Appendix D: Down Syndrome (DS) Research-Related Meetings Since 2014

Outcome Measures for Clinical Trials in Individuals with DS

Sponsored by *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH)

April 23-24, 2015

Summary

For two days in April 2015, at NIH in Bethesda, Maryland, NICHD sponsored a meeting to identify instruments that can assess DS clinical trial pharmaceutical or behavioral outcomes. For several months prior to the meeting, participants met via teleconference in three working groups to identify domains and measures in the areas of cognition, behavior, and medical issues, respectively, that could address Food and Drug Administration (FDA) requirements for patient-reported outcome measures that could be used in clinical trials.

Dr. Michelle Campbell, a member of a study endpoints team in the Office of New Drugs at the FDA, gave an overview of Measurement Issues from the perspective of the FDA. She noted that target population input is needed to develop a certain measurement instrument, and that it can be difficult to incorporate different perspectives of responses to treatment. Dr. Campbell provided some resources for stakeholders that can be used to work with the FDA on drug and measurement development.

Dr. George Capone, of the Kennedy Krieger Institute, and Dr. Jeannie Visootsak, then of the Roche Innovation Center, gave an overview of current industry and clinical trials. Dr. Capone described an unmet need in the field of pediatric cognitive enhancement (cognitive pharmacology) and the recent interest in testing existing cognitive enhancement medications in the DS population. He listed examples of medication trials that proved to be helpful, as well as trials that did not, and emphasized the need for studies using psychotropic medications on behavior targets such as maladaptive behaviors or psychiatric disorders. Dr. Visootsak described the varying attitudes that parents of children with DS have towards clinical trials, and the successes and challenges of one clinical trial, including

challenges such as arranging transportation to the clinic, the need for a parent to miss a workday, and the time of day testing is done.

During the meeting, further discussion was held among members of the three working groups on cognitive, behavioral, and medical issues. The Cognition Working Group discussed important cognitive outcomes, focusing on the categories of language, executive functioning, memory and learning. The Behavior/Social/Emotional Working Group discussed how people with DS may have more social problems, but fewer behavior problems, than individuals with other types of developmental disabilities, and discussed associated mental health diagnoses in DS including inattention, autism spectrum disorders, and dementia. The Medical/Physical Working Group broke down outcome measures by organ systems and suggested that DS-Connect could be a tool to collect families' natural history data.

Working groups were tasked to develop three short-term (to be completed within 18 months) and three longer-term goals for future clinical trials.

The Medical/Physical Working Group reported that their short-term goals were to: (1) work out a model for diagnosis and treatment based on organ systems; (2) evaluate the appropriateness of treatments for individuals with DS; and (3) partner with other groups that are working on related medical/physical issues. The group's long-term goals were to (1) evaluate co-occurring conditions and identify tests that are the gold standard for each condition, linking them to phenotypes; (2) identify problems in aging individuals with DS and develop guidelines for treatment in consultation with other groups; and (3) apply this model across all organ systems.

The Cognition Working Group's short-term goals were to (1) specify principles for standards for data collection and evaluate measures for adequacy; and (2) provide a list of measures for current and imminent clinical trials. The measures would be classified as "good enough for now" or "not recommended for use," identify gaps where there currently are no appropriate measures; and (3) identify what measures are being used across research sites. The group's long-term goals were to (1) create a toolbox, perhaps using domains of functioning, and stratified by age and level of function; (2) create a consortium to pool data across sites; and (3) create a battery with applicability across languages and cultures. In addition, the group came up with the following cross-cutting long-term goals: (1) engage parents of children with DS in research; (2) advance the neuroscience of DS in humans, particularly in children; and (3) obtain a grant to address issues related to measurement across domains and multiple sites.

The Behavior Working Group's short-term goals were to (1) identify additional members for the Working Group, including parents, DS experts, and experts on related topics; and (2) identify collaborations with the other working groups, such as common data elements, sleep apnea and behavioral outcomes, and biomarkers and behavioral outcomes. The Behavior Working Group had the following long-term goals: (1) identify current or developing technology to provide naturalistic measurement of target concepts, including tests such as LENA (Language ENvironmental Analysis); (2) expand psychometric properties, sensitivity to change, and normative data for key measures in DS; and (3) apply principles of advanced quantitative analysis to best characterize change in clinical trials.

