National Institutes of Health INCLUDE Project: Alzheimer’s Disease Clinical Trials in the Down Syndrome Population Planning Meeting

Meeting Summary
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The National Institutes of Health (NIH) INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (INCLUDE) Project: Alzheimer’s Disease Clinical Trials in the Down Syndrome Population Planning Meeting took place November 7, 2018, at NIH in Bethesda, MD. The following is a summary of what happened at the meeting in chronological order.

1. Welcome and Introductions

In recorded remarks, NIH Principal Deputy Director Lawrence Tabak, DDS, PhD, welcomed attendees to the first workshop of the INCLUDE Project and provided background information on the initiative. Congress, in its FY 2018 omnibus appropriations, tasked NIH with launching a comprehensive, trans-agency effort to address critical health and quality of life needs for individuals with Down syndrome. That effort, now known as the INCLUDE Project, involves 14 NIH Institutes and Centers, with funding of 49 awards in FY 2018, several of which support ongoing efforts in Alzheimer’s disease clinical research—an issue of concern among caregivers of individuals with Down syndrome. The meeting also addresses another concern in the Down syndrome community: the full inclusion of individuals with Down syndrome in clinical research. He concluded by saying the purpose of this meeting “is to explore how we can make sure that individuals with Down syndrome benefit from these advances as much as we all hope to in the future.”

1.1. Overview of the NIH INCLUDE Project

Based on language in the FY 2018 Omnibus, Congress directed the NIH Director

To develop a new trans-NIH initiative-involving, at a minimum, NICHD, NIA, and NCI-to study trisomy 21, with the aim of yielding scientific discoveries to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for Alzheimer's disease, cancer, cardiovascular disease, immune system dysregulation, and autism, among others. This initiative shall bring together research results that will be available to academic researchers, nonprofit organizations, and industry researchers. Funding for this trans-NIH initiative will supplement, not supplant, existing NIH funding levels for Down syndrome research. The agreement directs NIH to report to the Committees on Appropriations of the House of Representatives and the Senate within 180 days of enactment of this act on the structure, leadership, and key areas of focus for the new trans-NIH initiative for fiscal years 2018 through 2022.

Building on NIH's research plan on Down syndrome, which was updated in 2014, significant consideration was taken into identifying its research priorities. Specifically, five major research areas: pathophysiology of Down syndrome and disease progression; screening diagnosis, and functional measures; treatment and management; research infrastructure; and Down syndrome and aging, helped to form the foundation for INCLUDE (www.nih.gov/include-project).
The appropriated INCLUDE funding is going toward three components: the 1) conduct of targeted, high-risk, high-reward basic science studies on chromosome 21; 2) assembly of a large cohort of individuals with Down syndrome for comprehensive analysis and biomarker evaluation; and 3) inclusion of individuals with Down syndrome in existing and future clinical trials while building an infrastructure for such trials. Through the third component, NIH seeks to overcome shortcomings in clinical trials, including extremely limited medication trials in the Down syndrome population, which have been underpowered; the need to test how commonly used medications affect individuals with Down syndrome; and the need to develop clinical measures appropriate for Down syndrome.

NIH will also leverage some of its existing resources, the DS-Connect® patient registry (which launched in 2013 and is focused on engaging individuals with Down syndrome and their families about clinical trials and for gathering health information for future clinical trials) and the Down Syndrome Consortium, an NIH-led public-private partnership, to meet the INCLUDE Project goals.

1.2. Overview of DS-Connect® and the Down Syndrome Consortium
The Down Syndrome Consortium was formed in 2011, with the goal of providing a forum for the discussion of current research on Down syndrome and and implementation of the NIH research plan. One of the Consortium's first projects was to create DS-Connect® (https://dsconnect.nih.gov) — a secure, confidential online survey tool to collect basic information about individuals with Down syndrome from them and their families. DS-Connect® enables researchers to use de-identified data from individuals with Down syndrome to develop studies on related medical issues and treatments. Researchers can also use it to recruit study participants, although professionals do not have direct access to participants to protect their privacy. DS-Connect® has supported about 30 studies to date. DS-Connect® also comprises several survey modules. A new module, added in 2018, aims to help researchers understand the transition to adulthood among individuals with Down syndrome. DS-Connect® also provides multiple resources for individuals with Down syndrome and their families and caregivers, including a specialty provider registry.
NIH aims to include 6,000 participants by the end of 2018, use DS-Connect® to support and help recruit for INCLUDE-funded projects, and support research by linking DS-Connect® data with biospecimen repositories and databases.

