EXECUTIVE SUMMARY

The Office of HIV/AIDS Network Coordination (HANC) facilitates communication, coordination and harmonization across the Division of AIDS (DAIDS)-funded HIV clinical trial networks. With the support of the National Institute of Mental Health (NIMH), HANC facilitates a trans-institute, cross-network Behavioral Science Working Group (BSWG). The BSWG organized a meeting of about 20 neuroscientists and other investigators in Seattle, WA on April 26, 2011. The focus of the meeting was to discuss methods for standardizing neurocognitive assessments in HIV-related clinical trials and create a consensus of recommendations to guide the field in future research.

Key Points of Discussion:
- Review of assessments in major network and non-network studies
- Normative Data
- Challenges in Longitudinal Studies
- International Study Assessments
- Data Analysis Challenges

Key Priorities:
- Consider criteria for test selection and methods for standardizing neurocognitive test batteries
- Examine methods for data sharing and establishing a common database
- Standardize covariates and methods for collecting them; particularly in the treatment domain
- Identify a common list of correction factors
- Discuss methodology for adjusting for learning effects and strategies for gathering baseline data
- Assess limits of generalizability with available data sets
- Discuss how to control for confounders and common screening approaches; identify when to test
- Prioritize norms based on network studies

DETAILED MEETING SUMMARY

The meeting was designed to encourage cross-collaboration in the measurement, analysis, and implementation of behavioral and social science objectives and interventions. Representation was from ACTG, INSIGHT, and IMPAACT networks, as well as other interested parties with strong community representation. These partners included Community Partners, Adolescent Trials Network, NICHD, Forum for Collaborative HIV Research and PHACS.
The meeting objectives were to:

- Review neurocognitive assessments in major network and non-network studies, and identify challenges in conducting HIV neurocognitive interventional and observational research.
- Summarize available normative data sets (U.S., International, and Pediatric and Adolescents), and define limitations and appropriate uses of the data sets.
- Define challenges in assessing longitudinal changes in neurocognitive assessments both in interventional trials and observational cohorts.
- Identify challenges in studies evaluating outcomes with high variability and expected relatively minor changes.
- Discuss selection of normative data for international studies, identify elements of commonality for international trial neurocognitive assessment tools, and identify training needs and challenges in developing neurocognitive assessments for multi-country trials.
- Identify unique statistical design issues in trials assessing changes in neurocognitive performance.
- Discuss unique challenges in the analysis of neurocognition in observational cohorts.
- Discuss challenges in analyzing neurocognitive performance accounting for intra-patient variability, overall high variability and confounders.

PLENARY

The opening session keynote by Kevin Robertson (ACTG, INSIGHT) provided an overview of neurocognitive domains, challenges, and adjunct and normative data in network and non-network clinical trials. It was suggested that if enough commonality exists across studies and networks in terms of domains of functioning, the group could come up with a “metadatabase” of neurocognitive assessments. The database could include a data dictionary, and a common set of forms so that data points would be the same and could provide recommendations about intervals used in assessments so that comparisons and meta-analysis across studies would have common intervals. The database could improve data management and test selection, so tests that perform best in the field would be more widely utilized. The database could also include common training materials already available for other networks/studies to use.

However, the group discussed potential issues related to data selection, access, and management, including:

- Budget constraints hinder studies from getting controls that inform decisions
- For international settings, no reliable information exists regarding the generalizability of one country’s standard in comparison to another’s
- Lack of consensus on a “gold standard”
- Phenotype complexities surrounding the type of cognitive impairment (multi-factorial, confounders, etc.), and difficulty in finding patients with progressive impairment
Controversy over the significance of asymptomatic neuropsychiatric impairment (ANI) and how ANI is assessed; ascertainment is a big issue (do we stratify different levels of impairment? do we have adequate assessments to measure impairment?)

- How many neuropsychological performance measures are needed to compose a whole battery? It is difficult to get a reasonably sized-battery approved and resourced.
- How to put it all together if people are getting different tests in longitudinal studies?
  - How do we pick the people who are fluctuating vs. experiencing steady cognitive decline? Where is the baseline for this person? Can this be standardized and studied? HIV-related neurocognitive impairment does not have a clear trajectory
  - Informants can be in denial; the pediatric world relies significantly on informants

NEW REFERENCE TABLE OF NEUROCOGNITIVE ASSESSMENTS
Jeffrey Schouten presented a new reference table of network protocols involving neurocognitive assessments with a brief summary of the tests batteries used. This table will be updated periodically and maintained on the HANC portal. This table could be a useful reference to stimulate cross-protocol analyses and identify strategies for standardization.