The meeting participants concluded the meeting by discussing mutual aims, and the publication of a paper with a summary of the meeting. The work that developed from the meeting, led by Dr. Anna Esbensen at Cincinnati Children's Hospital Medical Center, was summarized in the *American Journal of Intellectual and Developmental Disabilities* in 2017 (PMID: 28452584) and focuses on outcome measures in the areas of cognition and behavior.

Alzheimer's Disease (AD) Clinical Trials in the DS Population Planning Meeting

Sponsored by the Office of the Director, NIH, in conjunction with the NIH-wide INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project Working Group.

November 7, 2018

Summary[15]

On November 7, 2018, at NIH in Bethesda, MD, the NIH sponsored the first workshop of the INCLUDE Project to discuss emerging opportunities for AD clinical trials in the DS population. This preliminary planning meeting was designed to set the stage for future workshops to bring together all relevant stakeholders to fully engage on this topic, which is of great importance to the DS community. Representatives from NIH, clinical researchers, and other members of the DS and AD communities participated. The participants discussed lessons learned from NIH-supported AD clinical trials in DS, lessons from NIH-supported clinical trial initiatives for AD in genetically at-risk populations, and lessons from other clinical trials in DS. Previous experiences in this area and promising new scientific advances were

[15] AD Clinical Trials in the DS Population Planning Meeting: Full Summary (PDF 228 KB)

discussed. It was recognized that the INCLUDE Project, launched in Fiscal Year 2018, will continue to support a broad range of research to address critical health and quality of life needs for individuals with DS, and that clinical trials to prevent and/or treat AD in the high-risk DS adult population are a high priority for the initiative.

Key Outcomes

Participants discussed what research support and infrastructure may be needed for clinical trials aimed at preventing the development of AD in individuals with DS. The group identified the need to identify appropriate endpoints and biomarkers to measure if the clinical trial had succeeded, as well as the timeframe needed to demonstrate efficacy of the trial. Studies that are part of the NIH-funded Alzheimer's Biomarkers Consortium—Down Syndrome (ABC-DS) project, that are following adults with DS longitudinally to identify biomarkers that predict onset of dementia, may be very informative to accomplish this goal. A second goal is the harmonization of measures (neuropsychological, neuroimaging, biomarkers, and others) across studies to maximize productivity and efficiency. In addition, the group discussed infrastructure needs that could support clinical trials in adults with DS, and those that could be leveraged for this purpose. Finally, there was discussion about the barriers to recruitment and retention in clinical trials, and mechanisms to address these issues.

Alzheimer's Association: Intersection of DS and AD: A Continuing Conversation

Sponsored by the Alzheimer's Association and the Global Down Syndrome Foundation (GDSF); with scientific input from the National Institute on Aging and NICHD at NIH; in collaboration with the LuMind IDSC Foundation

March 12-13, 2019

Summary

Building on the earlier meeting in November 2018, the Alzheimer's Association and GDSF held a meeting in collaboration with National Institute on Aging, NICHD, and LuMIND IDSC Foundation entitled "Intersection of DS and AD: A Continuing Conversation." The workshop was intended to strengthen the collaborations among the leading groups addressing AD and DS research, and to continue preparations for clinical trials of AD in individuals with DS, with symposium topics spanning basic, clinical, and translational science.

Welcoming remarks were given by Frank Stephens, a DS self-advocate. The keynote presentation given by Dr. Michael Rafii from the University of Southern California, discussed the intersection of AD and DS. Session topics included: Epidemiology of Alzheimer's and DS, Factors Impacting Risk for AD in DS, AD Imaging Biomarkers in DS, AD Non-Imaging Biomarkers in DS, Biological Underpinnings of DS and AD, Practical Considerations for Clinical Trials, Clinical Interventions and the Landscape of AD trials in DS, and Next Steps and Future Initiatives.

Workshop participants noted the similar patterns of pathology between DS and AD through neuroimaging studies, although AD may begin at an earlier age in individuals with DS. 'Omics data may suggest other biomarkers; for example, DS-AD is a genetically driven form of dementia, while sporadic AD in the general population is not. In addition, the triplication of the amyloid precursor gene (APP) and other genes located on chromosome 21 may impact the development of AD in ways specific to individuals with DS and AD.

