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Conference Proceedings

Down syndrome: National conference on patient registries, research databases, and biobanks ☆

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ABSTRACT

A December 2010 meeting, "Down Syndrome: National Conference on Patient Registries, Research Databases, and Biobanks," was jointly sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) in Bethesda, MD, and the Global Down Syndrome Foundation (GDSF)/Linda Crnic Institute for Down Syndrome based in Denver, CO. Approximately 70 attendees and organizers from various advocacy groups, federal agencies (Centers for Disease Control and Prevention, and various NIH Institutes, Centers, and Offices), members of industry, clinicians, and researchers from various academic institutions were greeted by Drs. Yvonne Maddox, Deputy Director of NICHD, and Edward McCabe, Executive Director of the Linda Crnic Institute for Down Syndrome. They charged the participants to focus on the separate issues of contact registries, research databases, and biobanks through both podium presentations and breakout session discussions. Among the breakout groups for each of the major sessions, participants were asked to generate responses to questions posed by the organizers concerning these three research resources as they related to Down syndrome and then to report back to the group at large with a summary of their discussions. This report represents a synthesis of the discussions and suggested approaches formulated by the group as a whole.

1. Introduction

Down syndrome (DS) is the most common genetic cause of intellectual and developmental disabilities (IDD) and results in most individuals from triplication of the smallest human autosome, chromosome 21 (Trisomy 21). DS affects individuals of all ethnic and ancestral groups, and its birth prevalence in the U.S. population is about 1:691 live births (http://www.cdc.gov/ncbddd/birthdefects/data.html) [1]. Although many people have discussed the creation of contact registries, research databases, and biobanks to speed the pace of discovery in DS research, the great expansion of technology and private investment in research in the past ten years has renewed considerable interest in these resources among families, clinicians,

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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advocates, and researchers who study DS. The purpose of this conference was to bring together all four communities to discuss the best strategies to enhance an increasing transition from basic and clinical research to clinical trials and rational translational therapeutic approaches to ameliorate the effects of DS in individuals of all ages, ancestry, and socioeconomic status. In part, the mechanism chosen was to provide the DS community with examples of existing successful models of registries, databases, and biobanks, as these do not exist at a national level for people with DS. This need for research resources was made apparent by the objectives of the NIH Research Plan on Down Syndrome published in 2007 (http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5695).

This 2-day conference was sponsored jointly by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH), and the Global Down Syndrome Foundation (GDSF)/Linda Crnic Institute for Down Syndrome and held in Bethesda, MD. The focus of this conference was to discuss three types of organized support for research: contact registries, research databases, and biobanks. Contact registries often are formed and maintained by organizations and researchers to facilitate participation by individuals in research projects or clinical trials. Often one significant outcome of a contact registry is to facilitate communication among families and self-advocates who share information about their condition with one another. Research databases are created by researchers and clinicians as outcomes of specific projects that have a defined question or to gather standardized longitudinal information about the natural history of a given condition. Biobanks consist of repositories of samples of tissues, organs, or fluids collected from individual donors during life or by donation after death.

The birth prevalence of DS has demonstrated some increase in the past several decades in Western countries, most likely related to the increase in maternal age [2]. In addition, the number of newborns with DS who survive infancy and childhood with DS has also increased greatly. Overall, people with DS live longer, enjoy better quality of life, and integrate as productive members of the workforce of many societies around the world [3–5].

The meeting began with welcoming remarks from Dr. Yvonne Maddox (NICHD) and Dr. Edward McCabe (Linda Crnic Institute for Down Syndrome). The question presented to the group at large was not whether, but how best, to create a contact registry, a research database, and a biobank to facilitate DS research and treatment. Attendees were encouraged to plan for a future that would advance DS research and improve the lives of individuals with DS and their families.

Two speakers then presented their experiences with issues relevant to the creation of registries that encourage participant involvement in research activities. Dr. Sonja Rasmussen (Centers for Disease Control and Prevention (CDC)) provided the CDC perspective on the use of surveillance data to inform public health action [6]. Population-based surveillance is crucial to CDC's activities because it defines the magnitude of specific health problems and their risk factors and creates a source of participants for future studies, but there can be challenges in establishing a surveillance system for individuals with disabilities [7], including those with DS. Health surveillance systems use a number of different study designs that must be balanced (e.g., few people with considerable individual data or more people with fewer data entries per person). These designs are most useful when they are population-based because they then consist of a representative sample of individuals selected from a defined source population and are not a selected group who might have different access to health care or different demographics than the total source population of interest.

Surveillance registries may be population-based with active ascertainment and multiple data sources within the same geographic area for a single condition, like DS, or multiple conditions; or they may use hospital data from a multi-state area to monitor the health care received for a specific condition to lessen the incidence of premature death and disability resulting from that condition. Data from population-based surveillance systems have allowed us to recognize that people with DS now live longer than in the 1980s, but racial disparities persist with regard to longevity [8,9]. In addition, surveillance data have demonstrated that children with DS are more likely to receive a diagnosis of an autism spectrum disorder than children in the general population [10].

Four key issues to consider when setting up a surveillance system for DS are: (1) the system of data collection, (2) the amount and type of data to collect, (3) how to manage and maintain the data, and (4) how to ensure patient confidentiality. Decisions on these key issues depend on the goals and objectives of the surveillance system.

Dr. Roger Reeves (Johns Hopkins University School of Medicine) and later in the day, Dr. Stephanie Sherman (Emory University), provided overviews of their participation in a September 2010 meeting on DS Registries sponsored by the National Down Syndrome Society (NDSS) in Washington, D.C. Dr. Reeves reported on two of the four breakout groups: Design and Governance & Ethics, with the other two being Stakeholder Engagement and Resources. Dr. Sherman provided additional details from the discussion of the Design group.

The Design workgroup's overall design philosophy was tripartite: to build trust, to be transparent, and to begin small and build with time. It recommended two goals to achieve by September 2012. The first was to implement a simple version of a national DS contact registry and begin its pilot-testing. Implementing the registry would involve developing content, data control guidelines, governance, and marketing, as well as potential strategies for achieving these. The registry could contain information such as contact information, availability for clinical research projects and basic demographics to determine eligibility. Of three possible methods of data entry, curation, and storage discussed, all require data verification but vary based on the process of data entry. For effective marketing of the registry to prospective registrants, people with DS and their families must understand the importance and potential risks of the registry. Successful marketing to scientists and clinicians requires that the registry have scientific credibility. Governance is necessary to ensure the equitable use of data for approved projects and to maintain transparency. A steering or executive committee would manage overarching concerns, such as finances, administration, marketing, and data access, and a project review committee would review project applications and allow access to the registry.