2. NIH-Supported Alzheimer’s Disease and Down Syndrome Clinical Trial Resources

The following is a brief overview of three NIH-funded clinical trials, two of which are funded under INCLUDE.

2.1. Alzheimer’s Biomarkers Consortium – Down Syndrome (ABC-DS)

ABC-DS is a collaboration of two NIH-funded longitudinal studies that began in 2015. The first, Neurodegeneration in Aging Down Syndrome (NiAD), is being conducted at the University of Pittsburgh, University of Wisconsin–Madison, University of Cambridge (United Kingdom), and University of Washington in St. Louis. The researchers sought to recruit 180 subjects with Down syndrome at least age 25 (10% with Alzheimer’s disease) with 40 sibling controls. The other study, Alzheimer’s Disease in Down Syndrome (ADDS), is being conducted at Columbia University, Harvard University, and the University of California, Irvine. For that study, researchers sought to recruit 200–225 subjects with Down syndrome at least age 40 (25% with Alzheimer’s disease). Both studies involve a series of tests to assess cognitive decline over time.

Researchers have been able to recruit and retain participants with Down syndrome in the studies, and they are able to cooperate with the various testing they are subject to. The studies could advance the field by providing information on the time course of amyloid deposition, which could also be used as a biomarker to recruit individuals with Down syndrome for clinical trials. For example, based on the data collected so far, few participants under age 40 tested positive for amyloids. So, researchers designing a clinical trial to target amyloid may want to revisit the need for recruiting participants under age 40. It could also help in measuring intervention outcomes.

The ABC-DS research team has shared participants’ PET scans with Banner Research, who is using that data to conduct a power analysis, based on the selection of amyloid as a target. The same should be possible with Tau. In addition to providing new information on imaging biomarkers, the studies are helping to identify those neuropsychological measures that are most sensitive to early changes in cognitive functioning. At the moment, measures of episodic memory appear to be a strong candidate. And the studies are expanding researchers’ understanding of biomarkers, including possible treatment targets, the role genetics (including genes involved in inflammatory processes), and risk factors.

Participants suggested that the researchers publish the harmonized research protocol, which members of the research team endorsed and added that they also plan to make the data open-source.

For more information, visit www.nia.nih.gov/research/abc-ds.
2.2. Alzheimer’s Clinical Trial Consortium (ACTC)
The ACTC is a cooperative agreement with NIA launched in 2017 to provide a clinical trials infrastructure for Alzheimer’s disease and other age-related dementias to accelerate research. It is led by researchers from the University of Southern California's Alzheimer’s Therapeutic Research Institute (ATRI), Harvard Medical School, and the Mayo Clinic in Rochester, MN. The coordinating center resides at ATRI, but it is a distributed infrastructure, spread out across the country, and currently supporting 35 performance sites. ACTC—a novel mechanism—does not include projects; it includes the development of a mechanism to select projects and work with investigators to develop grant applications to fund the project that will be conducted by ACTC. ACTC accepts applications for phase I–III trials.

There are several ABC-DS sites that participate in ACTC, and the INCLUDE Project seeks to help leverage ACTC and ABC-DS to efficiently conduct Alzheimer’s disease clinical trials in the Down syndrome population. So far, the ACTC-DS (specific to Down syndrome research) advisory committee (some members include ABC-DS principal investigators) has identified 18 sites with experience or interest in conducting studies.

For more information, visit www.nia.nih.gov/research/dn/alzheimers-clinical-trials-consortium-actc.

2.3. National Alzheimer’s Coordinating Center
The NIA Alzheimer’s Disease Centers Programs, just underwent a strategic planning process that resulted in about 160 recommendations, many of which have been adopted, as reflected in recently announced grant requests for applications. All of the Alzheimer’s centers (which also cover other age-related dementias) have a clinical core through which they see participants annually and collect a uniform dataset, which is shared with the National Alzheimer’s Coordinating Center (NACC). NIA currently funds about 30 Alzheimer’s centers around the country. The centers conduct research on all aspects of Alzheimer’s disease, as well as provide diagnostic and educational services for patients and families. NACC is at the beginning stages of a six-step process of adding a Down syndrome module to the uniform dataset.

The NIA Alzheimer's Disease Centers are well-coordinated with the ACTC and ABC-DS sites, many of which are one in the same.

