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

Meeting Summary

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 0.004 T

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.

3. Down Syndrome Professional and Advocacy Group Resources and Initiatives

3.1. Alzheimer’s Association

For more information, visit

>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?