The Design workgroup recommended a second goal for the upcoming year: to initiate a Down Syndrome Centers of Excellence Clinical Consortium that would incorporate clinicians and researchers. Activities for the first year should focus on specifying the consortium's goals, infrastructure, membership, and other basic characteristics.

One needs to confirm parents' and self-advocates' interest in a registry before moving forward. Since a registry has the potential to be misused or administered incorrectly, care must be taken in its creation. A “graduated functions” model for the registry, which would allow for baseline functionality and the addition of more complexity as needed, might be useful for building consensus while creating a registry of sufficient functionality. The platform chosen for a registry should serve the multiple needs of clinicians and investigators as well as those of all users.

The Governance & Ethics workgroup highlighted some of the topics that must be considered when creating a registry. These include informed consent procedures, especially for individuals who will be brought into the national registry from another registry; rules for access; and data/information ownership. This committee also emphasized that every interaction connected to the registry will require some level of governance. This group agreed to continue to work on developing basic demographic elements that should be collected in such a DS registry.

2. Patient registries

Three presentations focused on examples of successful patient registries that already exist and the models upon which they are built.

Contact registries can benefit clinical research by providing accessible, current, high-quality data that can help researchers plan clinical trials and enroll participants into trials. Ms. Sharon Terry (Genetic Alliance) discussed the Genetic Alliance Registry and Biobank (GARB; www.geneticalliance.org). Dr. Petra Kaufmann (National Institute of Neurological Diseases and Stroke (NINDS)/NIH) described several registries created for the study of neurological disorders affecting children and adults. Dr. Leonard Abbeduto (University of Wisconsin) discussed the creation of a ToolBox for a Fragile X Research Registry.

Ms. Terry introduced GARB, with the key principles of: (1) sustainable stewardship; (2) open access; (3) active engagement of affected individuals and their representatives to ensure trust; (4) state-of-the-art, standards-based, extensible and flexible technology; (5) cross-condition, phenotype-based database systems; and (6) cost-effective solutions that use an existing, shared infrastructure. GARB contains clinical information, bar-coded biospecimens, and data fields that can be queried; member organizations also receive training, regulatory form templates, centralized institutional review board (IRB) services, sample collection and tracking, and electronic and paper records, among other services. Each member organization has a biobank oversight committee, which works with the vendor to customize the platform for each group's needs and determines who will have access to its collection of data and samples [11]. Participation is not inexpensive; an initial fee of $20,000 is followed by an annual maintenance fee of $20,000 for each participating organization.

Dr. Kaufmann described several model registries. In some examples, individuals may self-register to participate in different clinical trials. Their data may be released to investigators only after IRB review. Information may include genetic reports and longitudinal data, as well as existing information registrants have entered. One registry, the International Spinal Muscular Atrophy (SMA) Patient Registry (https://smaregistry.iu.edu) is supported by several advocacy groups. Its data are owned by the University of Indiana. Some international consortia, such as Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD; http://www.treat-nmd.eu/resources/patient-registries/overview/), are federated from different national databases of several neuromuscular diseases. Although self-identified, these registrants must have a genetically confirmed diagnosis for their genetic and clinical information to be used in trials. As an incentive, these registrants receive automatic reports of their personal data over time. Self-reported data are often inconsistent, so more than two full-time employees curate the data and a steering committee controls data access. Another registry, PatientsLikeMe (http://www.patientslikeme.com/), is an online, patient-controlled registry that serves as a networking site for individuals with a given condition to compare their disease experience with that of others. Companies who wish to inform members of this registry about upcoming trials are charged a fee to do so. Finally, the Friedreich's Ataxia Research Alliance Patient Registry (http://www.curefa.org/registry/) only contains self-reported data; it serves primarily to notify patients about active trials, based on their age and geographic location. It has been very successful, and its custom-designed platform is supported by volunteers. The cost of these registries ranges from $10,000 per year to over $140,000 per year.

Dr. Abbeduto described a Fragile X Research Registry (http://www.fragilexregistry.org) that leverages the existing infrastructure of the Intellectual and Developmental Disabilities Research Center (IDDRC) network, merging and expanding two existing Fragile X contact registries from two IDDRCs, with plans to integrate additional fragile X registries from other sources in the future. Obtaining IRB approval and creating data standards has allowed this Registry to: enroll new participants via the internet; invite participants in existing registries to add themselves to a single registry; improve its website functionality; and draw upon the infrastructure of other national Fragile X organizations. Decisions about whether an investigator's research would qualify to access the contact registry are made by a governing body. Other efforts include developing a manual of operations and procedures, creating a "registry toolbox" with standards and tips for creating a registry, and studying how to improve recruitment of subjects.

3. Breakout group session 1: patient registries

Individual participants were assigned to one of four groups for each of the three breakout sessions. Each breakout group was given a specific set of questions to discuss and formulate responses to in the form of a summary slide presentation. The first session focused on questions related to contact registries.

3.1. Group one

This group, co-facilitated by Dr. Edward McCabe and Ms. Lisa Kaeser, considered one central question: What are the short- , mid- , and long-term goals of a DS contact registry from the perspectives of various stakeholders (parents, medical care providers, researchers, government)?

The group agreed that the development of the contact registry is, in itself, the short-term goal; its establishment would greatly facilitate effective clinical research. The registry could begin small so that there is no delay. A potential starting place was to form partnerships with institutions that may already have "grassroots" registries.

The majority of the discussion focused on who should be consulted and who should run a contact registry. The roles of parents and self-advocates need to be clearly articulated, and their concerns (such as a family's privacy) should be addressed. Several breakout participants felt strongly that a registry would only work if it were run by parent groups. Recruitment is all about relationships, and recruiting families is both an art and a science. For example, families need to be convinced that there are good reasons to participate in a registry, e.g., that eventually research will lead to better care. Participants in a registry may also expect some sort of feedback from any clinical trial in which they participate.