For more information, visit www.nia.nih.gov/research/dn/national-alzheimers-coordinating-center-nacc.
3. Down Syndrome Professional and Advocacy Group Resources and Initiatives

3.1. Alzheimer’s Association
The Alzheimer's Association's work in addressing Alzheimer’s disease in the Down syndrome population started in 2012 with a workshop. Also participating in the workshop was the Linda Crnic Institute for Down Syndrome and the Global Down Syndrome Foundation. The outcomes of the workshop included a set of research priorities: target identification and drug development, clinical and pathological staging, cognitive assessment and clinical trials, partnerships and collaborations with the ultimate goal to deliver effective disease-modifying treatments, and launch of the Down syndrome and Alzheimer’s disease professional interest area ISTAART, which stands for the International Society to Advance Alzheimer’s Research and Treatment. The Association has partnered with the Global Down Syndrome Foundation to fund two initiatives, comprising about 10 projects.

For more information, visit www.alz.org/ISTAART.

The National Task Group on Intellectual Disabilities and Dementia Practices, is a task group, composed of a variety of stakeholders and organized in 2010, focused primarily on advocating for services on behalf of individuals with intellectual disabilities who have dementia or Alzheimer’s disease, as well as their caregivers. It also supports related research. In 2012, the task group developed a national action plan that identified the issues the country faces and potential solutions. The plan has driven much of the work of the task group, including the creation of the National Task Group-Early Detection Screen for Dementia (NTG-EDSD), a screening instrument used worldwide; practice guidelines; and an evaluation of the Serial Assessment of Function in Dementia (SAFD), used to assess functional decline. The task group also provides training and technical assistance.

For more information, visit http://aadmd.org/ntg.

3.3. The Down Syndrome Medical Interest Group – USA (DSMIG-USA)
The DSMIG-USA sponsors a valuable listserv for providers to get advice on the care and treatment of patients with Down syndrome. It hosts workshops and working groups, one of which is developing healthcare guidelines for adults with Down syndrome. Another working group is investigating the phenomenon of regression in individuals with Down syndrome, particularly among teenagers and young adults who previously were high functioning and experience a precipitous decline.
A recent survey of DSMIG members found that as few as 2% of adults with Down syndrome have access on a regular basis to providers with expertise on their condition.

For more information, visit www.dsmig-usa.org.

3.4. Global Down Syndrome Foundation (GDSF)
The Global Down Syndrome Foundation (GDSF), formed in 2009, is part of a network of organizations—including the Linda Crnic Institute for Down Syndrome, Anna and John J. Sie Center for Down Syndrome at Children’s Hospital Colorado, Rocky Mountain Down Syndrome Center, and a new Adult Clinic for Down Syndrome—that provides research, medical care, education, and advocacy. GDSF supports 40 labs and more than 200 scientists, providing $1 million annually to support research in Alzheimer’s disease; cognition, autism and brain function; leukemia; stem cells and development; advanced genetics and genomics; and immunology.

For more information, visit www.globaldownsyndrome.org.

3.5. LuMind Research Down Syndrome Foundation
Since the LuMind Research Down Syndrome Foundation began in 2004, it has supported 15 observational studies and clinical trials, developed multiple assessment scales (it is currently working on an Alzheimer’s disease assessment scale), and contributed to discovering new targets for research in cognition and other areas. LuMind is particularly focused on supporting Alzheimer’s disease research in the Down Syndrome Clinical Trials Network (DS-CTN). LuMind’s efforts also include the development of an assessment scale for early memory decline in adults and an ACI-024 clinical trial in adults with Down syndrome.

For more information, visit www.lumindrds.org.

3.6. T21 Research Society
The Trisomy21 (T21) Research Society was formed about 5 years ago to promote common resources (repositories, biobanks, registries), promote open science and co-creation, promote education and training of young researchers and practitioners, harmonize protocols and lead medical innovation in Down syndrome and Alzheimer’s disease, and conduct public outreach to explain (recent) findings to the general public and patients. This work is organized under several committees, but for the purposes of this meeting, focus was given to the clinical committee. The T21 Clinical Committee encourages open dialog among researchers to harmonize protocols and share findings. Seven clinical trials are in progress (three in Europe and four in the United States), and the committee, among other things, is focused on identifying a core battery for cognitive assessments and developing new clinical outcome measures for the prodromal stage of Alzheimer’s disease.