NORMATIVE DATA PANEL: MODERATOR NED SACKTOR (ACTG)

Ned Sacktor presented an overview of neurocognitive normative data sets from ATN 071 and PHACS. He provided the following considerations and key objectives to guide the discussion:

- Summarize available normative data sets (US, International, Pediatrics/Adolescents)
- Define limitations and appropriate uses of the available data sets
- Methodology and sample sizes
- Demographics, etc
- Selections of Tests and Domains
- Reliability and Validity in normative data
- Using Normative Data: assessing appropriate norms for comparison

The group discussed study demographics from MACS, ALIVE and WIHS to ascertain the generalizability of the data. The MACS cohort was a well-educated group of men, predominantly Caucasian, with limited drug use in seronegatives. ALIVE enrolled IDUs, predominantly African American men and women, with a significantly lower level of education. WIHS was a predominantly African American, female-only cohort.

The group suggested using published test norms and also applying regression models to correct for age, education, regional/geographical norms, linguistic and literacy abilities, ethnicity and gender. The group discussed the issue of how to collect and standardize covariates for the database. Covariates that need to be addressed:

- Important to assess HIV-relatedness
- Possible synergy of comorbidities on NCP
- Sample size considerations
- Synchronize treatment initiation in future cohorts
- ARV prescription history and duration of infection (need to collect good data)
CHALLENGES IN LONGITUDINAL STUDIES PANEL: MODERATOR BOB HEATON (UCSD)

Bob Heaton (UCSD), Lucette Cysique (University of New South Wales) and Constantin Yiannoutsos (Indiana University) presented on the following challenges in longitudinal studies:

- Methodology for Adjusting for Learning Effects: the methodology should relate to study purposes, and we need standardized comparison/normative data
- Screening vs. On-Study Data Assessment: determine when to test
- Control for Confounders and Track & Common Screening Approaches: assess effort and possible algorithms. It is important to track substances people are using as well as changes in medication, ongoing systemic illnesses, and changes in psychiatric status. The field needs a standardized way of screening for all of these things.
- Standards for Training—QA/QC: the expense is a barrier to implementation
- Form Standardization and Sharing
- Need Older and Adolescent Age Group Norms: This may require updated versions of existing tools. Copyright and license fees are a challenge.

INTERNATIONAL STUDY ASSESSMENTS PANEL: MODERATORS EDWINA WRIGHT AND LUCETTE CYSIQUE

Edwina and Lucette co-presented on challenges in developing neurocognitive assessments for multi-country trials. Discussion centered on how to prioritize norms, pilot normative data, and identify other places where the tests have been given to see the limits of generalizability, such as nutritional assessments.

Recommendations and/or Considerations:
- Prioritize norms based on network studies; focus on developing norms for top enrolling international sites that are paired with US research institutions
- Assess limits of generalizability with available data sets
- Pilot normative data—there are challenges in developing pilot studies before a parent study, but possibly can be done in parallel
- Training must ensure all staff understand the way standardized tests are meant to be understood, and formal written language vs informal spoken language issues; definitions of depression; socioeconomic factors/quality of life; urban/rural
- Personnel changes and training—important to plan for staff turnover

SUMMATIVE DISCUSSION

The group discussed standardizing the following domains:

- Correction factors: education, age, etc.
- Covariates; how to collect and HIV-relatedness
- Methodology for adjusting for learning effects
- Tracking and cofounders
• Training QA & QC
• Standardizing form data
• All age group norms
• Common database elements; systematic selection of tests and standardization of tests
• Challenges with ANI
• Generalizability of available data sets with respect to norms
• Network priorities for norms
• Functional assessments

There is a need to establish a uniform measure for functional assessment if the ANI diagnosis is to be pursued. It is hard to assess if the patients comes alone for evaluation and are not engaged in activities that require higher function (such as balancing a checking account or driving). The group suggested using a summary score, the global deficit score which highlights impaired performance over normal to above average performance. The challenge in using this approach is that some tests are more important for some populations than others, so that looking at domains is also important. Determining effect size is an important issue in neurocognitive research, as is the inclusion of a control group where possible. An emerging area is the use of appropriate norms for change over time.

Another approach put forth by the group is to issue a recommendation based on the research question (e.g., if testing treatment effect—randomized trial; if testing prevalence—normative data and large battery of tests; longitudinal design and detecting cognitive decline—determine a standardized approach.) Finding those who will progress can be difficult, so the group identified the need to find a measure for defining the population that will get worse. A potential avenue for investigating this would be a link between MACS and CHARTER. In addition, neuropsychological tests are very sensitive but not specific, so that there can be variation in performance unrelated to HIV, such as substance abuse, premorbid intellectual functioning, and comorbid conditions such as cardiovascular disease. It is important to assess and control for these confounding conditions. Otherwise, the variation due to other conditions can be larger than a treatment effect (the variation of the instrument is bigger than the signal), and/or treatment effects may require more time to detect. In this case, linking cohorts for longer longitudinal studies or conducting shorter term trials with long-term inference could be helpful. Using a large battery and selecting those with the weakest performance could be useful for future longitudinal assessment, as seen in dementia cases where individuals decline most rapidly in the areas where they are weakest.
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Peer Aagaard  
INSIGHT  
Community Partners Member  
Copenhagen HIV Programme  
Borgmester Godskeens Plads 5-3tv  
DK 2000 Frederiksberg, Denmark  
peerkbh@gmail.com