As registries are being established, new technologies need to be utilized. A registry needs to be designed with longer-term goals in mind, allowing for additional components later. Social networking may be an efficient way to reach out to potential registrants, particularly parents of adolescents and young adults. However, to achieve a cross-section of the overall DS population, more than one strategy will probably be necessary to address health disparities, geographic distribution and lifespan issues. Special efforts may be needed to recruit minorities or other underserved populations. Outreach efforts focused on pediatricians and other primary care providers who serve these groups may be beneficial, particularly if they are given additional useful information. Health care providers need to be assured that their practices will not be disrupted and be given information on what their patients may expect. University Centers for Excellence on Developmental Disabilities (UCEDDs) are mandated to provide culturally competent care, and might serve as a platform to build upon.

3.2. Group two

This group was co-facilitated by Dr. Linda McCabe and Ms. Dana Bynum. Questions for consideration by the group included: Who should "own" and operate the DS contact registry? Who is responsible for maintaining it? What accountability should there be and to whom?

First, the group discussed what is really meant by "ownership" of a contact registry, suggesting alternatives such as "gatekeeper", "guardian", or "stewardship". The "owner" is the entity responsible for the registry, the one who assures that it is trustworthy (i.e. protects privacy), appropriate, attractive, and can command the respect of families. A range of possible hosts for a contact registry was presented,

including a university (which may have experience managing this type of resource), the funder (NIH or one of its contractors, or CDC, possibly with a steering committee). Because of concerns about longevity and funding, some members of the group were uncomfortable with a single institution housing the registry. To continually respond to the DS community, collaboration should be a requirement for hosting the registry, which should be subject to regular recompetition.

The group did not endorse a specific entity that would be responsible for maintaining the DS registry, although members reiterated that it should be focused on DS and not get lost among other conditions. At the same time, a registry must eventually incorporate a wealth of data so that the host remains willing to maintain it, since sustainability is critical for research. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has many registries that meet high standards and may serve as models. NIAMS has found that the contract mechanism works best for its purposes, but a cooperative agreement might also be feasible.

While a DS registry would need to be accountable to all of the community's stakeholders, families, in particular, must be able to ascertain some benefit from participation. Some may want to know whether the information will be used to eliminate DS. In exchange for keeping their contact information current, families/individuals with DS could receive regular updates on research, possibly through an annual conference. The possibility of research outcomes being shared with the families was also discussed, although the group concluded that this decision would be up to the researchers, not the responsibility of the registry host. As parents age, siblings will also need to be educated on the importance of continued participation. To get further input from parent groups, advocacy groups and others may offer to post information on the internet and invite comments.

3.3. Group three

This group, which was co-facilitated by Ms. Michelle Livingston and Dr. Mary Lou Oster-Granite, considered the following questions: What are the issues around the technology/software that should be used for the DS contact registry? How is consistent and accurate data entry ensured? What issues may arise, and which can be managed/controlled?

In discussing which system to use, the group emphasized that it would make sense to use an existing registry model (e.g., OpenClinica, ResearchMatch), rather than reinventing one. The goal is to create a virtual “phone book”, probably web-based, and secure (i.e. removing personally identifiable information). The registry could be combined with useful resources and information for parents, and a subscription fee could be charged to keep the registry solvent.

Key issues include: who would enter the data? (patients/families or investigators?), and who has access to those data? In addition, the data must be completely consistent across sites and even among DS investigators.

The group noted that it might be difficult to move a standardized tool (e.g., a data dictionary) into an established research environment. As the registry is being built, it must be accessible (similar to the National Database for Autism Research (NDAR) autism registry), although it also may be difficult to merge existing contacts into a new registry because of consent issues. To address the possibility that some potential participants may not have access to the internet, suggestions included a central phone line to provide data and verbal consent, or provide a computer terminal with internet access at a clinical site.

3.4. Group four

This group was co-facilitated by Ms. Michelle Sie Whitten and Dr. Melissa Parisi. It considered several questions, including: What model is best for the DS contact registry? Does that differ depending on different stakeholders? What model offers the best protections for individuals/families?

Similar to other groups, this group agreed that the best approach would be to seek good models from around the country for a contact registry. The members also agreed that a national registry would be optimal, with the possibility of eventually expanding to become an international registry. However, the DS population is large, and it may be preferable to start with small numbers and limited content. Decisions on what information to include for a registry may require a balance between content and the representativeness of the global population. Any registry should be developed with the goal of feeding into a research database. For example, the Fragile X Research Registry makes choices about the information collected based on projected uses. The autism registry (NDAR) was built on an interactive platform so that investigators could add information. This may need to be a requirement for participation.

The registry should engage the widest range of potential participants, at least initially (“shallow but a start”). Some parents may be willing to share basic data but choose not to have their children participate in clinical trials. Although it is natural that families will want to know how participation in a registry will benefit them, it is also important that they understand that research takes time to produce results. Obtaining a representative sample will be a challenge, one that can be met by recruiting participants from locations where they spend time, such as schools and clinics. One approach is to ask schools to hand out flyers with information on how parents can contact the registry.

Privacy concerns may be addressed in several ways. The registry could begin with requiring only the information needed to be contacted about a clinical trial. The Fragile X Research Registry only allows families to enter this basic information, and researchers do not contact families unless they have agreed to participate in research. Parents also want choices about the types of research they would consider for their children, and how often they would like to be contacted. When children become 18, they may need to be reconsented to keep their data in the registry. Opting out of the registry should not be made difficult.

4. Research databases

Four presentations focused on existing or recently created research databases that different groups currently use for the study of a variety of rare and more common diseases or conditions. For the purpose of this discussion, the use of the term "research database" is confined to a registry with patients' clinical and medical information that could be used to inform research efforts. Dr. Jeffrey Krischer (University of South Florida; USF) discussed the experiences of The Rare Diseases Clinical Research Network (RDCRN) Contact Registry. Dr. Susana Serrate-Sztein (National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS/NIH)) shared lessons learned from a number of their Research Registries. Dr. Elaine Collier (National Center for Research Resources (NCRR/NIH)) informed the participants about the Clinical and Translational Science Awards (CTSA) and their experience with informatics supporting research. Mr. Dan Hall (National Institute of Mental Health (NIMH/NIH)) then discussed the model for research repositories adopted by the National Database for Autism Research (NDAR).