Key Outcomes

Workshop participants identified gaps in understanding the biological underpinnings, the role of risk factors, and the best biomarkers for DS-AD across the lifespan of the disease, including vascular markers, inflammatory markers, oxidative stress, neuronal excitation, brain calcification, and cerebrovascular disease markers. Workshop participants discussed the many international research consortia and collaborations underway to advance the understanding of DS and AD.

More research is needed to better understand the risk factors for dementia in DS. Future directions included a need for increasing the number of postmortem brain tissues from people with DS and AD available for study and establishing a consensus research framework for DS-AD, including a core assessment battery. In addition, participants suggested establishing longitudinal measures to better understand progression of disease. Participants discussed current clinical trial networks and infrastructure for multicenter collaborations that are currently underway and spoke about the need to expand utilization of brain banking, data sharing, evaluation across studies, pharmacological and non-pharmacological intervention studies, and combination therapy approaches (PMID: 32544310).

Planning a Virtual DS Cohort Across the Lifespan Workshop

Sponsored by the Office of the Director, NIH, in conjunction with the NIH-wide INCLUDE Project Working Group

September 23-24, 2019

September 23 Videocast

September 24 Videocast

Summary

NIH sponsored a workshop with the goal of designing and assembling a large cohort of individuals with DS to develop a comprehensive genomic, epigenomic, transcriptomic, and proteomic map to help understand the predisposing risk and protective factors that underlie DS. NICHD Director Dr. Diana Bianchi began the meeting by giving an overview of the NIH INCLUDE project. INCLUDE involves 18 NIH institutes and centers with the goals of increasing research specific to people with DS and encouraging inclusion of people with DS in all aspects of research, especially clinical trials. As a result of funds received in the Fiscal Year 2018 appropriation, NIH funding for research on DS rose to a total of $60 million. All funded projects must share their data and use DS-Connect®: The DS Registry for recruiting participants in clinical studies whenever possible.

David Egan, an adult with Down syndrome and a member of the public-private DS Consortium, was introduced by his older brother, Marc Egan. Mr. Egan emphasized the need for continued research, saying that people with DS are living longer but are now at risk for developing more adult conditions such as AD. Mr. Egan has taken part in research studies since he was a child, not with the expectation that scientists would change him, but so that he could reach his full potential.

Dr. Melissa Parisi, Chief of NICHD's Intellectual and Developmental Disabilities Branch, set the stage for the workshop: to bring together clinicians, researchers, data scientists and biostatisticians, NIH staff, self-advocates, family members, and advocacy group members; to identify the clinical components of DS and the 'omics and biospecimen needs; to develop best practices for data harmonization and data sharing; and to identify information technology needs for the field. Dr. Parisi also gave an overview of the DS-Connect® registry, a resource for people with DS and their families that includes health information surveys, a list of crowdsourced healthcare providers, and a portal for professionals who want to examine the data, conduct a survey, or use the registry to recruit for a clinical study.

Meeting participants heard from researchers who described existing cohorts in DS on a wide range of health topics, such as cardiac defects, communication and hearing issues, sleep, and cancers. Data scientists and clinicians also discussed research approaches and tools, such as AD, cognitive assessments, standardized phenotyping, and recruitment of diverse populations.

Breakout sessions participants discussed clinical aspects of Down syndrome. The group discussing co-occurring conditions produced a helpful graphic of three domains that significantly affect long-term outcomes for people with DS—mental health and behavior, growth and metabolism, and sleep. This group also described a minimum common dataset that could be collected from new cohorts prospectively. The breakout session focused on 'omics collection identified whole genome sequencing as the highest-priority research need, noting that the data must be coordinated with phenotypic and other information about study participants. The group also was interested in other 'omics, such as metabolomics and proteomics.

The breakout group covering biospecimen storage and distribution presented pros and cons of having a centralized biorepository, identified the tissues most useful for research, and shared helpful guidelines and policies to help facilitate tissue donation and access, including having a biorepository review committee to ensure equitable distribution of tissues for research.

