

Clinical Trials in Down Syndrome for Co-occurring Conditions Across the Lifespan

Virtual Workshop May 7–8, 2020

Day 1: Thursday, May 7, 2020

NIH Welcome

Diana Bianchi, M.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); Cochair, INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Steering Committee

Dr. Bianchi opened the meeting at 8:30 a.m. ET.

The National Institutes of Health (NIH) INCLUDE project has three components:

1. Conduct targeted, high-risk, high-reward basic science studies on chromosome 21 (to be discussed at a workshop in the fall of 2020)
2. Assemble a large study population of individuals with Down syndrome across the lifespan (the topic of a workshop in September 2019)
3. Include individuals with Down syndrome in existing and future clinical trials (the focus of the current workshop)

Thanks to Congress's generosity, NIH funding for research on Down syndrome has increased dramatically in recent years, from \$24.3 million in 2016 to \$86 million in 2019. Much of this increase was due to the congressional appropriation for the INCLUDE project.

NIH plans to create a new agency-wide plan that will update both the 2014 NIH research plan on Down syndrome, [Down Syndrome Directions](#), and the 2018 [INCLUDE Project Research Plan](#). Dr. Bianchi encouraged all participants in this workshop to respond to the NIH request for information ([NOT-HD-20-013](#)) to gather input on updates to NIH research plan on Down syndrome by July 10, 2020.

Workshop Introduction

Laurie Ryan, Ph.D., National Institute on Aging

Dr. Ryan welcomed participants to this virtual workshop, which would cover many aspects of the co-occurring conditions in Down syndrome throughout the lifespan. She then reviewed the themes of the workshop sessions.

Prenatal Treatment: Clinical Trial of the Future?

Diana Bianchi, M.D., NICHD

One reason to consider prenatal treatment for Down syndrome is that atypical development (e.g., slowed growth of the cerebellum) can be seen in the fetus before birth. Furthermore, screening and diagnosis for Down syndrome are part of standard prenatal care, and the more than 30 promising preclinical studies in mice and 26 completed clinical trials of 13 different interventions have not identified any intervention that results in clinical improvement in individuals with Down syndrome.

A personalized approach to prenatal treatment could improve fetal brain growth and connectivity as well as neurocognition. Dr. Bianchi described preclinical studies to compare the phenotypes of the three most

commonly used mouse models of Down syndrome, determine the best endpoints for evaluating therapy, analyze integrated transcriptomes of humans and mice, and perform proof-of-principle experiments using candidate therapies in human cells and mice. The first test molecule, apigenin, achieved its therapeutic effects in mice, and preclinical studies are exploring apigenin further to prepare for a future clinical trial.

Session 1: Pediatric and Developmental Conditions

Cochairs: Priya Kishnani, M.D., Duke University, and Steve H. Abman, M.D., University of Colorado Denver

Cardiopulmonary Conditions

Ashraf Harahsheh, M.D., Children's National Hospital

Children with Down syndrome have higher risks of congenital heart disease, pulmonary hypertension, dyslipidemia, and acquired heart diseases. They also have a lower risk of in-hospital mortality with biventricular repair than other children. However, children with Down syndrome and certain risk factors (e.g., pulmonary vein stenosis, extracardiac anomalies, significant atrioventricular valve regurgitation) have a much higher risk of dying after univentricular repair than children with Down syndrome who do not have these risk factors.

Up to one-third of children with Down syndrome have pulmonary hypertension, regardless of whether they have congenital heart disease. This condition has a multifactorial etiology. For example, children with Down syndrome have higher levels of antiangiogenic factors as well as smaller and fewer alveoli. They are more susceptible to upper and lower respiratory tract infections, which can lead to pulmonary arterial hypertension. These children also tend to be shorter than other children, so a higher body mass index (BMI) might not have the same implications for children with and without Down syndrome.

Research gaps include how best to counsel patients who have Down syndrome and dyslipidemia as well as their families, the types of echocardiogram measurements needed in children with Down syndrome, and therapy for pulmonary hypertension in children with Down syndrome, especially those with congenital heart disease or a single ventricle.

Sleep Conditions

Role of Sleep for Cognitive Development in Down Syndrome

Jamie Edgin, Ph.D., University of Arizona

At least half of children with Down syndrome have serious sleep disturbances, including obstructive sleep apnea (OSA), throughout the lifespan. Sleep should be measured in clinical trials of children with Down syndrome, because it correlates with cognitive and brain function in Down syndrome and could relate to treatment response. Furthermore, sleep status could moderate responses to interventions and side effects, and it correlates with behavior and attention, especially symptoms of attention deficit hyperactivity disorder (ADHD) and executive control. Sleep also correlates with verbal IQ and total vocabulary in children with Down syndrome.

Polysomnography offers the most comprehensive assessment of sleep, and actigraphy can measure sleep-wake patterns over several days. These measures correlate with communication in Down syndrome. Caregiver reports are useful for identifying correlations between sleep and behavior, but they do not address the full spectrum of sleep deficits.

Future types of research could include:

- Studies that use polysomnography, actigraphy, and caregiver reports to measure sleep in natural history, longitudinal, and intervention trials of children with Down syndrome
- Comparisons of in-home polysomnography or abbreviated metrics to laboratory polysomnography outcomes
- Assessments of sleep interventions using developmentally appropriate and sensitive cognitive outcomes
- Studies to determine when in development and how sleep might affect learning
- Consideration of sleep as a moderating factor in all upcoming Down syndrome trials
- Use of sleep as a cognitive and neural endpoint in Down syndrome

Sleep Apnea in Children with Down Syndrome

Daniel Combs, M.D., University of Arizona

OSA is associated with adverse cognitive, quality-of-life, and cardiovascular effects. The prevalence of OSA in people with Down syndrome ranges from 31% in infants to up to 100% in adults. OSA risk factors in children with Down syndrome include anatomic structure and low muscle tone, and adverse effects can consist of lower verbal IQ, adaptive function, verbal fluency, and left ventricular function along with poorer quality of life.

The standard OSA treatments in children with Down syndrome are adenotonsillectomy and, if this procedure is not effective, positive airway pressure (PAP) therapy. Adenotonsillectomy resolves OSA in 90% of typically developing children but less than one-third of children with Down syndrome, although this procedure does reduce OSA severity in the latter population. Hypoglossal nerve stimulation is an emerging treatment that seems promising. However, myofunctional therapy, anti-inflammatory medications, and weight loss do not appear to be effective in children with Down syndrome. Mandibular advancement devices can be used only in individuals who have all of their adult teeth, and their use in individuals with Down syndrome has not been studied. A research priority is rigorous studies of OSA treatment in children with Down syndrome.

