add to longitudinal data

Richer longitudinal data

Allows new modeling trajectories:

- Some participants are followed for almost 10 years, but not all – need statistics/modeling to smooth this data out
    - Recent pub looks at impact of APOE-e4 and elevated amyloid on disease trajectories – rich longitudinal panel – increased trajectories on several AD measures when compared to negative controls
    - Extended follow-up picks up conversion CN to MCI: need to go out 6-8 years to see this

<u>New participants groups (SMC, eMCI)</u>

Increases the breadth of data across the disease process and fills in gaps:

- SMC and eMCI fit in between CN and MCI on baseline measures as expected (AV45 SUVR, FDG-PET, hippocampal volume, ADAS-Cog)
    - SMC are similar to CN but both have clusters of subgroups – the earlier you go the more heterogeneity there is
    - Clusters are based on imaging, CSF, hippocampal volume, APOE alleles – for the most part clusters look healthy, pre-AD like, maybe some vascular (see slides for details)

- Looked to see if we could pick up change in the new groups:
    - Focused on SMC ApoE4 carriers to see if new measures could pick up changes in this group at 12 months on 4 new cognitive/functional measures (RAVLT, ADAS, MMSE, FAQ)
    - Do not see much change in CN or SMC, but other groups show decline; need more data

<u>New measures (eg, amyloid PET, memory tests)</u>

Increase depth of data on ADNI participants:

- We now have amyloid imaging for all participants – is this new measure prognostic? How early do changes show up?
    - Too early to tell for CN or SMC but eMCI have been followed for longer
        - 2 year data shows that amyloid imaging (AV45) has prognostic value in eMCI and may be more informative than ERC thickness and FDG
- For memory tests, 12 month data show amyloid positive participants change more and do worse on several tests (LDEL, LIMM, MMSE, RAVLTDEL, RAVLFORGET)

<u>PPSB Update – Susan DeSanti</u>

ADNI Special Issue pub – PPSB Perspective http://www.ncbi.nlm.nih.gov/pubmed/26194317

ADNI Private Partner Scientific Board (PPSB) – see slide for full list of partners

- Several new partners have recently joined (Abbvie, Cerespir, Cogstate, Lundbeck, Lumosity)

<u>PPSB – Overview and 2015 Key Deliverables</u>

- Have been focused on working with ADNI core leaders on ADNI-3 grant proposal
- In the pre-competitive space PPSB evaluates gaps and recommends projects to accelerate drug development

<u>Clinical Endpoints Working Group (includes Due Diligence team)</u>

- Current activities are focused into 4 Workstreams:

- pAD/MCI Endpoints and Methods
  - Working on formal comparison of pAD/MCI composite endpoints/methods; preliminary results generated from ADNI data sets
- Novel Tests for pre-MCI
  - Completed work on Population Characterization in the Early Stages of AD
- List of Datasets
  - Produced full list of datasets available to compare pAD/MCI composite endpoints

- Computerized Cognitive Batteries
  - Completed due diligence and selected computerized battery to pilot; CogState Brief Battery (CBB) pilot study is underway with first sites active in July 2015
  - Goal is 200 ADNI-2 participants with MCI and controls; approx. 33 ADNI-2 clinical sites are expected to participate – will compare onsite vs. remote testing
  - CBB data will be downloaded and shared approx. every month
  - This data will help determine if this test will be usable in clinical trials

Due Diligence Process for ADNI 3 clinical tools

- Format of DD process has seven individual workstreams (see slide)
- Each workstream will use agreed upon template to collect and evaluate data on a variety of assessments
- This work will provide final recommendations to the ADNI Clinical Core
  - PPSB has had discussions with ADNI Clinical Core – will review proposals from ADNI PPSB and Clinical Core to discuss similarities/differences and to integrate into one proposal for the ADNI 3 grant

Biofluid Biomarker Working Group

- Broad group of pharma and diagnostic companies; interface with GBSC, CAMD CSF project
- Coordinates industry input into ADNI Biomarker Core activities (biofluid biomarkers assays, data management, sample collection)
- Promotes biofluid biomarker best practices for prognostic and diagnostic use (beyond ADNI)
- Will assist in the ADNI-3 grant application development
  - Due diligence evaluation for selection of ADNI-3 Aβ and tau CSF assays
  - Identification/consideration of novel CSF biomarkers to include in ADNI-3 (eg, alpha-synuclein, neurogranin, TDP-43)
  - Identification/consideration of novel blood biomarkers to include in ADNI-3