As discussed by Dr. Krischer, the RDCRN comprises investigators who study more than 90 different rare diseases at 150 clinical sites and 55 patient advocacy groups. Its purposes are to (1) inform people with rare diseases about clinical research activities, (2) identify populations for participation in research, and (3) facilitate study enrollment. The centralized, NIH-funded Coordinating Center obtains and maintains Health Insurance Portability and Accountability Act (HIPAA) or IRB approval for its clinical sites to use the contact registry and research database. Individuals and family members with a rare disease consent and enter their data at the RDCRN website (http://rarediseasesnetwork.epi.usf.edu/), by paper or by telephone. Modifications to the basic form allow investigators to collect a second, more detailed level of information for specific studies, using “treed” questioning. All communications with

the registered participants are automated, such as targeted trial information or other announcements. The registry also facilitates communication between registrants and investigators and provides the former with targeted medical information. Consortia within the RDCRN plan to expand the types and sources of data included in the registry. The RDCRN coordinating center plans to enhance the information it provides to patients and researchers, expand patient-reported data and physician-reported data, and actively market and recruit around the world. A project hosted by the RDCRN, the Patient Registry Item Specifications and Metadata (PRISM; http://prism.epi.usf.edu/) Library project, funded by the National Library of Medicine, NIH, seeks to improve access to existing standardized registry questions and promote data standards to increase data sharing.

Dr. Serrate-Sztein discussed NIAMS' current funding of a number of contracted registries and databases to universities to facilitate research on rare diseases that have few well-characterized patient cohorts, specimens, or animal models. Their registries range in cost from $350K to $1.3M per year. Recompetition occurs every five years and the contracts have built-in termination clauses that activate for unsuccessful registries. Scientific Advisory Boards oversee these NIAMS databases, and the contracts have specific milestones, targets, and evaluation metrics. Each registry proposal must pose a research question, and this has been critical for the success of an individual registry. Successful NIAMS registries include the Neonatal Lupus Registry (http://neonatallupus.com/neonatal-lupus.html), the Juvenile Idiopathic Arthritis Registry (http://clinicaltrials.gov/ct2/show/NCT00783510), and the North American Spondylitis Consortium. These share several common characteristics: (1) formation around a specific interesting and timely research question, (2) strong and steadily involved collaborators and leadership, (3) readily updated technology, and (4) a strong dissemination plan. Successful registries must eventually "sunset", ending their support from NIAMS, but by this time, many are self-sustaining. Several NIAMS registries have experienced pitfalls that sometimes led to failure. Some could not recruit or enroll enough patients, usually because of a delayed definition of inclusion and exclusion criteria and delayed consensus on which data to collect. Others had "bottlenecks" when collecting a large amount of data that required further review, hindering the use of the registry and database.

Dr. Collier gave an overview of the CTSAs. The CTSAs have supported two successful informatics projects: Research Electronic Data Capture (REDCap; http://project-redcap.org/) and ResearchMatch (https://www.researchmatch.org/). Investigators use REDCap primarily for clinical study or trial management. Investigators find it easy to set up, use, and control. REDCap mandates secure practices and employs an iterative workflow to study design and data analysis. Its flexibility allows support of diverse types of research and non-research projects such as registries. Available in several languages, REDCap provides a wide array of services, such as data de-identification, participant scheduling support, and multisite data collection. In addition, the system is free to institutions that sign an agreement to join the REDCap Consortium and to provide feedback. Through this consortium, investigators drive improvements in the platform.

ResearchMatch is a disease- and institution-neutral, volunteer national recruitment registry that began in October 2009. As of June 2011, over 15,700 individuals have registered, and the pace of registration continues to escalate. Individuals who are interested in participating in a trial, or their parent, guardian or caregiver, register on the website and provide basic information about their demographics and health. Researchers with IRB-approved protocols at participating institutions can use the registry to identify potential (de-identified) study participants who meet their inclusion criteria, free of charge. ResearchMatch then sends emails to potential participants, who then indicate whether or not they are interested; if so, ResearchMatch releases their information to the investigators for follow-up and potential enrollment. To date, 10 individuals with DS have registered. ResearchMatch is interested in creating "treed", condition-specific questions to ask at registration and in linking to http://ClinicalTrials.gov and MEDLINE®.

Mr. Hall, manager of NDAR, discussed NDAR's goals, size and nature of its data. As an NIH-funded resource, NDAR currently supports data for more than 60 NIH grants, including 15,000 subjects and 25,000 data elements (clinical, phenotype, imaging, genomics). NDAR has become federated with other autism resources and repositories, such as the Autism Genetic Resource Exchange (AGRE), PubMed, and the Interactive Autism Network (IAN). The NDAR management team has learned several important lessons about running a research repository. One needs to create a standardized identifier for each research subject (Global Unique Identifier; GUID) (different from an institutional patient identifier [PID]) to enable data aggregation. At an early stage, one must decide what types of data the repository will support and create an explicit data dictionary. NDAR has learned that a community definition is the best way to define data. In the documents and regimens that support data use in NDAR, program announcements mandate very specific terms for data sharing. NDAR is integrated with IAN, a self-registry of 32,000 people affected by autism that serves as an intermediary for contact between investigators and potential study participants, facilitating data aggregation and research recruitment. IAN registrants consent to their data being available for queries from researchers in NDAR who have access permission. Overall, NDAR has learned that the three essential elements of a registry are: community-defined data; unique, non-identifying, cross-project, research-subject identifiers; and a fair, enforceable, and clear regimen for data sharing.

5. Breakout group session 2: research databases

The members of each of the four groups were redistributed from the previous breakout group session, providing not only different perspectives, but also allowing the participants to better understand others' views with respect to research databases.

5.1. Group one

This group, co-facilitated by Dr. Linda McCabe and Ms. Dana Bynum, considered three questions: What are individuals/families concerns associated with participating in a DS research database and potentially, clinical trials, and how should those be addressed? What outreach and information efforts are needed to encourage participation, and by whom? Will the results of the studies that use the data be shared with the families?

Members of the group expressed common concerns: the use of and access to the information (including potential abuse and potential refusal to provide coverage by insurers), the ability to opt in or out, the lack of immediate benefit to those who participate (relative to future generations), and the need to offer benefits to this generation. Concerns from parents about exploitation are not unique, so it is important that parents and self-advocates be part of a diverse steering or executive committee. Group members also felt that careful sharing of test results with study participants was a necessity. Such sharing might vary for different kinds of tests, or might accompany genetic counseling.

