219th NIDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-council Meeting – Open Session
May 12, 2022

Attendees

DDEMD Sub-committee Members: Dr. David D'Alessio, Dr. Debra Haire-Joshu, Dr. Philipp Scherer, Dr. Elizabeth Seaquist, Dr. Michael Snyder, Ms. Niecy Johnson (subject matter expert)

DDEMD Staff Members: Dr. Kristin Abraham, Ms. Folashade Akanni, Dr. Beena Akolkar, Dr. Guillermo Arreaza-Rubin, Dr. Shavon Artis Dickerson, Dr. Olivier Blondel, Dr. Miranda Broadney, Dr. Henry Burch, Dr. Art Castle, Dr. William Cefalu, Dr. Maureen Monaghan Center, Dr. Brad Cooke, Dr. Thomas Eggerman, Mr. Neal Green, Dr. Carol Haft, Dr. Albert Hwa, Dr. Teresa Jones, Dr. Maren Laughlin, Dr. Jean Lawrence, Dr. Yan Li, Dr. Hanyu (Maggie) Liang, Dr. Barbara Linder, Dr. Saul Malozowski, Mr. Louis Martey, Dr. Saira Mehmood, Mrs. Heidi Otradovec, Dr. Salvatore Sechi, Dr. Corinne Silva, Dr. Lisa Spain, Mr. Kyle Sullivan, Dr. Karen Teff, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Ashley Xia, Dr. Norann Zaghloul

NIDDK/NIH Staff: Mr. Terry Barnes, Dr. Najma Begum, Dr. Greg Germino, Ms. Connie Jenkins, Dr. Ann Jerkins, Mr. Tim Kerns, Ms. Van Nguyen, Dr. Charlene Repique, Dr. Elena Sandovich, Dr. Thomas Tatham, Ms. Melissa Voss, Ms. Shalanda Wellington, Dr. Kenneth Wilkins

Other: Dr. Kathleen Sakamoto, Dr. Sheryl Sato

Welcome and Approval of January 2022 Sub-committee Minutes (Dr. Cefalu)

Dr. Cefalu welcomed Council members to the session and provided an overview of the planned presentations. The minutes from the last Sub-council meeting (January 27, 2022) were approved.

Council Member/Staff Transitions (Dr. Cefalu)

New Council members (Dr. Elizabeth Seaquist and Ms. Davida Kruger), a new Subject Matter Expert (Ms. Niecy Johnson), and a new DEM staff member (Dr. Hanyu [Maggie] Liang) were then welcomed by Dr. Cefalu.

Special Diabetes Program (SDP) Update (Dr. Cefalu)

Dr. Cefalu started by providing some background information on the SDP, a trans-HHS program administered by NIDDK. Funding for the SDP began in 1998 with a five-year commitment for funding. Over 26 years, the SDP has provided approximately $3.39 billion to Type 1 Diabetes (T1D) research. The SDP allows for stable, long-term investment in T1D research and currently, $150 million per year (since 2004) has been provided to support ambitious, large-scale, high-risk, high-reward projects, many of which might not be able to be supported using the NIDDK's discretionary appropriations. Dr. Cefalu noted that $150 million in 2022 does not have the same

purchasing power as in 2004 so there is a need for very good planning to ensure that the money is spent appropriately and in the most effective manner. The Diabetes Mellitus Interagency Coordinating Committee, chaired by Dr. Cefalu, meets every two to three years to comment on new scientific proposals presented for consideration of SDP support, and what they see as key gaps and opportunities for T1D research.

Ongoing Research Programs funded by the SDP consist of programs/consortia as well as investigator-initiated grants in response to new and existing funding opportunity announcements (FOAs). Dr. Cefalu discussed the six goals of the SDP along with examples of projects that DEM supports to meet the goals.