Take a Breath: Post-Influenza–Like State in Down Syndrome

Michael Yeager, Ph.D., University of Colorado, Denver

Infectious lung disease accounts for 54% of hospital admissions for persons with Down syndrome, and their average length of admission for this disease is two to three times that of people without Down syndrome. Furthermore, people with Down syndrome have 62 times more respiratory tract infections, and they are much more likely to be hospitalized, be intubated, or die because of their higher risk of acute respiratory distress syndrome. Finally, infectious respiratory disease accounts for more deaths in people with Down syndrome than those with any other medical condition.

In people with Down syndrome, the lungs might be in a chronic state of susceptibility to severe *Streptococcus pneumoniae* pneumonia that is similar to post-viral infection in individuals who do not have Down syndrome. Mouse and cell studies show that similarities include fulminant remodeling, higher interferon (IFN) and interleukin 10 signaling, lower toll-like receptor signaling, upregulation of platelet-activating factor receptors, and immune cell dysfunction.

Infectious Diseases in People with Down Syndrome

Andrew Nowalk, M.D., Ph.D., University of Pittsburgh Children's Hospital

Persons with Down syndrome have a higher susceptibility to infections for many reasons, including immunologic differences (e.g., lower chemotaxis, poor antibody production); cardiac, pulmonary, and gastrointestinal diseases; and anatomic differences in the head, eyes, ears, nose, and throat. Infections, especially in the respiratory tract, continue to be one of the leading causes of death in this population. The risk of aspiration

pneumonia and all other lower respiratory tract infections and the risk of death from these respiratory diseases are dramatically higher in people with Down syndrome.

Dr. Nowalk highlighted some immunologic differences between people with and without Down syndrome. For example, those with Down syndrome have fewer lymphocytes and T and B cells and more CD4 and natural killer cells. These immunologic differences lead to differences in the impact of infections. People with Down syndrome, even if they do not have congenital heart or lung disease and were not born prematurely, have an increased risk of dying from respiratory syncytial virus (RSV). Palivizumab reduces the risk of hospitalization for RSV significantly in people with Down syndrome. Treating all children younger than 2 who have Down syndrome with palivizumab would have a favorable cost–benefit ratio, because it could reduce admission rates by 50%.

Gaps and opportunities related to infectious diseases in people with Down syndrome include:

- Organisms responsible for pneumonia in persons with Down syndrome
- The impact of comorbidities on infectious diseases
- Health disparities and access to care
- Changes in comorbid conditions with age
- Responses to vaccines
- Correlation between Th17 numbers and autoimmunity
- Immune differences and progression to disease
- Sinus disease, health care–related infections, other respiratory viruses, and community-acquired pneumonia in adults with Down syndrome
- Prospective data on RSV prophylaxis
- Management of complicated sinus disease

Janus Kinase (JAK) Inhibition in Down Syndrome: Treating Autoimmunity and Beyond

Joaquin Espinosa, Ph.D., University of Colorado, Denver

More than 60% of adults with Down syndrome have at least one autoimmune condition, and approximately 25% have at least one autoimmune skin condition. Trisomy 21 activates the IFN response, multiple cell types show transcriptional signatures indicating hyperactive IFN signaling, and four of six IFN receptors are encoded on chromosome 21. All three types of IFN use JAK1 or JAK2 for signaling.

One way to “normalize” the IFN response in people with Down syndrome might be to inhibit JAKs by repurposing JAK inhibitors (e.g., ruxolitinib, tofacitinib, baricitinib, upadacitinib) that have U.S. Food and Drug Administration (FDA) approval. These therapies have been tested in clinical trials for conditions that are more common in people with Down syndrome, including alopecia areata, atopic dermatitis, and psoriasis.

Dr. Espinosa is planning a Phase II single-arm clinical trial, funded by the INCLUDE project, of tofacitinib treatment for active autoimmune skin conditions in adults with Down syndrome. This trial will determine the treatment’s safety profile and its impact on immune dysregulation and immune skin conditions.

Leukemia in Children with Down Syndrome: Treading Carefully with Clinical Trials

Jeffrey Taub, M.D., Wayne State University

Children with Down syndrome have a 33% higher risk of acute lymphocytic leukemia and a 150% higher risk of acute myelogenous leukemia (AML) than children without Down syndrome. At least 10% of newborns with Down syndrome have transient abnormal myelopoiesis, a preleukemia condition. After recovery, these infants have a 30% risk of subsequent AML.

Children with Down syndrome and leukemia respond well to AML therapy. However, their risk of toxicity might lead to physician bias against enrolling patients with Down syndrome and leukemia into clinical trials or to offer these patients other therapies. Guidelines for supportive care for patients with Down syndrome are now available. Dr. Taub called for the inclusion of children with Down syndrome in all clinical trials for primary and relapsed leukemia with the same intent to cure as for children without Down syndrome.

Central Nervous System Conditions

Down Syndrome and ADHD

Anna Esbensen, Ph.D., University of Cincinnati

Many features of ADHD in typically developing children, such as an inability to play or take part in leisure activities quietly or difficulty waiting for their turn, are common in children with Down syndrome. Clinicians can have difficulty determining whether behaviors in children with Down syndrome result from intellectual disability or ADHD. ADHD in Down syndrome and typically developing children has similar psychological characteristics, but children with intellectual disabilities and ADHD have different activity behaviors and attention problems. Dr. Esbensen believes that 10% to 45% of children with Down syndrome have ADHD.

In clinical trials in children with intellectual disabilities and ADHD, response rates to stimulants and behavioral treatments ranged from 37% to 75%, but these children had a greater risk of some side effects (e.g., social withdrawal). Although consensus guidelines recommend stimulants as first-line treatment for ADHD in children with intellectual disabilities, most clinical trials in this population have excluded children with Down syndrome, because they have a higher risk of serious cardiovascular events.

Research gaps are as follows:

- How to accurately diagnose ADHD in children with Down syndrome
- Safety and efficacy of stimulant medication for ADHD—would need to address concerns about cardiac safety, given the high rate of congenital heart disease in children with Down syndrome, and differential responses to medication

Cognition in Down Syndrome

Laura Hahn, Ph.D., University of Illinois at Urbana–Champaign

Cognitive skills develop more slowly in children with Down syndrome than would be expected for their chronological age. Many children with Down syndrome also struggle with executive functioning. Clinical trials in children with Down syndrome might need to control for cognition because of its variability in this population. Cognition offers a way to measure change or growth as a result of an intervention, and it can influence other domains of functioning (e.g., learning, literacy, school readiness, social processing). Some cognitive skills, especially those associated with executive function, could be targets for clinical trials.