Others expressed concerns about peer review of DS research; lack of reviewers' familiarity with DS; their misconceptions and their perceptions of significance (not seeing DS as a disorder, but as a variable condition); the lack of ownership of DS by any single NIH Institute or Center (despite the activities of the Trans-NIH working group), since NIH should play a major role in the support of medical research; and the need to reduce barriers and be inclusive to the benefit of all.

Creating a website and research database would help parents to better understand the medical issues, protect their children medically and socially, and prevent exploitation; present concrete information in understandable language for families, caregivers and health care providers; and help researchers better communicate with families. A

participant asked those present to "think big" for the database and thought that families would enthusiastically participate. Since almost all organ systems are affected by DS, the database could be framed in terms of public health, because there are very few data available on the effects DS has on a given individual's overall health and well-being.

Information centers could facilitate outreach by creating trust and bonds with families and also with well-respected advisors (physicians, primary care givers, etc.), including those in DS clinical centers, UCEDDs, and IDDRCs. Such centers could also facilitate meetings, perhaps in neighborhoods and churches, that foster face-to-face communication among parents, self-advocates, and consultants, thereby promoting transparency and trust. There was also agreement that minimizing stress and reducing the number of medical procedures (like blood draws) would be helpful. Getting pharmaceutical companies to invest in and develop drugs, developing protocols to reduce stress and pain, and translating best practices into the medical community are other important considerations.

Ways to share the results with families and caregivers led to discussion of several issues, such as disseminating the most recent information to parents (possibly through a facilitated forum or focus groups), identifying unanswered questions, providing families an appreciation of how research affects them through identification of milestones, problems, and solutions, and placing immediate needs in the context of longer timeframes. Some felt social networking might facilitate outreach to adolescents and young adults.

5.2. Group two

Group 2, co-facilitated by Dr. Edward McCabe and Ms. Lisa Kaeser, considered two questions: What issues might arise relating to privacy and confidentiality of information that will be included in a DS research database? How should issues of consent/assent/permission be addressed?

Although medical information is protected in medical databases, personal identifiable health information in research databases does not necessarily have the same protections. Therefore, one must take care with personally identifiable information. There are needs for centralized IRBs, consortium agreements, and regulatory approval for data collected with the intent to publish. Children are vulnerable populations, but those with DS are even more vulnerable. Adults with DS have the added issue of consent, often by guardians that may vary in their roles and advocacy in different parts of the country (e.g., some states use court-appointed advocates).

Education of members of IRB panels is important to understand issues surrounding features of DS, challenges of adverse event reporting, nuances of outcome measures, and appreciation of issues associated with re-consenting of adults with DS. Many pharmaceuticals have never been tested in children, especially those with IDD.

Issues of consent/assent/permission are more the purview of research based on the database, not the database itself. Issues also differ between cognitive community research and those of IRBs. Families need to address issues of guardianship before the age of 21, and the need for a legal advocate representation (LAR) may be important if the individual can give assent, but not consent (i.e., informed consent needs to be "informed").

Participants considered various forms of information facilitation, visual and auditory cues, iPads, multi-language materials, pictorial or video representations of medical procedures, etc. Interpretation of the specific rules and procedures that apply to the age of consent vary among states. They discussed issues involving collection of minimal personal health information (PHI), care in releasing data, the need for involvement of bioethicists from the beginning, and pooling strategies to de-identify data. Issues of privacy and personal information sharing are changing through the impact of social networking.

5.3. Group three

This group, co-facilitated by Ms. Michelle Livingston and Dr. Mary Lou Oster-Granite, considered four questions: What interface is most user-friendly and accessible to maximize participation? Who would "own" the DS research database, and how would it be maintained, particularly if the database grows (internationally)? Who funds the database over the longer term? What costs are associated with that?

Models of information databases (like REDCap) or the IAN model already exist and could be utilized by the DS community to create a research database that would interface with a contact registry (such as ResearchMatch), biobank and electronic medical records. Adults with DS need to be part of the research database, so outreach/marketing must be considered, and advocates need to participate as well. Participants discussed various strategies for outreach, including creation of a web portal, a step-wise approach and use of existing infrastructure for local outreach. Staff associated with the database could serve as intermediaries between the researchers and potential participants, and systems such as REDCap could help to gather protected information from electronic medical records.

Basic research databases need to be expandable, to branch off into different projects and bring advocacy/patient groups into consensus. Oversight could be provided by a coalition composed of advocacy, government (NIH, CDC), and other interested groups. To access such a database, researchers need to provide assurance that data sharing will occur.

5.4. Group four

Group 4, co-facilitated by Ms. Michelle Sie Whitten and Dr. Melissa Parisi, considered two questions: What data are essential to include in a DS research database? What database forums (models) already exist and could be adapted?

A research database needs to collect certain information (like karyotypes) at the outset, yet tailor that information in an age appropriate manner. The information should be goal-oriented and needs curation; it is critical that knowledgeable experts review the content for accuracy and meaning. Researchers would identify what information they need for specific research projects. By linking the contact registry, research database, and biobank together, a multi-project database could be created to facilitate sharing of data by researchers. Although regulations restrict data collection and use, the restrictions should be incorporated into the linked structure and made clear to registrants and researchers.

Creating a narrative about the value of a registry and research database to present to funders and the public that clarifies the public health need for these resources clearly is very important. This narrative might discuss the co-morbid conditions, such as Alzheimer disease, that are common in people with DS that also affect the general population. It might also discuss the low incidence of cancer and cholesterol problems in people with DS, a fact that alone could increase the enthusiasm of many potential funders for supporting this research.

The research database needs a consistent battery of tests with validated data elements (including functional testing), ascertainment of health and mental health issues, associated birth defects, family information and participation, clinician input, etc. The database should consider collecting medical health, mental health, medications, service needs, services used, barriers to care, geographic information and demographic information with the flexibility to increase information collection in the future. There should be continuity of follow-up over time (chart review, nurse visits) for longitudinal studies and mechanisms in place to share data (informing parents about the use of aggregated data in the database for different studies). The database should be flexible and contain common elements and customized elements, as well as quality of life indicators that are scientifically sound and acceptable to the DS community.

Although more than 600 trials for DS have been initiated, the numbers of individuals participating in individual trials is usually quite small, and the ability to extrapolate to the broader community is limited.