ADNI PPSB Input – MRI Core

- ADNI-2 – recommendation and adoption of standardized analysis set for comparability of reports in literature
- ADNI-3 – recommendations in preparation:
  - All MRI sequences will be run at all sites
  - For DTI, TF-MRI and ALS 2-tiers employed – basic or advanced; sites with advanced capabilities will run these sequences

PET Endpoints Working Group

- Recent publication of PET Endpoints efforts http://www.ncbi.nlm.nih.gov/pubmed/25457431

- For ADNI-3 – review the PET section of the proposal – recommendations given to ADNI/NIA that the proposal should include the potential for several tau PET ligands

Questions/Discussion

Q: Are the number of CSF collections decreasing?

A: There has been a decline; fall off is more than expected but the burden is high for longitudinal LP

- There are plans to do a review of the sites to find out what may be influencing decline; efforts have been made to improve the collection eg, letters about the importance/value of CSF

EPAD Update – Jose Luis Molinuevo

EPAD is a public-private consortium and is part of the IMI-AD Platform (EMIF-AD, AETIONOMY, EPAD)

- Goals:
    - Develop an infrastructure to enable the undertaking of adaptive, clinical studies for the ongoing development of drug candidates or drug combinations for the prevention of AD dementia
    - Deliver a standing, double-blind proof-of-concept adaptive trial that is sustainable beyond 5 years of IMI funding

EPAD Design and Workflow (see slides for details)

- 8 work packages (work streams) – deliver and support clusters
- 5 scientific advisory groups
- Network of ~30 EPAD Trial Delivery Centers

Patient Recruitment

- EPAD aims to accelerate patient access and trial enrollment by providing a pre-identified, trial-ready cohort of 6,000+ subjects for targeted trial recruitment process
- Evaluation criteria for the inclusion of subjects into the EPAD Registry (N=24,000), EPAD Cohort (N=6,000) and EPAD Trial (N=1,500)
- EPAD Trial Delivery Centers (TDCs) (~30 across Europe) will be expected to recruit 200 participants to the EPAD Cohort and 50 of these to the EPAD PoC Trial

EPAD Registry

- 24,000 people at risk for dementia
- Many pulled from EMIF-AD protocol

EPAD Cohort

- 6,000 people selected for monitoring
- The EPAD Registry will replenish the EPAD Cohort
- The cohort will include pre-dementia subjects with limited exclusion criteria
    - Age 50-80; no clinical dementia (this will be a prevention trial so no mild AD)
    - No PS1, PS2, or APP mutation
    - Willing to participate in EPAD PoC Trial
- The cohort will be a trial-ready population that includes
    - Cognitively Normal – Biomarker Negative
    - Cognitively Normal – Biomarker Positive
    - Prodromal AD/MCI due to AD

EPAD Longitudinal Cohort Study (LCS)

- Subjects in the EPAD Registry will go to EPAD LCS
- The main aim of the EPAD LCS is to be a readiness cohort for the EPAD PoC Trial
- The EPAD LSC will provide:
    - Biomarker, cognitive, clinical and risk factor data
    - Use disease models for risk stratification and subject selection
    - Provide pre-randomization data (PoC Trial); allows for powerful analysis of interventions

EPAD Proof of Concept (PoC) Trial

- 1,500 people selected for clinical trial; adaptive design
- Intervention with drug candidates or combinations of candidates (TBD)
- Drugs will be first be evaluated for changes in biomarker target (Bio PoC)
- If drug shows biomarker success it then goes on to cognitive/clinical evaluation (Cog PoC)
- This design allows early decisions on progression to longer-term clinical outcomes

Questions/Discussion

Q: There was concern that 1500 subjects for the PoC Trial may not be a large enough sample to test multiple drugs against placebo in a short period of time – might this be underpowered?
A: They do not think it will be underpowered, but the bigger concern may be getting to the 6000 people in the readiness cohort – to ensure the "funnel" is working

- This would be a significant accomplishment and would increase the feasibility of subsequent studies

AIBL – Chris Rowe

Australian ADNI – better known as the Australian Imaging, Biomarkers and Lifestyle Study of Aging (AIBL) – started in 2006

- Total recruitment to date is 1550 participants; follow up has been ongoing for over 7 years at 18-month intervals; still actively recruiting MCI and AD