For more information, visit www.t21rs.org.
4. Lessons from NIH-Supported AD Clinical Trials in Down Syndrome

4.1. Vitamin E in Aging Persons with Down Syndrome Trial, the International Down Syndrome and Alzheimer’s Disease Consortium
This completed study originated back in the 1990s as an anti-inflammatory drug trial based on the inflammatory hypothesis of Alzheimer’s disease. In the beginning, there were some questions about the study design, because results from other studies on anti-inflammatory interventions were not that encouraging. Researchers considered alternatives, including NSAIDs, anti-amyloid drugs, cholinesterase inhibitors, and memantine, but ultimately settled on vitamin E, an antioxidant treatment strategy. At the time of this study, there was interest in slowing the progression of the disease, so the study's primary hypothesis was that high dose of vitamin E would slow clinical deterioration in aging persons with Down syndrome over a 3-year period, presumably through its antioxidant action. The Brief Praxis Test was used to measure deterioration.

Results from the study showed that the vitamin E intervention had no effect on slowing deterioration. Other observations included a rapid rate of conversion to dementia (about 11% per year) among adults with Down syndrome age 50 and older. About 25% of the study sample had dementia at baseline. Also, the Brief Praxis Test and adapted Clinical Global Impression of Change scale performed as expected.

As this study only looked at one possible antioxidant, and people should not take the results to mean that no antioxidants will work to slow deterioration.

For more information, visit https://clinicaltrials.gov/ct2/show/NCT00056329.

4.2. 3 Star Study (ACI-24)
The ACI-24 Phase Ib study aims to test whether stimulating the immune system (T-cell independent pathway) to produce antibodies that target oligomeric and fibrillary amyloid beta proteins can prevent plaque accumulation and enhance plaque clearance. The topline results are expected to be released in late 2020. The vaccine, ACI-24, is currently in a Phase II trial for sporadic Alzheimer’s disease in Europe.

For more information, visit https://clinicaltrials.gov/ct2/show/NCT02738450.
5. Lessons from NIH-supported Clinical Trial Initiatives in Other Genetically At-Risk Populations

5.1. Alzheimer’s Prevention Initiative (API)
The idea for API began with a desire in the 1990s to accelerate the evaluation, approval, and availability of Alzheimer’s disease preventive interventions. The impetus was the discovery of the genetic component of late onset Alzheimer’s disease. Thus, API was created, which consists of prevention and theragnostic biomarker development trials that involve participants with a genetic predisposition for Alzheimer’s disease. API also supports study enrollment, risk assessment and risk disclosure, stakeholder collaboration, and data and sample sharing. Studies include a 5-year trial of the amyloid antibody therapy, crenezumab, in people who are carriers of the \textit{PSEN1} E280A genetic mutation, being conducted in Colombia, and a multinational trial of an immunotherapy and BACE inhibitor in older unimpaired adults who are homozygous for APOE4.

Several recommendations, based on lessons learned from API, are to: establish the scientific means and enrollment resources needed to rapidly test promising treatments; aim for maximal impact and accelerated approval, even before the approval pathway has been established; provide mechanisms to support interest and enrollment in trials; further develop the infrastructure needed to support Alzheimer’s disease trials in persons with Down syndrome; identify and address the scientific, regulatory, financial, ethical, social, organizational, and logistical challenges; incorporate best practices when appropriate and establish new solutions when needed; capitalize on longitudinal cohort data to inform your trial design, endpoints, and power; work closely with persons and families every step of the way; actively involve other stakeholders; forge public-private partnerships; aim to have the greatest impact on the field; and pay attention to the details.

For more information, visit \url{http://banneralz.org}.

5.2. Dominantly Inherited Alzheimer’s Network – Therapeutic Unit (DIAN-TU)
The initial NIH funding for the DIAN and DIAN-TU study was instrumental in getting sites in other countries to participate. Because of the large number of participants and longitudinal design, the researchers have been able to reliably estimate, through biomarkers, the period of time between initial accumulation of amyloid and onset of Alzheimer’s disease symptoms, which can help inform clinical trial designs. There was specific emphasis on the importance of designing observational trials in a manner that will allow the research team to use the natural history data in clinical trials as a control. In addition, this study was greatly impacted by public-private partnerships, as the support was needed to be able to react and adapt to inevitable challenges. Other lessons learned from DIAN-TU included the development of a master protocol to be able to study multiple therapies, diseases, or both; and, meaningfully engaging study participants and other stakeholders.
6. Lessons from Other Clinical Trials in Down Syndrome