Interpretation of the results of cognitive measurement in children with Down syndrome can be challenging, because their scores might appear to plateau or decrease over time even when the children are gaining skills, and the lowest possible score might not accurately represent their abilities, because measurements in this range are not very sensitive. One possible solution is to develop z-scores based on deviations in IQ scores that account for performance below the lowest score. Another option consists of raw or growth scores that do not take age-based norms into account, or test batteries could be developed for people with Down syndrome. Measures that can capture changes in development and are linked to functional outcomes would be most clinically meaningful.

Communication and Language Intervention

Speech, Language, Articulation

Ann P. Kaiser, Ph.D., Vanderbilt University

Language development and speech development are typically delayed in children with Down syndrome, resulting in challenges in productive syntax, comprehension of complex syntax, inferential language, and conversational pragmatics. However, these children have strengths in receptive vocabulary, social engagement, affect expression, and visuospatial skills. Almost all children with Down syndrome could benefit from early communication interventions and continuous support for language development.

Only a few randomized controlled treatment trials have included children with Down syndrome. Furthermore, the treatments studied were brief and targeted specific skills, and the studies did not measure the impact on long-term development. Children with Down syndrome do make gains with interventions for speech and language deficits. Phenotype-specific treatments might be more effective than standard treatments in these children.

Factors Affecting Listening and Speech Perception in Children with Down Syndrome

Lori Leibold, Ph.D., Boys Town National Research Hospital

More than half of people with Down syndrome have hearing loss. In children with Down syndrome, chronic otitis media can lead to permanent hearing loss, which can result in less cumulative language exposure, language delays, difficulty hearing speech in noise, and reduced spatial hearing abilities. Other barriers to understanding speech in noisy environments for this population include impairments in executive functioning, weakness in receptive and expressive syntax, and weakness in verbal working memory.

Dr. Leibold is using a supplement to an R01 grant funded by the INCLUDE project to characterize speech-in-speech recognition in 60 children with Down syndrome, identify characteristics that affect speech-in-speech recognition, and identify factors that could improve speech-in-speech recognition in challenging environments.

Improving Augmentative and Alternative Communication for Individuals with Down Syndrome

Krista Wilkinson, Ph.D., Pennsylvania State University

Augmentative and alternative communication (AAC) is a set of tools and interventions that support communication in individuals whose speech does not meet their receptive or expressive communication needs. AAC can benefit individuals with Down syndrome whose speech is difficult to understand as a result of oral dysmorphologies and low muscle tone.

Social stories are brief and simple stories that include text and photographs or line drawings. These stories break down various activities into their components. Video visual scene displays are brief videos that illustrate the steps of activities and offer programmed communication opportunities. Social stories and video visual scenes in clinical trials could help maximize informed consent or assent by promoting participants' understanding of what they will be doing or undergoing. These tools can reduce anxiety and offer opportunities for self-advocacy during the clinical trial because communication opportunities can be built directly into them.

Dr. Wilkinson is using eye-tracking technologies to characterize and optimize visual attending in children with Down syndrome. Small, easily made changes to AAC displays can significantly affect the likelihood that children with Down syndrome will pay attention to distracters, and grouping symbols in space can guide their attention.

Session 1 Q&A

Q: What are the implications of the sex differences in the activity levels in mouse studies for clinical trials?

Dr. Bianchi: Studies that evaluate responses to therapies need to pay more attention to sex.

Q: Most treatments used in adolescents and adults with Down syndrome have not been tested in children or infants because of safety concerns. What are the risks of interventions used in pregnant women?

Dr. Bianchi: The NIH Task Force on Research Specific to Pregnant Women and Lactating Women is developing recommendations for research on safe and effective therapies for pregnant and lactating women.

Q: Have any studies compared language development in children with Down syndrome who have early inclusive social experiences and those who do not?

Dr. Esbensen: Some studies have compared the impact of mainstream and inclusive education programs on academic milestones in children with Down syndrome.

Q: Why are you studying JAK inhibitors in a Phase II and not a Phase IV study?

Dr. Espinosa: Although the trials use FDA-approved drugs, these drugs are approved for other conditions. The trials I described are testing these drugs in people with Down syndrome for the first time. Safety is therefore a primary endpoint, and the impact on skin conditions and immune dysregulation is a secondary endpoint.

Q: Do JAK inhibitors have side effects with long-term use?

Dr. Espinosa: Different JAK inhibitors have slightly different side effects, and some of these agents are associated with a high risk of thromboembolism and herpes zoster infection.

Clinical Trials in Down Syndrome: Strides to Date

Priya Kishnani, M.D., Duke University

Ongoing clinical trials in people with Down syndrome are addressing a wide range of issues, including cognition, dementia, pulmonary disease, OSA, obesity, and leukemia. Challenges for clinical trials of cognition interventions in Down syndrome include interindividual variability, lack of standard endpoints to assess efficacy, and placebo effects. Questionnaires might not capture actual changes, participant skills could be over- or underestimated, and the same informant needs to complete multiple visits. Indirect measurements can be too difficult or too easy, and few test batteries cover the entire age range of interest. In addition, people with Down syndrome might have motor limitations, impulsivity, and limited attention span.

Research opportunities are as follows:

- 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
- Continued collaborations with NIH and the Down Syndrome Medical Interest Group

Panel: Considerations for Participation in Clinical Trials—Pediatric and Adult Populations

Moderator: Priya Kishnani, M.D., Duke University

Frank Stephens, Self-Advocate; Global Down Syndrome Foundation

Mr. Stephens reminded researchers that people with Down syndrome are first and foremost people who need to be treated with respect and not simply as members of research cohorts. Any reports of research results

collected from people with Down syndrome should give prominent credit to these people for their contributions. Members of the Down syndrome community can make a huge difference for themselves and the rest of the world by participating in research, and they should not miss this chance. People with Down syndrome can be the keys to unlocking a cure for many conditions.

[Benjamin Handen, Ph.D., Clinician; University of Pittsburgh](#)

Dr. Handen listed challenges for clinical trials in people with Down syndrome, such as reaching potential participants (especially those in minority communities), identifying outcome measures and assessment tools that can reach the broadest number of potential participants while avoiding floor effects, ensuring consistent use of assessment procedures at different sites, identifying treatment targets, and developing validated tools for use in people of different cultures and people who speak different languages. Differences in laws and regulations can also hamper research on people with Down syndrome.

[Emily Chesnut, Parent and Advocate](#)

Research is so important to advancing knowledge and care in all areas of life. The most significant hurdle for clinical trials with children who have Down syndrome is consent or assent to participation, because the parent needs to explain the importance of the work and its potential long-term benefits as well as the need for invasive procedures. Blood draws can be traumatic. However, Ms. Chesnut's daughter, who has Down syndrome, loves participating in cognitive research.