The outreach and participant engagement breakout group suggested ways to reach out to the DS community, such as through community health workers, to ensure recruitment of minority populations. The DS-Connect® registry could be leveraged to facilitate participation and community engagement.

Day 2 of the workshop focused on data integration and harmonization among DS cohorts, including data infrastructure needs for interoperability, and the development of common data elements. Additional needs were identified, such as having a template for broad consent (addressing issues of consent and assent in individuals with reduced decisional capacity), achieving diversity of study participants, and strategies to engage a range of communities (including rural populations).

Key Outcomes

Six working groups were developed as a result of the meeting: Four Data Standardization and Harmonization Working Groups (Existing Cohorts, Minimal Common Dataset, Biospecimens, and Global Unique Identifiers (GUIDs)/Linkages), a

Community Outreach Working Group, and a Clinical Trial Readiness working group. Each group developed a final project, such as a recommendation for NIH or a survey of Existing Cohorts of people with DS. In addition, the NIH INCLUDE Project published an RFA titled "Development of the INCLUDE Project Data Coordinating Center" (RFA-OD-20-007), resulting in the funding of 3 integrated components: an Administrative and Outreach Core, a Data Management Core, and a Data Portal Core that together will meet the data coordination needs for the INCLUDE Project. The multi-institutional Data Coordinating Center will support investigations of a large cohort of people with DS for data sharing, data access, and integrative analysis to enable novel investigations into Down syndrome co-occurring conditions across the lifespan. The Clinical Trial Readiness working group also published a summary of its discussions (PMID: 35321660)

Clinical Trials in DS: NIH INCLUDE Project Virtual Workshop

Sponsored by the Office of the Director, NIH, in conjunction with the NIH-wide INCLUDE Project Working Group

May 7-8, 2020

May 7 Videocast

May 8 Videocast

Summary[16]

Dr. Diana Bianchi, Director of NICHD and INCLUDE Steering Committee Co-chair, provided an overview of the INCLUDE project. NIH funding for research on DS has increased dramatically in recent years, from $24.3 million in 2016 to $86 million in 2019, largely due to the specific congressional appropriation for the INCLUDE project. Dr. Bianchi also mentioned the new agency-wide research plan that will be created to update the 2014 NIH research plan on DS, which will be merged with the 2018 INCLUDE Project research plan.

Dr. Laurie Ryan, National Institute on Aging (NIA), explained that the goal of this workshop is to learn about aspects of the co-occurring conditions in DS throughout the lifespan. Dr. Bianchi then presented her work on prenatal treatment for DS. A personalized approach to prenatal treatment could improve fetal brain growth, neural connectivity, and neurocognition.

[16] Clinical Trials in DS Full Summary (PDF 375 KB)

Investigators and clinicians gave meeting participants an overview of conditions that affect people with DS in childhood and adolescence, including cardiopulmonary conditions, sleep conditions and sleep apnea, lung disease, infectious diseases, autoimmune conditions, leukemia, ADHD, and deficits in cognition, communication, and language. Dr. Priya Kishnani, Duke University, discussed clinical trials in DS. Current research opportunities include: partnerships between academic researchers and industry to conduct randomized, placebo-controlled clinical trials; development of suitable outcome measures; collaborations with researchers who focus on other areas of developmental disabilities; and continued collaborations with NIH and the DS Medical Interest Group. A panel of self-advocates, clinicians, parents and siblings of people with DS, and researchers noted the need for diversity in clinical trials. Another session covered non-pharmacological and lifestyle interventions, including physical activity, cognitive stimulation, and music and social engagement in DS, in part to prevent onset of AD. Investigators also gave an overview of conditions that affect adults and the aging population with DS. In this session, clinicians and researchers detailed challenges to defining obesity in DS, central nervous system conditions such as AD, and regression. A noted research gap in this area is the limited availability of specimens to study the neuropathology of AD in DS. In addition, clinical guidelines are needed for identifying AD and dementia in adults with DS.

After hearing updates about currently funded INCLUDE clinical research studies, workshop participants discussed how to create the infrastructure and tools for DS-related clinical trials, including use of several existing trial networks. The group discussed linking registries and future projects utilizing these resources.