6. Biobanks

Five presentations focused on issues associated with various forms and models of Biobanks. Dr. Melissa Parisi (NICHD/NIH) discussed the NICHD Brain and Tissue Bank for Developmental Disorders. Dr. Dorit Berlin (Coriell Institute for Medical Research) described the resources for DS research at the National Institute of General Medical Sciences (NIGMS)/NIH and National Institute on Aging (NIA)/NIH Repositories, both housed at the Coriell Institute. Dr. Yaffa Rubinstein (Office of Rare Diseases Research (ORDR)/NIH) provided insights into the creation of a Global Rare Diseases Patient Registry (GRDR) linked to a Rare Diseases Human Biorepository Database (RD-HUB). Dr. Cathy Bodine (and by telephone, Dr. Karl Pfenninger, University of Colorado at Denver) discussed the Translational Nexus, an integrated biobank, databank, and patient registry. Finally, Dr. Stephen Williams (SomaLogic, Inc.) discussed biobanks from a biotechnology perspective.

Dr. Parisi described the NICHD biobank (http://medschool.umaryland.edu/btbank/), operated by the University of Maryland for the past 20 years, and created at the request of advocacy groups. As the only dedicated pediatric bank for developmental disorders in the world, the bank contains about 85,000 samples, mostly brain, from individuals with more than 400 different disorders as well as brains from individuals with typical development, which serve as important controls. Hundreds of investigators worldwide have received samples for their work, resulting in close to 1000 publications. Currently, there are 89 donors with DS, and at least 18 publications have resulted from research using these samples. All donors or their guardians give consent for donation according to applicable regulations; about half arrange for donation before death. Donation is free and facilitated by cooperating pathologists. An additional advantage is that the bank is associated with NICHD. Collection procedures do not interfere with open-casket viewing. Many of the donors come from Maryland, because the biobank maintains a close relationship with the Baltimore medical examiner. Strict criteria for tissue distribution ensure fair and equitable allocation of samples to legitimate research projects. NICHD and two IRBs must approve all protocols that use tissue from the bank. Additional committee review is necessary to distribute tissues that are in limited supply.

Dr. Berlin discussed the Coriell Institute for Medical Research (www.coriell.org), an independent, nonprofit organization, which provides cell lines and DNA samples to investigators. Coriell's 101 cell lines with trisomy 21 or abnormal chromosome 21 reside in the NIGMS and the NIA public repositories. All trisomy 21 samples have karyotypes, confirmed diagnoses, and include clinical remarks. There are also 20 samples in an NIA DNA panel, some of which have an *APOE* genotype. Researchers use cell cultures and DNA samples for many types of research, the most common of which include functional studies, induced pluripotent stem cell (iPSC) line development, and as positive or negative controls for assay development.

The Coriell repositories can also be a resource for those who submit samples. Advantages to submitting samples include free cell culture and biobanking services, as well as receipt of a cell line or DNA sample for each specimen submitted. Samples with chromosomal aberrations receive G-banded karyotyping and chromosomal microarray analysis and genotyping. Genotyping data are posted on the database of Genotypes and Phenotypes (dbGaP; http://www.ncbi.nlm.nih.gov/gap). Submission can also fulfill patients' wishes for a specimen to be used in research, although individual donors do not receive results from their samples. Coriell currently collaborates with several disease-specific organizations that submit samples for specific established collections.

Dr. Rubinstein discussed repositories and registries for rare diseases. Although any given condition is rare, their cumulative public health burden is significant. Because these disorders are so uncommon, no single institution, and in many cases, no single country, has sufficient numbers of subjects to conduct meaningful clinical trials. In addition, geographic dispersion of subjects has been a major impediment to recruitment into clinical trials. After a disease-specific population is defined, many different types of data can be entered. Once these patient registries are established, researchers are more likely to conduct research on a given rare disease. Unfortunately for registry developers, there is no established forum for sharing experiences and exchange information. Each time a new registry is developed, it is started from scratch using a different platform and different standards. As a result, registries cannot talk to each other, share data, or exchange information. In recognition of these barriers and the need for registries, the ORDR is proposing to establish a Global Rare Diseases Patient Registry (GRDR) to help locate and identify rare diseases patients around the world [12]. The idea is to develop an infrastructure for an internet-based platform with common data elements utilizing a rare disease registry platform (http://rarediseases.info.nih.gov/files/GRDR_CDEs.pdf). The infrastructure would aggregate data from existing and newly established rare disease registries. The registry would serve as a research resource of aggregated information from new and existing registries to accelerate the development of therapeutics and cures for rare diseases. The GRDR will link to RD-HUB, a publicly accessible and searchable database of biorepositories/biospecimens [13]. RD-HUB will improve researchers' access to human biospecimens and facilitate global sharing of material and data among investigators.

Drs. Bodine and Pfenninger introduced the Nexus, which brings together a biobank, databank, and registry at the University of Colorado IDDRC, focused on advancing research on individuals with neurodevelopmental disorders. Currently, 42 of its 241 registered participants have DS. The Nexus links each biological sample to many types of information, including electronic medical records and behavioral data, thus making the data as useful as possible for clinical trials, epidemiologic studies, and cellular and molecular research. Eleven clinics within two hospitals share a single enrollment coordinator and refer enrolled patients through standardized evaluation processes. Data (e.g., genotype, imaging, behavioral assessments) are entered into REDCap and linked to samples. The Nexus contains different levels of access. To select and access data, investigators need both IRB and Nexus approval. One IRB-approved umbrella protocol governs Nexus. Cooperation of referring clinical investigators is critical to the Nexus' success. Participating investigators have priority access, two-year data protection, and free biorepository services. The Nexus will begin targeted fibroblast collection for iPSC generation shortly and will establish a cooperative network with other IDDRCs or other centers for data-sharing and biobanking.

Dr. Williams described the perspective of a biotechnology company, SomaLogic, which is working to identify protein biomarkers that can aid in understanding disease and in developing diagnostics and therapeutics. Biobanks also play important roles in biomarker identification. SomaLogic's search for protein biomarkers led to development of a set of reagents for protein measurements, called SOMAmers. SOMAmers can measure very small amounts of many different proteins. With them, one can identify a few biomarker proteins, whose concentrations change under particular conditions, out of more than 1,000 proteins in a sample. With these biomarkers, SomaLogic can build a diagnostic paradigm to test a blinded set of several hundred clinical samples from people with the condition of interest. SomaLogic can obtain these samples quickly and cheaply from biobanks, rather than from a clinical trial. SomaLogic links biobank case samples to consistent clinical data and matches them with equivalent controls. Biobanks also process and manage their samples in an efficient, consistent, and high-quality manner. This helps avoid

identifying false biomarkers, which can occur if there is inconsistency in sample collection and handling among sites.