[Marilyn Bull, M.D., Clinician; Riley Hospital for Children at Indiana University Health](#)

Clinical research in children requires unbiased recruitment and inclusion of people with Down syndrome who have different racial and ethnic backgrounds. Busy clinicians need help to recruit and manage study participants as well as adequate incentives for retention. Parents need compensation for travel and time off work to enable their children to participate in research. Children should play a part in the decision about participating in research, and information about the research should be presented in a way that they can understand.

[Michelle Sie Whitten, Parent and Advocate; Global Down Syndrome Foundation](#)

The Global Down Syndrome Foundation is the largest nonprofit organization in the United States focused on research and medical care for people with Down syndrome. Ms. Whitten listed challenges and related opportunities for clinical trials in Down syndrome. For example, motivating people with Down syndrome and their families or caregivers to participate in research can be challenging. However, research provides opportunities to benefit directly (by gaining medical information, for example).

[Florence Lai, M.D., Clinician; Massachusetts General Hospital and Harvard Medical School](#)

Outreach to optimize research participant can include education (including for professionals and caregivers), educational videos for families and caregivers, and grand rounds. Clinics for adults with Down syndrome are logical settings for introducing the concept of research. Researchers can form teams with local practitioners who

have patients with Down syndrome. Other venues for educating people with Down syndrome and their caregivers include Special Olympics events, and lectures and social media can generate interest in research.

Retention of participants requires making study visits a positive experience by, for example, providing meals, free parking, overnight lodging, and a caring and attentive staff. Staff need to make sure that participants are comfortable by allaying their fears and, when needed, holding their hands.

David Egan, Self-Advocate

Mr. Egan has participated in research since he was 6 months old, and he continues to volunteer for research as an adult. His father and brother also participate in Down syndrome studies. Research throughout the lifespan is critical, not because people need to be cured of Down syndrome but because the syndrome is associated with complex health challenges. Mr. Egan encourages families with children of all ages who have Down syndrome to volunteer for research. Studying the extra chromosomes in these individuals could unlock discoveries that will benefit people with Down syndrome and the larger population.

Kathleen Egan, Parent and Advocate

Encouragement for people with Down syndrome to participate in research throughout the lifespan must begin early. Researchers came to Ms. Egan's home to observe her son when he was an infant, and Ms. Egan learned a great deal from these observational studies. Only a small proportion of individuals with Down syndrome participate in research, and many more need to participate to ensure the collection of high-quality data. Adults with Down syndrome might be more motivated to participate in research if doing so is a family effort. Furthermore, research results must be shared with families and the public.

Hampus Hillerstrom, Parent and Advocate; LuMind IDSC Foundation

The LuMind IDSC Foundation advances research awareness within and outside the Down syndrome community and informs families about the research advances that have already been made and the research advances yet to come. The foundation supports research, including clinical trials. Although parents want new drugs and other types of interventions to be developed, many are reluctant to participate in research that requires invasive processes. Parents need to understand that advances cannot be made without their participation, and this understanding will require mutual trust and respect.

Donna and Wayne Leigh, Parents and Advocates

Ms. Leigh and her husband have joined their 45-year-old son, who has Down syndrome, in studies. Her son is unlikely to benefit from these studies, but people with Down syndrome need to provide baseline information. The family's participation in clinical trials is teaching them about Down syndrome. Mr. and Ms. Leigh are thankful for the opportunity to work with dedicated professionals who are striving to improve the lives of adults with Down syndrome.

Brian Skotko, M.D., M.P.P., Physician and Sibling; Massachusetts General Hospital and Harvard Medical School

Less than 5% of families of people with Down syndrome have access to a Down syndrome specialty clinic. Therefore, 95% of families work with primary care providers who might not be familiar with the latest clinical guidelines, because they see few patients with Down syndrome. The Down syndrome community is eager to participate in research, especially when doing so is easy. An online trial followed 230 families who were assigned to virtual care or usual care from their primary care providers. People with Down syndrome, their caregivers,

and primary care providers were involved in all stages of the study. The virtual clinic was effective and well received, and Dr. Skotko hopes to implement this clinic in the summer.

Q&A

Dr. Kishnani asked the speakers to list one point that they would like to communicate. Dr. Bull said that diversity and racial disparities need attention. Ms. Whitten commented that committees could enable various stakeholders, including self-advocates, to identify ways to approach members of minority communities about research participation. Ms. Egan was pleased to learn about studies on cognition and behavior and not simply the biology and physiology of Down syndrome. Dr. Kishnani stated that clinical trial readiness requires infrastructure and that investments are needed in the next generation of clinicians to make future clinical trials possible. Dr. Skotko agreed, adding that several Down syndrome clinicians are retiring and that their clinics are closing, so their clinical expertise needs to be leveraged. Even if clinicians do not conduct research, they can identify research questions.

Session 2: Nonpharmacological and Lifestyle Interventions

Moderator: *Annie Cohen, Ph.D., University of Pittsburgh*

Lifestyle and Alzheimer's Disease in Down Syndrome: Physical Activity and Cognitive Stimulation

Sigan Hartley, Ph.D., University of Wisconsin–Madison

Most individuals with Down syndrome have evidence of early Alzheimer's disease pathology by their 40s, and approximately half have clinical dementia by age 55. However, they begin accumulating beta-amyloid plaques and develop clinical dementia at different ages. The Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS) has collected lifestyle and biomarker data using imaging and tests of cognitive function and dementia. The data show significant associations between time spent in sedentary activity and cognitive function in adults with Down syndrome who did not have dementia. Adults with Down syndrome who had more complex employment showed better results for motor planning and coordination, executive functioning, and attention than those with less complex employment.

Dr. Hartley and her colleagues want to determine how to train the attention of children with Down syndrome and maintain it longer. They are considering interventions used in other populations, such as people with autism spectrum disorder, that might be appropriate for children with Down syndrome.

Music and Social Engagement: Research and Future Directions for Individuals with Down Syndrome

Miriam Lense, Ph.D., Vanderbilt University

Social communication uses predictable, rhythmic behaviors, and individuals are sensitive to the timing of social engagement from infancy. Examples of rhythm and timing in social communication include speech rhythm, back-and-forth conversations, and coordination of gestures and facial expressions with speech. Young children engage in many rhythmic social interactions with caregivers by, for example, coordinating their facial expressions and vocalizations.

Dr. Lense is exploring the roles of music in social engagement and social communications. For example, she is using singing as a tool to study the rhythms of social interaction. Music and rhythm can also be used to facilitate speech production skills. One of Dr. Lense's studies is exploring music engagement and family well-being in children with Down syndrome or other disabilities.