AIBL Highlights

Overall AIBL has been working to refine methods and data for amyloid biomarkers and move to looking at other biomarkers, increasing the focus on genetics and modifiable lifestyle factors and how these impact rates of cognitive decline

- Amyloid accumulation for 30 years prior to finding plaque levels typical of early AD (Aβ PET)
- They see differences when stratifying by genes (APOE, BDNF, etc)
- See slower Aβ accumulation in people adherent to Mediterranean diet (data presented at AAIC)
- GWAS and SNP analysis are underway
- AIBL recently released 4.5 years of imaging data to LONI; open access to the AD community
    - Amyloid imaging at baseline, 3 years and 4.5 years (see slide for details); Aβ status is known for 371 subjects with 4.5 years of follow-up
- AIBL has implemented centiloid transformation for PiB and NAV4694 with Florbetapir to follow
- Many initiatives have formed via the AIBL Core (see slide for details); funding remains an issue

Tau Imaging

- Have about 100 subjects with tau imaging; Using several tau imaging compounds (AV1451, THK5117 – now replaced with THK5351)
- Implemented automated cloud-based technique – MilxView to tau imaging
- They are seeing tau uptake in the expected regions; see slides for detailed examples:
    - In normal controls (Aβ PET-neg) they see some mild off target binding but much less cortical binding than in participants with AD or MCI that are Aβ PET-positive
    - In patients with clinical diagnosis of AD (but AD PET-negative) the see high tau uptake in medial temporal lobe – this may be tangle predominant AD?

Screening for AD Drug Trials

New program in place to help find patients for clinical trials; did not want to take from AIBL cohort so this is a way to find new patients

- Currently many patients in state of Victoria go to 15 State funded memory clinics, they get a Dx and then go back to local physician and are lost to clinical trials
- To help retain these patients, AIBL offers free FDG and amyloid PET scans to memory clinics for patients with Dx of MCI or mild AD
- The patients are then referred to clinical trials by memory clinic staff or by AIBL
- All patients scanned go into AIBL to help build up the MCI/AD baseline data; about 20% have been Aβ PET-negative

A4 Trial in Australia

- So far over 1000 website registrants are interested; the goal is to enroll 100 study participants
- Aβ PET screening began in early 2015 and 50 participants have been screened to date

AIBL-Vets

- Study – AB/Tau deposition, microhemorrhage and brain function after TBI or chronic PTSD in Vietnam veterans
- They have some funding from the US DoD; recruitment has been a challenge

Future Directions for AIBL

- Continue to refine prognostic value and comparative effectiveness of imaging and blood biomarkers
- Further examine genetic and environmental influences of rate of decline in Aβ positive controls
- Create new pools of Aβ-positive participants for early intervention trials
- Serial tau imaging
- Use AIBL infrastructure to support more A4 and DIAN therapy type trials

Japan ADNI – Takeshi Iwatsubo

Japan ADNI (J-ADNI) – started in 2007; 7-year nationwide study

- 38 Clinical sites across Japan
- Goal was to recruit 600 subjects (successfully recruited 537)
- Subjects (Normal Control (NC), MCI and AD) are followed for 2-3 years
- Database contains data from 3000 cognitive tests, 2500 MRI scans, 1500 FDG-PET scans, 600 amyloid PET scans, 330 CSF samples
- The plan is to have all data publicly available this Fall 2016

Demographics

- The percentage of APOE-e4 positive participants is lower in the AD group for J-ADNI (59.6%) when compared to US-ADNI data (65.6%); but slightly higher for CN and MCI

Cognitive Tests

- MMSE, CDR-SOB, ADAS-Cog show cognitive decline rates over 3 years to have similar slopes for MCI and AD – this differs from the US-ADNI where MCI more so follows NC
- Data suggest that decline in MCI may be stronger in Japan when compared to US-ADNI participants

Conversion Rates

- There is a relatively high 1-year conversation rate (MCI to AD) in Japan (25.5%) compared to 16% in the U.S.
- Similar to the US-ADNI data, the conversation rate for MCI to AD differs by PET amyloid positivity
- There also appear to be differences in the rate of cognitive decline when factoring in amyloid positivity for MCI group

Amyloid PET and Hippocampal Atrophy

- For J-ADNI data they see similar trends to the US-ADNI when:
    - stratifying diagnosis (NC, MCI, AD) by PET amyloid positivity and APOE-e4
    - comparing hippocampal atrophy rates for NC, AD and MCI (progressors vs. stable)