Dr. Williams created a diagram with modifications proposed by Dr. George Capone (Fig. 1) to identify the steps needed to improve the lives of people with DS. This type of diagram, initially developed for use by the military, defines the ultimate goal of an endeavor and why it is important, and then specifies what needs to occur to make that goal happen.

7. Breakout group session 3: biobanks

The final breakout group assembly again rearranged the members of the four original breakout groups to provide better individual perspective with respect to biobanks.

7.1. Group one

Group 1, co-facilitated by Ms. Michelle Sie Whitten and Dr. Mary Lou Oster-Granite, considered three questions: What types of research related to DS make it essential to have a research resource such as a biobank? What tissues would be optimal to collect? What are the challenges with collecting these samples (e.g., procurement, quality control, regulatory issues), and how should these issues be addressed?

There is a need for basic research with human samples, particularly from individuals with DS. Such sample collection can facilitate clinical trials as well, by providing sufficient numbers of samples, and samples collected from across the lifespan. Since DS has a quite variable presentation, such collections can also enable identification of subgroups of individuals with medical, developmental, or behavioral co-morbidities, or those with positive health attributes. Important tissues to collect are blood for lymphoblastoid cell lines, skin for fibroblast cell lines and iPSCs, plasma, serum, and cerebrospinal fluid (CSF, if collected for another procedure). There should be a medical reason for collection of unusual tissues or those requiring special procedures. Such collection from a living individual allows that individual to serve as his or her own control, but siblings should also be considered a best alternative control. Longitudinal collection from well-characterized individuals is also vital, provided that there is a consistent method of collection through a network of federated clinical sites. Parental involvement is also essential to support the biobank, and families may be more willing to donate if they understand how research could benefit people with DS. Clarity of the purpose of sample collection and the type of research being conducted is essential to build trust in how the research will improve lives and provide transparent evidence for the potential for new treatments. Donation of post-mortem tissues (brain, particularly) and consent for that collection needs to be discussed early in the tissue donation process, to enable collection of as much phenotypic and genotypic information about the individual (e.g. medical history, karyotype, etc.) across the lifespan and obtained through a common evaluation platform.

7.2. Group two

This group, co-facilitated by Dr. Linda McCabe and Ms. Dana Bynum, considered three questions: What IRB issues are likely to arise in collecting tissues from individuals with DS (consent, etc.), and how should these be addressed? How is the information from the samples protected (confidentiality)? What can we learn from existing brain/tissue banks?

All tissue samples for genetic studies need to be obtained following informed consent procedures. First, the parents must give permission for their child to participate, and subsequently, consent must be obtained from the child who reaches age of consent or the required legal guardian if that child/adult cannot consent at that time. Re-consent may also be necessary as technologies evolve in the next decades. Members of IRBs need to be informed and educated regarding research with vulnerable populations, particularly those with intellectual disabilities. Transparency with the families is crucial, and efforts to protect confidentiality and identity need to be explained. No tissue is exempt from IRB approval if one contemplates genetic studies.

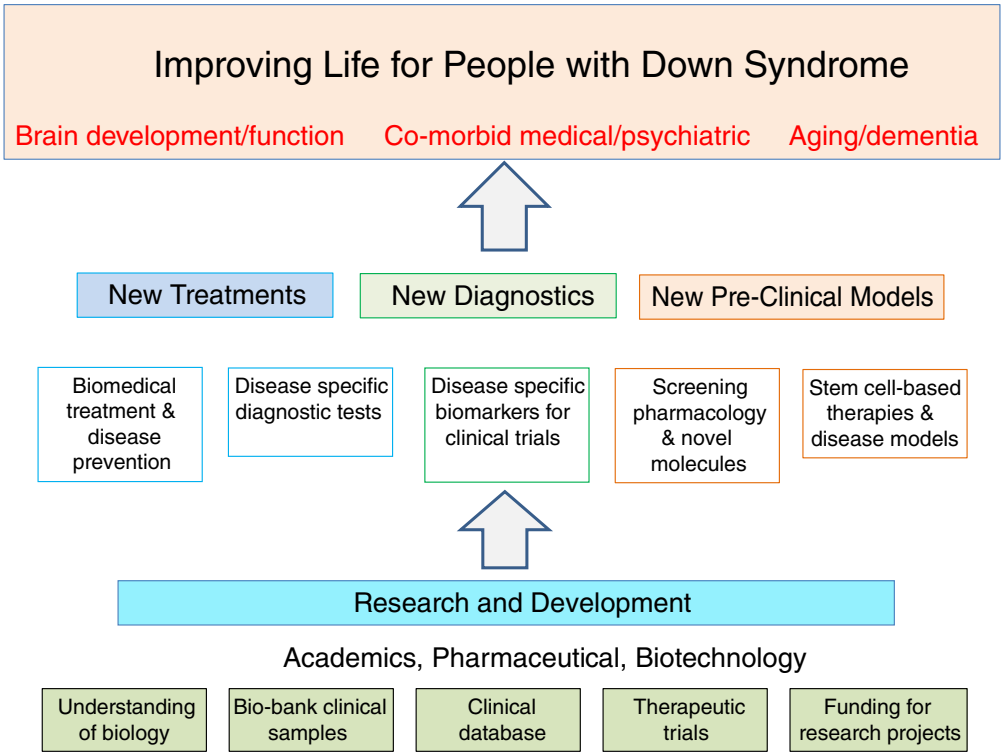

Fig. 1. Diagram illustrating the steps to achieve the ultimate goal of improving life for people with Down syndrome. The arrows represent the contributions of smaller goals in achieving larger-scale tasks.

Genetic counseling should provide the context for presentation of research results. Controls should be as closely matched as possible. Clinicians need to feel that their commitment to participate in biobanking is valued and strategies need to be developed to gain their full cooperation in the conduct of protocols generated to facilitate such collection. A biobank exclusively for samples from individuals with DS should receive serious consideration, since existing biobanks do not have many samples from individuals with DS.

7.3. Group three

This group, co-facilitated by Drs. Edward McCabe and Melissa Parisi, considered four questions under the theme of the need for a specific DS biobank: What logistical and technological issues arise during maintenance of a brain and tissue bank, and how should the issues be addressed? What are the costs involved with long-term maintenance of a biobank? Can expansion be accommodated? Should there be a centralized biobank, or several "regional" biobanks?