Session 2 Q&A

Dr. Cohen commented that infants and children with Down syndrome now undergo early interventions, and many interventions are provided in schools. She asked how to address the variability in stimulation received by children with Down syndrome in research. Dr. Hartley replied that stimulation does vary in adults with Down syndrome by region, type of employment, and quality of adult day programs. This variation needs to be captured to advocate for policies that will change the amount of cognitive stimulation or physical activity to which adults with Down syndrome are exposed.

Session 3: Adult and Aging Conditions

Cochairs: Annie Cohen, Ph.D., University of Pittsburgh, and Michael S. Rafii, M.D., Ph.D., University of Southern California

Challenges to Defining Obesity in Down Syndrome

Andrea Kelly, M.D., Children's Hospital of Philadelphia

OSA, which is common in people with obesity and those with Down syndrome, may exacerbate insulin resistance and is associated with higher blood pressure, dyslipidemia, and neurocognitive dysfunction. Another condition whose risk increases with obesity is diabetes, which could perpetuate neurocognitive issues in adults with Down syndrome.

The calculation of BMI relies on the ratio of weight to height, but it does not take body proportions into consideration. Use of BMI might lead to misclassification of obesity in individuals with Down syndrome, who tend to be shorter and have shorter legs than people without Down syndrome. Although the risk of obesity-related cardiovascular outcomes is lower in adults with Down syndrome, approximately 10% of these adults have heart disease, and 10% of deaths in this population are attributable to heart attacks. Furthermore, although men with Down syndrome seem to be protected from heart disease, the same is not true for women.

More data are needed on the relationship of BMI to dementia, Alzheimer's disease, OSA, and musculoskeletal issues in Down syndrome. An evidence-based definition of obesity in Down syndrome would also be useful. Longitudinal studies should assess the evolution and emergence of comorbid conditions, and sex and racial differences should be studied.

Central Nervous System Conditions

Alzheimer's Disease and Other Central Nervous System Disorders

Michael S. Rafii, M.D., Ph.D., University of Southern California

People with Down syndrome have a higher risk of vision and hearing problems, cerebrovascular disease, and Alzheimer's disease dementia. More than 83% of individuals with Down syndrome have vision problems, including cataracts, and at least one-third have hearing loss. In addition, 6% of children and 9% of adults with Down syndrome have seizures, and those older than 45 years with new-onset seizures are more likely to develop Alzheimer's disease. Conditions that can increase the risk of stroke in persons with Down syndrome include congenital heart disease, hypercoagulation disorders, moyamoya disease, and cerebral amyloid angiopathy.

A research gap is the neuropathology of Alzheimer's disease in Down syndrome. Many steps in this pathway are potentially druggable. Clinical guidelines are needed for identifying Alzheimer's disease and dementia in adults with Down syndrome.

Regression: A Review of Available Literature and Research Gaps

Michelle Palumbo, M.D., Massachusetts General Hospital

Regression in Down syndrome is typically characterized by a decline in functioning that often entails significant deterioration in or loss of skills of daily living, language, behavior, and motor function. In many cases, the onset of symptoms follows psychosocial precipitants, such as life events or medical problems.

Catatonia is defined as three or more of a long list of symptoms, including stupor, catalepsy, and mutism. First-line treatment typically consists of high doses of benzodiazepines, although electroconvulsive therapy can also be effective in patients who cannot tolerate lorazepam.

The available scientific literature consists of case reports, case series, and case-control studies that show variable regression symptoms, courses, and treatments. No treatment studies have been conducted in adults with Down syndrome.

Session 3 Q&A

Q: Have any studies of obesity evaluated siblings or parents as control group members?

Dr. Kelly: My coinvestigators conducted such a study perhaps 20 years ago.

Q: Have any studies identified the vitamin supplements that are most important for people with Down syndrome?

Dr. Kelly: I am not aware of such studies, but I have not examined that literature.

Day 2: Friday, May 8, 2020

Session 4: INCLUDE Clinical Trial Readiness (R21) and Clinical Trial (R61/R33) Grants

Session Moderator: Laurie Ryan, Ph.D., National Institute on Aging

Clinical Trial Readiness (R21) Grants

Epigenetic Silencing of Trisomy 21

Volney L. Sheen, M.D., Beth Israel Deaconess Medical Center and Harvard Medical School

Dr. Sheen has modified CRISPR-Cas9 to investigate the development of neurons and astrocytes in cortical organoid cultures derived from induced pluripotent stem cells of people with Down syndrome. He is also using this modified gene-editing technique to assess the impact of HSA21 by silencing it in cells from patients with Down syndrome. In addition, the study is examining mouse models to track cell type-specific transcriptomic changes and gene expression abnormalities over the lifespan.

Using Wireless Functional Near-Infrared Spectroscopy (fNIRS) to Study the Neural Correlates of Executive Function and Sleep Impairment in Down Syndrome

Nancy Raitano Lee, Ph.D., Drexel University

This study is characterizing executive function and prefrontal cortical function in youth with Down syndrome who have varying degrees of sleep disturbance. The study is also testing the feasibility of a child-friendly neuroimaging modality, fNIRS, in 66 children with Down syndrome and typically developing controls. A final

objective is to evaluate the effects of Down syndrome and sleep disturbance measured with actigraphy on prefrontal neuro-efficiency during completion of a psychometrically sound executive function test battery.

Acceptability and Performance on In-Home Polysomnography in Youth with Down Syndrome
Ignacio Tapia, M.D., Children's Hospital of Philadelphia

The testing required to diagnose OSA in children and adults with Down syndrome imposes duress on patients and families, is expensive, and is not always well tolerated. Dr. Tapia's study is assessing the tolerability, family-reported perceptions and experiences, and feasibility of in-home polysomnography in 35 participants with Down syndrome ages 10–20 years. The study is also evaluating the diagnostic accuracy of this approach for diagnosing moderate to severe OSA.

Measures of Pulmonary Health in Children with Down Syndrome
Emily DeBoer, M.D., University of Colorado Denver

The study's short-term goal is to identify accurate and feasible measures of lung function and airway inflammation for use in rigorous clinical trials of interventions to improve the pulmonary health of children with Down syndrome. The study's aims are to determine the effect of aspiration on lung function, inflammatory markers, respiratory symptoms, and quality of life in 75 children aged 3–18 years with Down syndrome. Enrollment, which was to begin in March 2020, has been postponed because of the COVID-19 outbreak.

Early Risk for ADHD Symptoms in Young Children with Down Syndrome
Deborah Fidler, Ph.D., Colorado State University

Little is known about the mechanisms underlying the risk of ADHD and its symptoms in children with Down syndrome. The objectives of this study are to identify early risk factors associated with ADHD symptoms in young children with Down syndrome and to improve the early detection and treatment of ADHD in this population. The study's first wave will assess cognitive control and biomedical risk in 76 infants with Down syndrome. In the second wave, the focus will be on evaluating executive function, sleep, and biomedical risk in the children from the original cohort who have ADHD symptoms at ages 4–5.

