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

Outcome Measures for Clinical Trials in Individuals with DS

Sponsored by 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

f the Kennedy Krieger Institute, and Dr. Jeannie Visootsak, ovation Center, gave an overview of current industry and ne described an unmet need in the field of pediatric cognitive ve pharmacology) and the recent interest in testing existing nt medications in the DS population. He listed examples of proved to be helpful, as well as trials that did not, and for studies using psychotropic medications on behavior aptive behaviors or psychiatric disorders. Dr. Visootsak attitudes that parents of children with DS have towards 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) w

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 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)

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, Pl2at17.76co col2 (r)-4 (c)-4 (h)]TJ -nna(t)4 (a)-6 (t1 (g)-9 (,)74 (ct)7 (u)4 c)-3 3 (r)nnd utl -0

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

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

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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.

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 w90034 (o s)-5 (w)P-w90034 (o s)-5 (wi) (-)T7(w)P-wgioc(s)-6 (-

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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