A network of biobank sites with uniform infrastructure, governance and regulation of samples is crucial. This network needs to share the same protocols and standardization of samples, whose types may vary, depending on cost of storage of samples, information and data. Such a network could also facilitate collection from persons of diverse ethnicities and demographic factors, and from a logistical perspective, could mitigate issues associated with timely and safe transport of samples and transport across state lines. Costs associated with biobanks are numerous and quite varied: family donations may involve transportation and their costs to come to the biobank; standardized collection of samples needs to be assured during surgical procedures; the bank must be monitored; security and privacy must be maintained; and the plans must include the need for expansion and the decision process in such expansion. Biobanks usually do not receive any product royalties for most of the samples that they distribute. When there is a successful product, however, a company may not be able to maintain a profit margin were it required to pay royalties to several different biobanks. As a counterexample, the Genetic Alliance controls 51% of the intellectual property of products created using its biobank samples, which allows it to maintain access and control. Another model for sustainability would be to charge a small fee per sample to maintain the operations of a biobank.

On the issue of incorporating individual biobanks into a larger biobank, there was willingness to share general repositories or cell lines, rather than specialized tissue collections created for a specific research project.

7.4. Group four

Group 4, co-facilitated by Ms. Michelle Livingston and Ms. Lisa Kaeser, considered two questions. What are the best ways to reach out to families regarding donation of tissues to the biobank? Who should conduct the outreach?

Awareness is critical for all involved: families, parent advocacy groups, and a wide range of professionals. Communication is essential at the time of collection regarding what the sample will enable researchers to learn. Sample collection can occur during clinical testing, with the option to decline donation by the family or self advocate. One approach now frequently defined by the IRB is to be "consumer-friendly". To collect invasive samples, including those obtained during surgical procedures, it is imperative to earn and establish the trust of the people agreeing to provide those samples. People are often more likely to give saliva, fingernail clippings, and hair follicles, than blood and skin biopsies. Advocacy groups can help to educate their constituencies on the need to participate and address issues of concern for hurt/injury, and what the child and family will get out of the donation. An emphasis on non-invasive procedures and the collection of cord blood, placenta and embryonic tissue through a trusted caregiver may encourage a willingness to donate. Counseling of adult self-advocates, who are prone to depression, about post-mortem donation is often a delicate issue that requires careful planning to reduce patient risk and anxiety. Physicians who are not the researchers need education to ensure better outcomes for the patients and their families. Respect for religious beliefs and involvement of community organizations and places of worship can be important outreach mechanisms, particularly for post-mortem sample donation. Since the donors are individuals, not subjects, the heart of outreach is the patient-physician relationship. Parent advocacy groups and families can help with outreach at annual conferences through materials at booths and events. The most difficult issue is brain donation; advocates need to invest time preparing materials to educate families about the condition itself and about tissue donation, not only from the individual but from other family members (who could serve as controls). Perhaps a better way to reflect the benefits of donation to a biobank would be to refer to the biobank as a "health discovery bank".

8. Conclusions and next steps

Dr. Maddox indicated that the meeting organizers would develop proceedings for publication in a medical journal, and would invite the conference participants to comment on them. The creation of a DS contact registry, database, and biobank must be a trans-NIH effort aided by efforts with DS advocacy groups. Drs. Edward and Linda McCabe have developed a commentary on the conference [14]. As a consequence of the meeting, NIH has released a request for information (RFI) to solicit input from the larger community (e.g., conference participants, other health care providers, investigators, organizations, families, self-advocates) on existing DS-focused registries, databases, and biobanks. With this information, NIH can release a solicitation for applications to create these resources. The advantage of a public RFI is that those attending the conference will be able to compete in future solicitations.

There was general agreement to create a contact registry, but disagreement on its membership. Most felt its creation should occur simultaneously with a collective effort to also create a research database and a biobank. Some felt that specialists should be entrusted with the technical aspects of these resources without wider input. Other attendees suggested a defined role for the larger community to discuss participant safeguards, accountability, messaging, and other aspects of these resources relevant to the public.

NIH could create a consortium to address some of these issues. Such a consortium could submit a response to a future solicitation as a single entity. This consortium, and its membership, would not be a center of excellence or have fiduciary responsibility. It would provide input on the process of creating a linked contact registry, research database, and biobank. A variety of opinions were expressed concerning the composition of such a consortium. In addition to individuals and organizations attending the conference, several felt strongly that the consortium should include others, such as those who conduct all types of research on DS (e.g., model systems, imaging, behavior), individuals with DS, and other groups with existing registries and biobanks. Others suggested limiting the consortium to those present at the conference, with the creation of technical workgroups focused on specific problems that could include those with particular expertise to serve on an ad hoc basis.

Such a consortium might form initially with those individuals and organizations present at the conference, but it should work to bring in others whose voices were not present. Although initially only a fraction of the DS community would be involved, the rest of the community needs to be informed about the conference and its outcomes. This will prepare the rest of the community for the RFI, which will include a synopsis of the conference and the questions that resulted from it. It is unlikely that others in the community would be able to begin redundant registry, database, or biobank efforts within a short period of time and that divergent efforts would harm the final goal.

Dr. Maddox told those present that an NIH solicitation for creation of these resources would likely take the form of a request for proposals rather than a request for applications because a contract might be the best mechanism. Furthermore, NICHD should probably not take active leadership in all aspects of this project; the consortium should recommend which organizations will be responsible for which pieces of this project.

Dr. Maddox closed by reading an excerpt from an article[1] that highlighted the strides that change agents, working together, have made in improving the lives of people with DS. She emphasized that those present at the conference must continue to work together at this time to create these necessary resources for DS. She reiterated her vision of releasing an RFI to receive the necessary information and creating a representative consortium to drive the process and work out the details of developing the registry, database, and biobank. She emphasized that although a registry should be created as soon as possible, it should be done correctly, and there are a number of details to work out before it is established.

Dr. Edward McCabe reminded the participants that there is urgency about the creation of a contact registry, since new DS therapies are nearly ready to test in clinical trials and individuals with DS need to be contacted to participate. He urged the conference participants to include individuals with DS in creation of these resources and to ask them what they want for themselves at every step of the endeavor.

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