Bronchus-Associated Lymphoid Tissue (BALT): Friend or Foe in Down Syndrome?
Michael Yeager, Ph.D., University of Colorado Denver

The investigators hypothesize that reduced BALT biogenesis and function in Down syndrome imparts immune suppression and predisposition to respiratory infection. The study is determining whether type I IFN antagonism restores biogenesis and obviates lung immune suppression and susceptibility to *S. pneumoniae* respiratory infection in the Dp16 mouse model of Down syndrome. A second aim is to determine whether direct modulation of BALT biogenesis obviates lung immunosuppression and susceptibility to *S. pneumoniae* respiratory infection in the Dp16 mouse model.

Down Syndrome, Early Cataracts, Eye Diseases, and Beta-Amyloid Conformers
Geoffrey Chang, Ph.D., University of California, San Diego

Cataracts are common in adults and children with Down syndrome, and reports of the contributions of beta-amyloid to cataracts are conflicting because of the probes used for detection. This project's first aim is to discover, produce, and validate antibodies (nanobodies) against different conformations of beta-amyloid protein conformer species. For the second aim, the investigators will test and validate their nanobody panel using eye

tissues and lenses from Alzheimer’s disease mouse models that recapitulate Down syndrome. The hope is to ultimately use the findings to treat cataracts with eye drops.

Clinical Trials Development (R61/R33) Grants

Medications for OSA in Children with Down Syndrome

Daniel Combs, M.D., University of Arizona

In the R61 phase, this study will evaluate the short-term efficacy of high and low doses of atomoxetine and oxybutynin treatment for 4 weeks for OSA and the treatment’s effect on health-related quality of life in 61 children with Down syndrome and OSA. The investigators hope to open this study for recruitment in June 2020. In the R33 phase, a 6-month, open-label clinical trial will evaluate the long-term efficacy of this treatment for OSA and its effects on both health-related quality of life and neurocognition.

Evaluating Assessment and Medication Treatment of ADHD in Children with Down Syndrome

Anna Esbensen, Ph.D., University of Cincinnati

The proportion of children with Down syndrome and ADHD who are treated with stimulant medication (the most effective ADHD treatment) is low. The reasons might include uncertainty about how to accurately diagnose ADHD in this population and the lack of clinical trials examining the safety and efficacy of stimulants in this population. Dr. Esbensen will conduct a triple-blinded clinical trial of methylphenidate in 30 children aged 6–17 years who have Down syndrome and ADHD to determine the optimal dose for the larger R33 clinical trial. The R61 trial will assess the short- and long-term safety and efficacy of methylphenidate treatment for remediating cognitive, behavioral, and functional impairments in children with Down syndrome and ADHD.

Safety and Efficacy of Tofacitinib for Autoimmune Skin Conditions in Down Syndrome

Joaquin Espinosa, Ph.D., University of Colorado, Denver

This Phase II, single-arm, open-label trial will evaluate treatment with tofacitinib, a JAK inhibitor, for 16 weeks, with 2-week follow-up, in adults aged 18–60 years with Down syndrome and an active autoimmune skin condition (alopecia areata, psoriasis, vitiligo, hidradenitis suppurativa, or atopic dermatitis). The trial will determine the treatment’s safety profile and impact on immune dysregulation, immune skin conditions, cognition, and quality of life.

Trial-Ready Cohort—Down Syndrome

Michael S. Rafii, M.D., Ph.D., University of Southern California

This study is forming a trial-ready cohort of 120 adults (aged 35–55 years) with Down syndrome who do not have dementia. Participants will undergo longitudinal cognitive and clinical assessment, genetic and biomarker testing, imaging, and biospecimen collection. The study will analyze the relationships between cognitive measures and biomarkers of Alzheimer’s disease to identify endpoints that best reflect progression of this disease for clinical trials in adults with Down syndrome.

Positive Airway Pressure for the Treatment of the OSA Syndrome in Children with Down Syndrome

Ignacio Tapia, M.D., Children’s Hospital of Philadelphia

The R61 phase consists of a mixed-methods study to identify factors that affect the acceptability and use of PAP to treat OSA in children with Down syndrome and identify family-centered outcomes to inform the R33 clinical trial. The study will use an intensive behavioral intervention consisting of cognitive and behavioral strategies,

operant learning, contingency management, motivational enhancement, and engagement strategies involving caregivers. In the R33 phase, the investigators will assess the effects of PAP adherence on quality of life, neurobehavioral outcomes, and health care utilization.

Session 5: Clinical Trial Infrastructure

Moderator: Steve Abman, M.D., University of Colorado Denver

Down Syndrome Patient Registries

Steve Abman, M.D., University of Colorado Denver

The Pediatric Pulmonary Hypertension Network (PPHNet) is a multidisciplinary network of clinical pediatric pulmonary hypertension centers that has created a longitudinal database to determine the natural history of diseases, comorbidities, and benchmark approaches. Dr. Abman has analyzed data in the registry on 157 patients with Down syndrome. Of these children, 69% had pulmonary arterial hypertension and 21% had primary lung disease. This analysis offers an example of the lessons that can be learned from registries.

DS-Connect®: The Down Syndrome Registry

Sujata Bardhan, Ph.D., NICHD

NIH leads the Down Syndrome Consortium, which is made up of several NIH Institutes and Centers, professional societies, foundations, and advocacy organizations. The consortium's first activity was to create DS-Connect, the Down syndrome registry, to collect demographic and health information from self-advocates, family members, and providers. The resulting cohort can be used for natural history and biomarker studies.

Families can use the registry to store all of the patient's medical history in a single place. Families, researchers, providers, and others can view all of the survey questions and deidentified responses. The site also offers a list of health care providers who care for adults and children with Down syndrome as well as a set of health care guidelines. A new portal will provide information from ClinicalTrials.gov about NIH-funded clinical trials that are recruiting individuals with Down syndrome, and researchers can submit applications to use DS-Connect to recruit participants for their studies.

Pediatric Trials Network (PTN): Clinical Pharmacokinetics and Safety Trials in Down Syndrome

Mara Becker, M.D., Duke University

NICHD launched the PTN to create an infrastructure for trials that improve pediatric labeling and child health by offering NIH prioritization for sponsorship of research on off-patent drugs in children and 6 months of patent exclusivity for pediatric studies. The PTN-Down Syndrome is a pediatric trial infrastructure to study off-patent therapies for improving the care of children with Down syndrome under the umbrella of the PTN. The project includes a pediatric clinical trials network for research on children with Down syndrome as well as a training program for clinical researchers.

The Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care is evaluating the pharmacokinetics of understudied drugs (guanfacine, dextroamphetamine/amphetamine, sertraline, and risperidone) administered to children with Down syndrome as standard care. This project will also train Down syndrome sites in clinical pharmacology research and clinical trials, identify the unique challenges for these patients and the clinicians that treat them, build relationships with thought leaders and staff, and collect pharmacokinetic and pharmacodynamic data on children with Down syndrome in real-world settings.

Pediatric Heart Network (PHN)

Julie Miller, M.P.H., HealthCore

The PHN is made up of seven sites in the United States, Canada, and South Korea along with a data coordinating center. The network has conducted Phase I, II, and III clinical trials; quality improvement studies; and observational studies. The PHN also offers a career day to fellows and junior faculty members from network sites to address clinical research design, case studies, and research funding.

With INCLUDE funding, the PHN will evaluate the impact of congenital heart disease on learning and development in 160 children with Down syndrome who have undergone complete atrioventricular septal defect repair and 160 children with Down syndrome who do not have major congenital heart disease. The study will compare neurodevelopment and behavioral outcomes between the two groups, identify predictors of neurodevelopment and behavior, and create a biorepository for future investigation of genetic predictors of neurodevelopment and behavioral outcomes in children with Down syndrome.

Alzheimer's Clinical Trial Consortium (ACTC)-Down Syndrome (DS)

Michael S. Rafii, M.D., Ph.D., University of Southern California

The ACTC-DS leverages the ACTC infrastructure to conduct Alzheimer's disease clinical trials in adults with Down syndrome. The consortium offers training in clinical trials in Alzheimer's disease. It has 15 sites in the United States and Europe, and it will collaborate with other consortia conducting research in people with Down syndrome.

The ABC-DS is made up of the Neurodegeneration in Aging Downs and Alzheimer's Disease in Down Syndrome projects. This consortium is identifying neuropsychological measures of cognitive decline as well as imaging, blood-based, and genetic biomarkers associated with the transition from normal aging to mild cognitive impairment and clinical dementia in adults with Down syndrome. More than 400 participants have enrolled in the study, and all of their baseline data are being made available online.

Session 5 Q&A

Q: How can a registry's infrastructure be sustained?

Dr. Rafii: For one registry we plan to create, we hope to obtain funding from NIH, Alzheimer's disease foundations, and industry for clinical trials.

Q: What is the role of FDA in the registries?

Dr. Rafii: The INCLUDE Clinical Trial Readiness Working Group has discussed bringing researchers and FDA together to agree on FDA requirements for clinical trials.

Q: What types of congenital heart disease do children with Down syndrome in PPHNet have?

Dr. Abman: Children with Down syndrome have high blood flow into the lung that might accelerate the development of pulmonary hypertension. Studies will continue to use PPHNet to explore whether children with Down syndrome have lesion-specific differences.

Q: How can registries be linked?

Dr. Bardhan: DS-Connect uses a global unique identifier that can be used to link its data with data from any database that collects the same types of data and uses the same software to generate unique identifiers for participants. An INCLUDE working group is discussing codes that can be used to link data from different registries.

Q: Do people with Down syndrome have an increased susceptibility to COVID-19?

Dr. Bardhan: We have added COVID-19 questions to DS-Connect. These data might provide infection and recovery data on people with Down syndrome.

Ms. Miller: PHN investigators hope to explore COVID-19 in children with Down syndrome, and a meeting will determine what contributions the network might make on this issue.

Session 6: Recruitment into Clinical Trials

Session Moderator: Michael S. Rafii, M.D., Ph.D., University of Southern California

Recruitment of Diverse Populations: Lessons Learned and Implications for Down Syndrome Research

Annie Cohen, Ph.D., University of Pittsburgh

Connectomics in Brain Aging and Dementia, a longitudinal neuroimaging and cognition study, will recruit 400 participants aged 50–89 years who have normal cognition or Alzheimer’s disease. To date, the study has enrolled 237 participants, of whom 52% are African American and all are female. Strategies that helped this study achieve its recruitment goals include the use of Pitt+Me, an online registry designed to reach communities that do not typically participate in research. The study also conducts targeted recruitment using social media and bus advertisements. Community engagement centers build long-term relationships with communities through such activities as monthly dinners and opportunities to meet investigators on an ongoing basis.

Flexibility in research strategies has been key. Study personnel remind participants to report any changes in their contact information. Participants cannot always take time off work to come to a research center, so the center must offer weekend and evening appointments. The study also uses trusted locations, such as community health centers, for research procedures that do not need to be done at a research center.

Down syndrome researchers seeking to recruit members of underrepresented communities can develop a community advisory board to identify barriers to research participation in people with Down syndrome. Focus groups can offer information on willingness to undergo various research procedures and on research needs in the Down syndrome community. Because of COVID-19, investigators need to communicate through remote strategies that might help them reach individuals they might not normally include in studies. Educational materials should be refined based on input from the focus groups, and these materials should be disseminated to the target communities through social media and community outreach events.

Consent

Recruiting Adults with Down Syndrome and Obtaining Their Consent to Enroll in Clinical Trials: State-Specific Policies and Requirements

Sharon Krinsky-McHale, Ph.D., New York State Institute for Basic Research in Developmental Disabilities

Dr. Krinsky-McHale described policies and regulations pertaining to research in individuals with intellectual or developmental disabilities. Many of these requirements were developed to protect individuals who are at risk of exploitation from research because of their limitations and social powerlessness.

New York State developed strict regulations regarding the participation of individuals with intellectual or developmental disabilities in research in reaction to the Willowbrook hepatitis study in the 1960s. This study injected children who lived at the Willowbrook State School, most of whom had severe disabilities, with live hepatitis virus after their parents were told that the injection could give their children immunity from the disease. At the time, the school accepted new residents only if they enrolled in this study.

New York State subsequently implemented the Willowbrook Permanent Injunction, which has been widely interpreted to apply to any New York State resident with intellectual or developmental disabilities. The standard only permits behavior modification, research, or hazardous or experimental treatment after approval from the resident, a caregiver, or a three-person special committee. The standard prohibits physically intrusive, chemical, or biomedical research or experimentation without a federally approved assurance of compliance with regulations for the protection of human subjects.

Until 2012, individuals with intellectual or developmental disabilities in New Jersey could not participate in any research without a court-appointed guardian ad litem. Currently, the only research that can be done with this population consists of studies that use minimal-risk procedures.