Dr. Gary Gibbons, Director of the National Heart, Lung, and Blood Institute (NHLBI) and Co-chair of the INCLUDE Steering Committee, closed the meeting by highlighting the importance of collaboration, outreach, engagement, and trust in the research community. The presentations and discussions from this meeting will give NIH guidance on how to continue to enhance its research portfolio in ways that turn discovery into enhancement of the lives and well-being of people with DS.

DS Research: The Intersection of Basic Science and Clinical Cohort Development

Sponsored by the Office of the Director, NIH, in conjunction with the NIH-wide INCLUDE Project Working Group

November 9-10, 2020

November 9 Videocast

November 10 Videocast

Summary

On November 9–10, 2020, the NIH in Bethesda, MD, sponsored a virtual workshop of the INCLUDE Project titled "DS Research: The Intersection of Basic Science and Clinical Cohort Development." The workshop focused on the first two components of INCLUDE: Conduct targeted, high risk-high reward, basic science studies on chromosome 21 and DS; and assemble a large cohort of individuals with DS across the lifespan. Representatives from NIH, basic and clinical researchers, self-advocates, and other members of the DS community participated in the 2-day meeting and gave presentations on the current state of the science and gaps with regard to basic research and cohort development. Meeting attendees also participated in a series of topic-driven sessions to discuss these issues and identify priorities for further research and development. More than 300 people registered to attend the workshop.

Dr. Diana Bianchi, Director of NICHD and INCLUDE Steering Committee Co-chair, provided an overview of the INCLUDE Project and summary of NIH DS funding. Initial funding for INCLUDE was awarded in the second half of fiscal year (FY) 2018, at a level of $23 million supporting 49 supplemental awards. Funding has increased steadily each year since. In FY 2019, $35 million was distributed among 43 awards. In FY 2020, the total amount of INCLUDE funding increased to $60 million supporting a total of 63 awards, of which 42 were new. NIH anticipates that this level of support will be maintained through FY 2022. Each year, projects have been funded in all three components of INCLUDE. Since 2019, the program also has supported a total of 24 new trainees, from predoctoral candidates to postdoctoral fellows to M.D. and Ph.D. scholars.

Two self-advocates and their families who have participated in clinical studies of DS gave the keynote presentations. The presenters offered their personal views on the

importance of engaging with participants throughout the course of the clinical study, making the experience personal and relevant, and sharing the outcomes of the study. The advocates emphasized the need to keep study participants informed about research updates using social media and understandable language and educate and engage potential candidates about clinical trials.

Presentations on co-morbidities associated with DS followed the keynote presentations, with discussions on neurodevelopment; behavior; cardiovascular disease and pulmonary hypertension; and respiratory and airway conditions. Additional presentations were given on cancer; autoimmunity and infections; endocrine, metabolic, and skeletal conditions; and aging and AD. The meeting then divided into Breakout Groups 1 (Development and Behavior), 2 (Heart and Lung), 3 (Cancer and Immunity), and 4 (Aging and Metabolic Conditions). The breakout groups identified some common themes, including the need for longitudinal cohort studies with well-validated endpoints, better animal and cellular models for preclinical data, more cohort diversity, integration of adult and pediatric cohorts into a single cohort across the lifespan, collection of “samples of convenience” from routine medical and surgical procedures, and better harmonization and linkage of databases. On the basic science side, the breakout groups discussed the need to bring together information on phenotypes of various mouse models, provide more funding opportunities for model development, and develop induced stem cells to generate lines from people with DS. It was announced that whole genome sequencing data on 2,600 people with DS, funded by INCLUDE, would soon be available to be shared with the community. Day one of the workshop ended with some closing comments from Dr. Gary Gibbons, Director of NHLBI and INCLUDE Steering Committee Co-chair.