J-ADNI2/AMED Preclinical AD Study

- The goal will be to look earlier in the disease process with a focus on preclinical AD
- 40 Clinical sites; 2 observational studies:
    - Preclinical AD (N=150) screened by amyloid PET and followed for 3 years
    - Early MCI (N=100) and Late MCI (N=100)
- The protocol will be similar to US ADNI-2, will implement FCSRT and E-Cog, 3T-MRI
- 3 CSF time points - baseline, 12 months, 36 months
- The goal is for these studies to facilitate the move towards clinical trials in prodromal AD and very early treatment in preclinical AD

China ADNI – Kungcheng Li

China ADNI (C-ADNI) – started in 2012 – supported by industry collaborators and the Chinese government

- There are currently 6 cities joined in the study across China
- Goal is to recruit 500-1000 subjects across 80+ sites
- 4 Test Groups: HC, early MCI, late MCI, mild AD
- As of June 2015 they have 85 participants
- Data collection in accordance with WW-ADNI (Neuropsych, Biomarkers, Imaging)

Progress and Preliminary Data

- Neuropsychological Testing
    - Baseline to 12 month follow-up:

  - MMSE - AD groups shows decline (all others no change)
  - MoCA – early and late MCI show decline, AD slight decline, no change for HC
  -
- Biomarkers
  - Only a few samples, looked at APOE type, AB42, AB40
  - The APOE-e4 rate appears to be relatively lower in Chinese AD; so far there are few positives, but that may change as they add participants

- MRI – have established standard protocol across all sites; improved QC and post-processing methods
  - Morphometry - preliminary results show differentiation between AD and normal elderly, but could not discriminate MCI
  - Normalization methods were done using a large database of Western people; this may not be suitable for Chinese people – they will instead use a new Chinese brain template based on 2000+ Han nationality Chinese people
  - TBSS - Preliminary results show found differences in white matter may be useful in detecting mild AD
- FDG-PET - 34 participants have undergone baseline FDG-PET – initial results show abnormal metabolic changes in mild AD
- Amyloid PET is set to begin in August 2015

Korea ADNI – Seong Yoon Kim

Korea ADNI (K-ADNI) – started in 2013; 6-year national project

- Goal is to recruit 500 subjects within the first 2 years and then follow up annually
  - Target Subjects: 5 Categories – HC, aMCI, vMCI, AD, SIVD
    - A main feature of K-ADNI is to the inclusion individuals with vascular MCI (vMCI) and subcortical ischemic vascular dementia (SIVD)
    - The vascularity aspect on the inclusion/exclusion criteria for vMCI and SIVD is defined by 3 factors (vascular risk factors, white matter hyperintensities (WMH), clinical judgment)
- Data will be collected annually for clinical, neuropsychology and MRI; for PET (FDG and amyloid) and CSF data will be collected at baseline and 24 months

Timeline of K-ADNI

- There have been unexpected delays in setting up the infrastructure; they are about 18 months behind
- Infrastructure should be complete by mid-2015 and the goal is to have patient recruitment complete by the end of 2016
- Clinical trial sites are ready for participants, but subject recruitment is still pending – this is in part due to MERS which has swept over Korean hospitals for the last several months

Difficulties in K-ADNI clinical sites

- Clinical site staff are not familiar with ADNI protocols and accustomization has been slow
  - K-ADNI is continuing to adapt to the ADNI protocol in an effort to harmonize cognitive

and neuropsychological testing
- Stabilization of the e-CRF system has been a slow process of trial-and-error
    - Collaboration between all staff is essential, they must address different design, data QA, etc from previous drug trials or cross-sectional registries

Argentina ADNI – Gustavo Sevlever

Argentina ADNI (Arg-ADNI) started in 2012 at FLENI – Institute for Neurological Research in Buenos Aires

- Recent pub describes creation of Arg-ADNI – the first South American ADNI
    - http://www.ncbi.nlm.nih.gov/pubmed/24864324
- FLENI has 2 institutes – one in Buenos Aires – the Memory and Aging Center and the other nearby which houses the PET scanner and cyclotron

Update Arg-ADNI

- They are at month 30 now and currently have about 60 participants
- At the 12-month follow up about 10% of those with early MCI and 25% with late MCI progressed to dementia
- In October 2015 they will complete the 30-month assessment
- Imaging (MRI, FDG-PET, amyloid-PET) at screening/baseline and 48 months
- They will also add tau-PET (AVID compound) at 48 months (will start tau PET scan in April 2016)