- Goal 1: Identify the Genetic and Environmental Causes of T1D
    - The TEDDY study was designed to screen a large number of infants for genetic susceptibility and evaluate for environmental exposures to determine what may trigger diabetes onset. Individuals are followed for 15 years or until the development of autoimmunity or T1D.
- Goal 2: Prevent or Reverse T1D
    - The Immune Tolerance Network, led by NIAID, uses SDP funding to support its activities related to T1D. The ITN develops and conducts clinical trials, each supported by mechanistic studies, of specialized immune tolerance therapies in four areas: autoimmune disease, allergies/asthma, organ transplantation, and T1D.
    - TrialNet, is an international clinical trials network that conducts trials of agents developed to prevent clinical diagnosis of T1D in people with early-stage disease and to slow disease progression in the newly diagnosed.
- Goal 3: Develop Cell Replacement Therapy
    - The Collaborative Islet Transplant Registry has compiled and analyzed islet transplantation data with the intent to capture all clinical activity in North America as well as at additional sites in other countries since 2001.
    - The Integrated Islet Distribution Program facilitates the distribution of human islets to biomedical researchers by establishing partnerships with qualified islet isolation facilities to prepare and distribute human islets.
    - The overall mission of the HIRN (Human Islet Research Network) is to better understand how beta cells are lost in human T1D and to find innovative strategies to protect or replace functional beta cell mass in diabetic patients. HIRN is composed of five scientific consortia with distinct but complementary missions.
- Goal 4: Improve T1D Management and Care
    - While there are no discrete consortia like in other goals, DEM has used SDP funds to accelerate progress on artificial pancreas and other T1D management technologies.
- Goal 5: Prevent or Reduce the Complications of T1D
    - A major ongoing program under this goal is the DRCR Retina Network, which is led by the National Eye Institute. The Network supports the identification, design, and implementation of multicenter clinical research initiatives focused on retinal disorders, including diabetic retinopathy. This program receives some SDP support and conducts some studies in people with type 1 and type 2 diabetes.
- Goal 6: Attract New Talent and Apply New Technologies to Research on T1D
    - DEM has supported many small companies via the SDP for sensor development, insulin and glucagon formulations, insulin delivery devices and AP controllers. In addition, NIH Gateway awards seek 1) to provide support for preliminary

research to ensure that a robust pipeline of talented new investigators continue to embark on successful careers in T1D research and 2) to provide an opportunity for new investigators to pursue their studies within the intellectual environment of large, ongoing collaborative research programs in increase understanding of key questions in the field, to network, and establish collaborations.

Dr. Snyder mentioned that the presentation was very helpful and provided a better idea of the full SDP landscape. Dr. Cefalu noted that during presentation today he hoped to show the Council members how new concepts presented by staff relate back to the full picture just presented. Dr. Haire-Joshu agreed with Dr. Snyder that the presentation was very helpful and allowed her to think of proposals in terms of the strategic plan. Dr. Seaquist also found the presentation to be very useful. She made special mention of the rigor required to setup the various programs and wanted fellow Council members to understand the amount of work required to get them off the ground. Dr. D'Alessio also found the presentation to be very effective. He thanked Dr. Cefalu for bringing up the importance of novel technologies for the management of T1D and mentioned that this is an area where the haves and have-nots can really be noticed. Dr. D'Alessio noted that NIDDK as an institute can't have a large influence on all aspects of T1D treatment so there needs to be more outreach to those parties with influence (including insurers, hospital systems, and other payers) to think about issues of equality in technology. Dr. Cefalu mentioned that there have been several FOAs that have tried to address barriers to technology adoption, but more are needed.

Diabetes Prevention Program Outcomes Study (DPPOS) (Dr. Linder)

Dr. Linder provided an update on DPPOs since the current phase is ending. She started by providing some background information on the Diabetes Prevention Program (DPP). The DPP was formed to answer the following question--Can we prevent or delay the development of type 2 diabetes in persons at high risk (impaired glucose tolerance, elevated fasting glucose, and overweight/obese)? 3234 individuals were randomized into three arms: intensive lifestyle, metformin, and placebo. Approximately 45% of the study population represented racial and/or ethnic minorities. The primary outcome results showed that the metformin reduced the incidence of type 2 diabetes by 31% compared to the placebo while the intensive lifestyle intervention reduced diabetes incidence by 58% compared to the placebo.

Next, Dr. Linder reviewed the phases of DPP and DPPOS and said that the goal of the current phase, DPPOS3, was to determine the effect of metformin on prevention of incident CVD. She noted that retention in DPPOS3 is very good with 70% of original cohort included. This also represents 96% of the available cohort, when accounting for deaths. Sex and racial/ethnic distributions have remained stable over the years of the studies and there has been no differential loss by original treatment assignment, so the current cohort is very representative of the original cohort. Dr. Linder then talked about translating DPP/DPPOS from efficacy research to public health. She noted that the intervention was found to be very costly to delivery, but various methods were developed to deliver it in a more cost-effective manner, leading to the development of the National DPP and Medicare DPP, through which insurance covers participation in certified programs.