The second morning of the workshop was divided into two concurrent sessions. The Basic Science session focused on the current state of DS mouse and cellular model systems. An overarching issue was the importance of knowing the background strain of the mouse model used in research studies because many factors can affect the mouse phenotype, such as the breeding strategy used to generate the mouse and how the genetic model was derived. One promising model is the TcMAC21 mouse, which has an extra mouse artificial chromosome containing the long arm of human chromosome 21, retains 93 percent of the human chromosome protein coding genes, and is not mosaic. Work has begun to put the human chromosome 21 in rats, which tolerate the human centromere better than mice and are rarely mosaic. With regard to cellular models, investigators can now use human-derived induced pluripotent stem cells (iPSCs) to study conditions common in people with DS, such as congenital heart defects, intellectual disability,

and AD. More researchers are now using three-dimensional cell cultures that allow cells to self-organize into organoids, including “mini-brains.” This method supports greater numbers of cell types and cell interactions than two-dimensional cell cultures. Another presentation described research generating neuronal cell lines containing the presenilin mutation from individuals with familial AD to use in three-dimensional cultures.

The Cohort Development session focused on the INCLUDE Data Coordinating Center and existing and future cohorts of individuals with DS. NIH has recently funded a project intended to create a data coordinating center (DCC) and a data portal to standardize, harmonize, and aggregate DS data into a virtual biorepository, with a goal of providing data access and analysis tools for transformative DS research. The findings of a survey of 57 existing cohorts and databases related to DS research will serve as a starting point for the DCC. Another presentation described a variety of options for linking data, including GUIDs, PCORnet, Datavant, and a referral code model that is being used in the DS-DETERMINED study. The Biospecimen Working Group has recommended that blood, brain tissue, cerebrospinal fluid, saliva, cord blood, surgical specimens, urine, and stool be collected for DS cohort studies. During the discussion, attendees suggested collecting additional biospecimens, such as liver tissue, heart tissue (myocardium), vascular specimens, autopsy specimens, amniotic fluid from prenatal diagnoses, and placental tissue, when available. The importance of linking biospecimens with clinical data and consents was emphasized. Attendees suggested leveraging DS-Connect®: The DS Registry to consent participants to broad sharing from past studies and to facilitate online consent for people with DS so they can readily provide a research blood sample during a routine visit to the doctor.

Following the concurrent sessions, Breakout Groups 5 (Ensuring Robust iPSC and Organoid Systems as Preclinical Models) and 6 (Ensuring Robust Animal Model Systems as Preclinical Models) discussed how to choose the best model system and ensure rigor and reproducibility, as well as determine what clinical and epidemiological data and biospecimens are needed for basic science studies. Both groups concluded that the model depends on the scientific question being asked and the analyses to be done, and they offered strategies for enhancing rigor and reproducibility of research findings. Group 5 said desirable data and biospecimens included clinical data on early brain development, cancer, iPSC lines from diverse populations (accompanied by related clinical data), plasma biomarkers, and a registry of available DS cells. Group 6 suggested clinical, cognitive, and disease phenotypes to aid mouse-to-human translation, cross-comparative data on mouse

phenotypes, clinical data on circadian rhythms and sleep, drug testing data, and respiratory and infectious disease natural history data.

Breakout Groups 7 (Clinical Phenotyping and Minimal Common Data Elements) and 8 (Biospecimens and Related Omics Datasets) discussed what biospecimens and clinical and phenotyping data should be collected and what clinical scenarios and fundamental scientific questions should be addressed by a large cohort study. The two groups suggested collecting basic medical history data across the lifespan, behavioral and cognitive metrics, and environmental data. Both groups emphasized that biospecimens must be linked to phenotypic data. They suggested collecting the biospecimens recommended during the cohort development concurrent session, along with a few of their own additions. Fundamental clinical and scientific matters included identifying the risk and protective factors associated with DS co-morbidities, conducting network gene analyses to determine which genes cause which phenotypes, and identifying the unique transcriptomic signatures in specific tissues of relevance to DS, such as heart and lung.

Six invited DS investigators were asked to discuss what basic scientists want clinical investigators to know and what clinical investigators want basic scientists to know. The panelists all agreed that communication with research participants with DS must be done in a way that does not make them feel devalued. Researchers should try to minimize the time commitment for participation and should consider ways to incentivize participants' research experiences. The panelists emphasized that future collaborative efforts should build on the dialogue begun among basic science and clinical investigators, people with DS and their families, and advocates.

The meeting closed with appreciation for the important feedback and information provided by all the participants, and with a reminder that the workshop discussions will inform the revised NIH DS research plan.