Preliminary Results (see slides for details)

- Clinical characterization at baseline – only see APOE-e4/4 genotype in participants with AD
- Recent publications looking at concordance of PiB PET and clinical diagnosis – includes 181 participants, 56 from Arg-ADNI
- Paper in press looking at correlation between cognitive reserve and AB42 in participants with MCI
- Another study has looked at the correlation of amyloid PET status (pos/neg) on memory

FLENI Brain Bank

- FLENI houses the only brain bank in Argentina; they do not yet have any brains from ADNI patients, but all patients are asked to consent to brain donation
- They have recently published a study with one of the AD families with presenilin 1 mutation
    - http://www.ncbi.nlm.nih.gov/pubmed/23489366

Future Studies

- Grant funding from National Scientific and Technical Research Council (CONICET)
    - Arg-DIAN (Prof John Morris/Buenos Aires)
        - Starting in August 2015 – to study an Argentine DIAN cohort of 40 participants
    - AD Biomarkers in Down Syndrome (PI: Dr. Ezequiel Surace)
        - Starting in May 2016 – to study an Argentine cohort of 10 participants

Question from audience asking if lumbar puncture/CSF is mandatory?
A: No it's not mandatory, but about 70% of participants agree

Europe ADNI – Giovanni Frisoni

Europe ADNI – E-ADNI – started in 2005, the first extension beyond the North American study

- E-ADNI is part of the larger PharmaCog Study
- Aim is to validate and quantify biomarkers that are sensitive to disease progression

E-ADNI - Update and Related Activities

Global Harmonization of Manual Hippocampal Segmentation

- There was recent *Alzheimer's & Dementia* Special Issue devoted to the EADC-ADNI Harmonized Protocol for Hippocampal Segmentation (Feb 2015; Volume 11; Issue 2)
- The protocols are available for downloading at http://www.hippocampal-protocol.net/SOPs/index.php
- Aim is to have a standard segmentation method of hippocampal volume (MRI images) for validation studies, diagnosis and clinical trials

PharmaCOG WP5/E-EDNI

- Enrollment in E-ADNI is going well and target goals are being met for timepoints ranging from 6-36 months of follow-up
- Hippocampal subfield segmentation data has recently been published http://www.ncbi.nlm.nih.gov/pubmed/26043939

Several studies are in preparation and data will be presented at AAIC:

- Multi-site hippocampal reproducibility
- Hippocampal subfield changes in MCI (patients that are AB-pos vs. AB-neg)
- Diffusion markers at baseline in MCI (patients stratified based on CSF pTau)
- Diffusion markers changes in MCI (patients stratified based on CSF AB42)
- Longitudinal reproducibility of resting-state fMRI – healthy elderly, multi-center
- Relationship between cognitive function (CANTAB) in participants with aMCI and AD biomarkers

CEREBRO

- New service for big data neuroimaging analysis (spin off of NeuGRID)
    - Provided by Swiss company "CEREBRO" through the neuGRID platform
    - Image analysis, algorithms for large datasets in a user-friendly environment
    - Analysis of MRI, PET to identify diagnostic markers for AD
    - Algorithm developers can make available their algorithms to the neuroimaging community
    - Collaboration with Human Brain Project

- Partners/Support – IMI-EMIF, GAAIN, EGI-Engage, FET Flagship

European Prevention of Alzheimer's Dementia Program (EPAD)

- please see EPAD Section for all details, progress and updates

GAAIN Demo – Priya Bhatt

GAAIN Overview

The Global Alzheimer's Association Interactive Network (GAAIN) has been in operation for almost 2 years

- Currently over 320,000 subjects in the database
- 16 countries are represented
- Many data partners have joined (data partners include studies, clinics and consortia that have collected data on Alzheimer's and aging)
  - GAAIN is in the process of on-boarding 90+ data partners
- Critical to GAAIN's success is the use of a cloud-based federated network that allows data ownership and adherence to polices
  - Data partners have connection to server that allows them full control of their data (they can switch data sharing on/off at any time)
  - GAAIN does not have an actual copy of the data – that control remains with the data partner
  - Retaining complete control of data has been expressed as the paramount concern for potential data partners