Obtaining Consent or Assent

Benjamin L. Handen, Ph.D., University of Pittsburgh

ABC-DS collects consent or assent for a variety of procedures, including blood draws, genetic tests, and various scans. Some but not all of the procedures are minimal risk. For the reasons Dr. Krinsky-McHale discussed, individuals living in New Jersey cannot participate in this study.

Before starting the consent process, families complete a detailed telephone screening process that covers such issues as history of scans and problems with blood draws, physical and cognitive limitations, and legal issues. During the call, staff members explain what the study involves and why their participation is important.

During the consent visit, the study team uses many visual aids to explain the study to participants and caregivers. Participants are told that they can leave the study at any time. Staff watch a 12-minute video with the caregiver and person with Down syndrome. The video describes the study procedures, and staff answer questions after the video ends. In Pennsylvania, adults with Down syndrome are assumed to be competent to sign consent forms for research unless they do not understand the consent materials. In the latter case, a proxy signs the consent form and the person with Down syndrome provides assent.

Session 6 Q&A

Q: Has progress been made in the use of remote consent processes?

Dr. Handen: Remotely assessing the understanding of an adult with Down syndrome would be challenging.

Dr. Krinsky-McHale: We send forms for caregivers or the person with Down syndrome to sign, so remote consenting would not be very different. However, recruiting new participants remotely would be challenging.

Dr. Cohen: When a study is introduced using flip books, study personnel can get to know the participant and family before these individuals come to the hospital, and these individuals can become comfortable with study personnel before they meet one another in person.

Dr. Rafii: Video chats could be scheduled for people who have learned about a study through social media and would like more information. Such conversations could lay the groundwork for future in-person communications.

Q: Does a central repository exist of legal statutes pertaining to the participation of individuals with Down syndrome in research?

Dr. Krinsky-McHale: Such a database would be valuable to researchers who want to determine the consent process they need to use for individuals living in different states. This information is difficult to find.

Q: How do investigators share study results with participants?

Dr. Handen: The types of information shared are determined by local institutional review board requirements. The University of Pittsburgh does not share positron emission tomography scan results because these scans are considered experimental and their meaning is not clear. However, investigators do inform participants and their primary care providers of significant magnetic resonance imaging (MRI) findings.

Dr. Krinsky-McHale: We also share MRI results but not neuropsychology findings unless participants or families ask for that information.

Reports from Breakout Sessions

The presentations in this session summarized two recent online breakout sessions.

Pediatric Issues and Considerations: Gaps and Opportunities in Clinical Trials in Children and Adolescents with Down syndrome

Steve Abman, M.D., University of Colorado Denver

Breakout session participants discussed the rationale for developing a multicenter clinical trial consortium for studies of children with Down syndrome. Such a consortium could address the limited understanding of disease mechanisms for many aspects of Down syndrome, the heterogeneity of comorbidities, the lack of multidisciplinary care beyond major centers, and the small number of patients at each center to provide the samples needed for multicenter trials.

Most current management strategies and preliminary data come from case reports or adult data, and clinical guidelines and age-relevant and disease-specific endpoints to assess clinical course and treatment response are lacking. Preliminary disease data on the disease mechanisms being targeted are needed. The network should bring together basic scientists, families, foundations, and companies.

A registry is needed to support better study designs and establish precise phenotypes and endotypes, natural history, and long-term outcomes. The database would characterize disease prevalence and support power analyses for clinical trials, and its data should be linked to a biorepository. In addition, training and experience conducting clinical research will be critical to help the next generation of clinical scientists develop strong clinical trial expertise in Down syndrome.

Adult Issues and Considerations: Gaps and Opportunities in Clinical Trials in Adults with Down syndrome

Annie Cohen, Ph.D., University of Pittsburgh, and Michael S. Rafii, M.D., Ph.D., University of Southern California

The topic that drew the most attention from this breakout group was recruitment. Recruitment challenges include the following:

- The legally authorized representatives of adults with Down syndrome often change, for example, from an aging parent to a sibling.
- Adults living in group homes might lack a legally authorized representative or informant who can consistently provide information on the study participant.
- Diverse populations sometimes do not have trust in research.

Recruitment opportunities include:

- Working with self-advocates to engage participants throughout the research process
- Using simple and accurate information that can be understood by individuals with Down syndrome and their families
- Leveraging the Down syndrome community's interest in Alzheimer's disease to recruit members of this community into Alzheimer's disease clinical trials

- Leveraging adult Down syndrome clinics, which are often trusted sources of information

Logistical challenges include differences in state regulations and policies regarding informed consent and the need to minimize the number of clinic visits and burden of participating in clinical trials. The best methods to assess target engagement in adults with Down syndrome need to be identified, and whether the same measures can be used in adults with Down syndrome as in trials of typical adults must be determined. Measures that can detect cognitive decline at an early stage, are sensitive to change, and can be used in individuals with more severe intellectual disability are needed. Safety-related challenges include the need for experienced sites to promptly identify and manage adverse events in studies in which participant reporting of these events might not be straightforward. In addition, clarity is needed on a regulatory pathway for new drugs for this population.

Breakout Session Reports Q&A

Q: How can clinical trial centers serve the Down syndrome community?

Dr. Abman: This is the role of many NIH-supported Clinical and Translational Science Awards, which support interactions with other sites in their regions and encourage community engagement in research.

Q: How should overall study results be returned to study participants?

Dr. Abman: Investigators have an ethical responsibility to make sure that participants receive study results.

Dr. Kishnani: All clinical trials, regardless of whether their results are positive, should be required to disseminate their results beyond the clinical study report to ensure that investigators and the broader field have access to these results.

Dr. Rafii: ClinicalTrials.gov has reporting requirements for clinical trials, and the NIH mandate for funded studies to publish their data within a year of data lock is helpful. However, industry-sponsored studies are not required to report their results.

Closing Remarks

Gary H. Gibbons, M.D., National Heart, Lung, and Blood Institute; Cochair, INCLUDE Steering Committee

INCLUDE started just 2 years ago because of advocacy from the community, NIH commitment, and generous support from Congress. This program is developing a portfolio that spans the spectrum and includes clinical research. Important insights have been gained from INCLUDE studies, and the capacity building (especially training for a cadre of investigators who will advance the field) that the program has accelerated provides confidence that this research trajectory will enhance the lives of people with Down syndrome.

The COVID-19 pandemic provides important reminders of the need to collaborate, and the discussions at this meeting have reinforced this message. The meeting showed the importance of outreach, engagement, and trust. Studies must include diverse participants and address research questions through partnerships. The history of excluding people with Down syndrome from clinical trials must end, and NIH is committed to changing this practice.

Dr. Gibbons thanked the organizers, speakers, and participants for their contributions. 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 Down syndrome.

Dr. Gibbons closed the meeting at 2:21 p.m.