6.1. CLEMATIS Trial of RG1662 (basmisanil) for memory and adaptive function
The following are some of the lessons learned from studies on donepezil and basmisanil. General challenges to the conduct of these clinical trials included inter-individual variability because of small sample sizes, lack of standard endpoints to assess efficacy, and placebo effects. Some of the challenges researchers encountered in measuring cognition through direct and indirect measurement were: questionnaires may not have captured actual changes in cognition, there was a risk of under- or overestimating participants’ skills, participants may have adapted to repeated testing, changes in the person accompanying the participant may have affected the study, behavioral observations may be subject to a floor or ceiling effect, motor limitations may be an issue, participants may get better at tests with repeated exposure, impulsivity and attention span may be an issue, and few test batteries cover the entire age range of interest. Other things to keep in mind when doing clinical trials include proper recruitment and communication with potential participants (e.g., establish realistic expectations, be sensitive to family concerns, get commitment from caregiver to be reporter throughout the study), obtain informed consent, think through study design challenges (e.g., order of procedures to minimize anxiety, properly estimate the time needed to complete assessments), and budget for participants’ travel. Several ideas for promoting participants’ comfort, include allowing time to establish rapport, providing adequate breaks with rewards, and encouraging parents to soothe but allow autonomy.

For more information on the CLEMATIS clinical trial, visit [https://clinicaltrials.gov/ct2/show/NCT02024789](https://clinicaltrials.gov/ct2/show/NCT02024789). For more information on the donepezil clinical trial, visit [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2665884](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2665884).

6.2. Scylo-Inositol Trial
To the knowledge of the meeting participants, this small study is the first anti-amyloid trial conducted in individuals with Down syndrome. Participants were able to complete all of the tests, including blood draws. It was found to be helpful for the study to have a volunteer with Down syndrome greet participants at the study site. The study demonstrated that individuals with Down syndrome respond differently to doses for adults in the general population.

For more information, visit [https://clinicaltrials.gov/ct2/show/NCT01791725](https://clinicaltrials.gov/ct2/show/NCT01791725).

7. Research Challenges: Open Discussion
A discussion was led about what is needed to support clinical trials to prevent the development of Alzheimer’s disease in individuals with Down syndrome. Several questions to promote thought on the topic.

> What would be appropriate endpoints to measure? How will we be able to gauge success (potentially based on discoveries from biomarker studies, including ABC-DS and those supported by other groups)? What is the timeframe to see efficacy?
> Can we harmonize measures (neuropsychological, neuroimaging, biomarkers, others) to maximize productivity of groups involved?
>What are the infrastructure needs to support a clinical trial in adults with Down syndrome?
>How can we overcome barriers to recruitment and retention?
What are the most promising pharmaceuticals for this population?
How can we avoid the pitfalls that have negatively impacted other similar trials in AD? In Down Syndrome?
How can we best leverage partnerships in this space?

One participant expressed concern about variability in the regulatory environment that goes across institutions, states, and even countries. It was noted that it is very important, especially for Phase I trials where direct benefit is unclear, to work out the issue of informed consent by individuals with Down syndrome. National advocacy and guidance would be incredibly helpful to inform this.

Another participant suggested a working group be formed that would at least include researchers from API and the DIAN study, focused on sharing ideas and lessons learned.

Another participant asked about what could be learned about harmonization of measures from the ABC-DS study, including risks and benefits. It was suggested that researchers with ABC-DS publish a paper on how the two studies approached harmonization. In response, NIH Program Staff mentioned harmonization under INCLUDE won’t stifle innovation; NIH wants to keep the research dynamic. Participants said under ABC-DS there is a harmonized core, but each program has its own procedures and measures of interest. Harmonization didn’t stifle innovation. But it’s important to get harmonization out of the way early, in the beginning.

A challenge brought up by participants is the standardization of electronic medical records and the issue of informed consent around obtaining and sharing data from those records.

In reference to a question about DS-Connect®, a consistent challenge across many of the studies about the Down syndrome population is recruitment of racial and ethnic minorities to participate in studies. NIA has just recently launched a national strategy to address this issue in Alzheimer’s disease research. It is also building a repository to include such things as recruitment and materials and trainings on how to conduct outreach.

A participant asked whether researchers should investigate immunotherapy interventions for Alzheimer’s disease in the Down syndrome population. In response, one of the participants said there’s more support for interventions that target amyloid and tau. There was concern also expressed about whether the assessments needed for immunotherapy interventions would be easy to do with participants with Down syndrome.

8. Next Steps: DS/AD Workshop in March 2019

The Alzheimer's Association, GDSF, LuMind, and other funding organizations will hold a workshop March 12–13, 2019, for Alzheimer’s disease and Down syndrome researchers. Participants will discuss, among other things, what studies funding organizations should get behind.