Rob Besaw, MPH  
HIV Forum  
Research Associate  
Forum for Collaborative HIV Research  
UC-Berkeley School of Public Health  
1608 Rhode Island Ave NW, Suite 212  
Washington, DC 20036  
rbesaw@hivforum.org

Pim Brouwers, Ph.D.  
NIMH  
Associate Director  
Infant, Child, & Adolescent Research Programs  
National Institute of Mental Health  
6001 Executive Boulevard, Room 6216  
Bethesda, MD 20892-9619  
ebrouwer@mail.nih.gov

David Clifford, MD  
ACTG  
Seay Professor of Neuropharmacology in Neurology  
Washington University in St. Louis  
Box 8111, Neurology, 660 South Euclid Ave  
Saint Louis, Missouri 63110  
cöffordd@neuro.wustl.edu

Lucette Cysique, Ph.D.  
University of New South Wales, Brain Sciences  
Department of Neurology,  
Xavier Building, Level 4, St. Vincent's Hospital 390 Victoria Street  
Darlinghurst 2010 NSW, Australia  
lcysique@unsw.edu.au

Stephanie Deyo  
IMPAACT  
ICAB member  
1530 NE 146th St., Apt 305  
Shoreline, WA 98155  
carries_mom08@comcast.net

Ron Ellis, MD, Ph.D.  
ACTG  
Professor of Neurosciences  
University of California, San Diego  
HIV Neurobehavioral Research Programs  
220 Dickinson Street, Suite B, Mail Code 8231  
San Diego CA 92103-8231  
roellis@ucsd.edu

Scott Evans, Ph.D.  
ACTG  
Senior Research Scientist  
Harvard University  
FXB-513, 651 Huntington Avenue  
Boston, MA 02115  
evans@sdac.harvard.edu

Rohan Hazra, MD  
Pediatric, Adolescent and Maternal AIDS Branch  
Center for Research for Mothers and Children  
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)  
National Institutes of Health  
6100 Executive Blvd., Room 4B11  
Bethesda, MD 20892-7510  
hazrar@niaid.nih.gov

Scott Letendre, MD  
ACTG  
Associate Professor  
University of California, San Diego  
220 Dickinson St, Suite A  
San Diego, CA 92103  
sletendre@ucsd.edu

Kay Malee, Ph.D.  
PHACS  
Psychologist  
Children's Memorial Hospital  
Northwestern Feinberg School of Medicine  
2300 Children's Plaza #155  
Chicago, IL 60614  
kmalee@childrensmemorial.org

Sharon Nichols, Ph.D.  
ATN  
Project Neuroscientist  
University of California, San Diego  
9500 Gilman Dr., #0935  
La Jolla, CA 92035  
slnichols@ucsd.edu

Peter Portegies, MD, Ph.D.  
University of Amsterdam  
Professor  
Academic Medical Center  
OLVG Hospital  
University of Amsterdam  
PO box 95500  
1090 HM Amsterdam, The Netherlands  
p.portegies@olvg.nl
Amy Ragsdale, MA
HANC
Special Projects Manager
HIV/AIDS Network Coordination (HANC)
1616 Eastlake Ave E, LE-500
Seattle, WA 98102
aragsdal@fhcrc.org

Kevin Robertson, Ph.D.
ACTG/INSIGHT
Professor
University of North Carolina
3504 Shady Creek Dr
Durham, NC 27713
robertsonkevin@neurology.unc.edu

Ned Sacktor, MD
ACTG
Professor of Neurology
Johns Hopkins University
234 Homewood Ter
Baltimore, MD 21218
Nsackto1@jhmi.edu

Jeff Schouten, MD
HANC
Director
HIV/AIDS Network Coordination (HANC)
1616 Eastlake Ave E, LE-500
Seattle, WA 98102
jschoute@fhcrc.org

Renee Smith, Ph.D.
PHACS
Psychologist
University of Illinois at Chicago
840 S. Wood St. M/C 856
Chicago, IL 60612
resmith@uic.edu

Carlos Velez
ACTG
Community Scientific Subcommitee of the ACTG
Proyecto ACTU, UPR-MSC
Biomedical Building II, 1st Fl. Room 100
San Juan, PR 00935
cvelezpuertorico@yahoo.com

Valerie Wjona, MD
University of Puerto Rico
Professor
University of Puerto Rico
Medical Sciences Campus
PO Box 365067
San Juan, PR, 00936-5067
valerie.wojna1@upr.edu

May Wong, Ph.D.
NIH/NINDS
Program Director, Extramural Research Program
Neuroscience Center, Room 2113
6001 Executive Blvd MSC 9521
Bethesda, MD 20892
wongm@mail.nih.gov

Edwina Wright, MBBS, FRACP
Alfred Hospital
Infectious Diseases Specialist
Commercial Road
Melbourne, Victoria 3004
e.wright@alfred.org.au

Constantin Yiannoutsos, Ph.D.
Indiana University
Professor
Indiana University School of Medicine
410 West 10th Street, Suite 3000
Indianapolis, IN 46202
cyiannou@iupui.edu