GAAIN Demo

- GAAIN Scoreboard
  - A front-end tool to illustrate the breadth of variables and subjects in GAAIN
  - Users can identify which GAAIN partners have data meeting their research objectives
  - Publicly available without a GAAIN account
- GAAIN Interrogator
  - Easy-to-use interface to study relationships of variables in self-defined study cohorts
  - Requires a free GAAIN Investigator Account
  - Data is represented graphically, users do not have direct access to any subject's data
    - For users to get access to actual data they need to apply and ask for it from data partner (GAAIN provides direct links to data partners)
    - The data partner controls who is allowed access and decides how much freedom is allowed to users

Data Sharing Discussion –Michael Weiner, Priya Bhatt

History of ADNI

- Mike talked about the history of ADNI; it came about from interest in biomarkers and biomarker standardization along with funding from the government and industry
  - They needed data faster, since public funds are being used data needs to shared

publicly, ended with question of how best to share data?
    - Decided they did not want to go through a process like Framingham, there is a long wait time for this
    - Instead decided they would release data without embargo
- There were concerns about data acknowledgement, bad publications, duplication of effort
    - ADNI has in place data sharing agreement, we've not see many bad pubs and yes there is duplication of effort but this can be very instructive
- There was the hope that ADNI would set precedent and others would follow this model but so far just the PMMI -- no one else has really taken this on

GAAIN

- What are the challenges with bringing in new data partners?
    - It takes some time and effort from initial contact for a data partner to get up and running; there are often many approval steps involved
    - Dealing with nomenclature/language/terminology – GAAIN works with data partners from beginning to understand what data they have and how to map it accordingly; GAAIN does mapping so data partners do not have to worry about this

- How does GAAIN ensure the quality of data?
    - All data must be de-identified, all data must have IRB (or its equivalent) approval, partners have to sign MOA

- Are there any restrictions in terms of file formats for data sharing?
    - The goal is to accept all data formats, but the imaging part is still in process

- Will GAAIN track publications coming from data used off GAAIN platform (similar to ADNI?)
    - Yes publications will be tracked and will also track the types of queries that are made on GAAIN to identify research trends, etc.

Discussion/Challenges - Global Data Sharing

What are the most important questions and what data do we need to answer them?

- Getting all of this data together and shared is great – but we need to think about the most important questions we want to ask and what data do we need to answer these?
    - Identifying, predicting and measuring decline to power clinical trials
    - With more datasets, longer time frames and getting placebo data from clinical trials this is another large longitudinal dataset we need to bring together

Placebo Data Project

- Goal: collect all longitudinal data from treatment studies - from placebo arm only in MCI and AD
    - There has been a lot of data collected but the signed agreements with FNIH do not allow for data sharing; right now interested researchers can only request the data be analyzed by the data holders (core investigators) – collaborative but not public
- A large part of placebo data is part of ADCS and they share all data once trials are complete and primary results presented

CAMD Database

- A solution to the challenge of these data sharing agreements could be to include their data in the

CAMD database; CAMD is in conversations with companies to do this, also CAMD does mapping so that is taken care of and all data speak same language

Brain Health Registry

- BHR will collect a vast amount of data using remote access and web-based registry
- What is the possibility of BHR data being uploaded to GAAIN for sharing web-based data?
    - Yes, they will share de-identified data with the limitation that the online cognitive data comes from partners and will need their permission to share

Country-specific regulatory issues

- Regulatory issues differ by country for sharing patient-level data outside of borders; there are countries who cannot get data out due to regulations – a future goal is to standardize this

Moving into competitive space

- Have been sharing in pre-competitive space; now moving to competitive space, how will this work, are we going forward correctly?
    - Lilly/AVID allowed amyloid imaging data into ADNI and into public domain right away and is doing the same for tau; we hope that other companies will follow suit
    - If there are any issues they should be shared so we can best address them

NIH and Data Sharing

- There is also the issue of a large amount of data being collected from NIH-funded grants that is not shared – NIH could help facilitate increased sharing of intramural and extramural data sharing – this is a challenge

Closing Remarks – Jim Hendrix

In closing, we thank all speakers and attendees and also want to recognize the ADNI members in attendance that did not present today, but bring great value to WW-ADNI:

- Sandra Black – Canada – part of North America ADNI – but recognize Canada's unique contributions
- Viji Ravindranath – India – looking forward to learning more about their progress
- Ana Luisa Sosa – Mexico – new member to ADNI

The next teleconference / Webinar is scheduled for:
November 13 / November 14
10:00 am Eastern/ 9:00 am Central/ 7:00 pm Pacific