Dr. Linder then talked about some results of DPP/DPPOS and recent publications. After 15 years of follow-up, DPPOS showed that the prevalence of microvascular disease was 28% lower in

those who did not develop diabetes ($p< 0.0001$). No differences were noted between the various treatment groups. Neither metformin nor lifestyle reduced incidence of CVD compared with placebo. Dr. Linder noted that, in this particular cohort, metformin and lifestyle intervention reduced the risk of T2D but may not provide additional protection against cardiovascular disease because glycemia, lipids and BP are well controlled.

A summary of DPP/DPPOS was then provided by Dr. Linder. The studies involve a unique cohort, have led to nearly 200 papers published and approximately 40 currently in preparation, have 25 years of samples/data provided to the NIDDK Repository, made changes in clinical care, and were a collaborative effort of many institutes including NHLBI, NCI, NIA, NEI, ORWH, and the CDC.

Dr. Snyder asked if there are food logs for all participants? Dr. Linder said no. Logs were done during the original DPP but not continued during DPPOS. Dr. D'Alessio said that the presentation was terrific and asked whether over time all groups lost weight. Dr. Linder said yes, but it is not clear if this is due to the lifestyle program being offered to all participants, or a reflection of aging-associated weight loss.

COVID 19 and New Onset Diabetes (Dr. Laughlin)

Dr. Cefalu noted that this project was done in a very expedited manner due to the public health need. He said that it usually takes much longer and thanked Dr. Rogers for his support and funding. Dr. Laughlin echoed Dr. Cefalu's comments.

Dr. Laughlin started by providing background information on COVID-19 and diabetes. She mentioned that scientific papers started to publish data indicating significant increases in rates of new onset diabetes since the start of the COVID-19 pandemic. This led to a number of questions including 1) Whether the SARS-CoV-2 virus may directly impact incidence rates in adults and youth? 2) Is this a new form of diabetes? And 3) Is it a consequence of pandemic conditions?

Next, Dr. Laughlin reviewed data that emerged in the literature concerning the problem. A study published in *Nature* showed that the burden of new diabetes was 40% higher in Veterans Administration patients with COVID-19 than both controls. A study published in *Diabetes, Obesity and Metabolism* noted that a comparison with flu shows that COVID-19 causes ~1.5x more DM than another common viral infection. The *Morbidity and Mortality Weekly Report* reported that new diabetes diagnosis in children occurred 31-166% higher following COVID-19 infections. Dr. Laughlin also mentioned that there are other pandemic related issues (such as increased sedentary behavior, weight gain, stress, depressive disorder, substance use, changes in sleep, changes in diet, and social determinants of health) that could be potential factors that cause an increase in the diagnosis of diabetes.

Dr. Laughlin noted that two new opportunities were created to study the newly identified problem. The opportunities fall under the following two categories: 1) epidemiologic analyses and 2) an incident DM cohort. For the epidemiologic analyses, NOT-DK-22-017 seeks to leverage extant large databases (EHRs; N3C; regional databases) to answer critical questions such as:

- What portion of incident DM is attributable to SARS-CoV-2 infection?
- Is COVID-19 severity associated with incident DM?

- What type is the incident DM (type 1, type 2, other)?
- How much remission occurs with COVID-19 associated new DM?
- Are pandemic conditions playing a role?

The NOSI will provide supplements to existing grants. The timeframe is very fast with the NOSI being issued on April 1st, 2022, and applications due June 1st, 2022. For the incident DM cohort, NOT-DK-22-018 will fund a controlled longitudinal observational clinical study to characterize new onset DM following COVID-19, and its clinical course. The goal is to develop a multi-center team to establish a longitudinal cohort of individuals (children and adults) who developed diabetes following SARS-CoV-2 infection, and to characterize the clinical course for 1-2 years. Questions that the study may answer include:

- Temporal and severity relationships between new DM and COVID-19
- Metabolic characterization & durability of post COVID-19 hyperglycemia
- Insulin sensitivity and beta cell response
- Response to therapies
- Risk factors for new DM associated with COVID-19
- Patho-immunologic features (autoantibodies)
- Effect of pandemic conditions, social determinants of health

Dr. Scherer thanked Dr. Laughlin for the fantastic overview of the program. He thought the speed of getting the various elements together was great. He noted that there is a lot of pressure from the public to get new information on COVID-19 and asked if any interventional studies into this topic could be started? Dr. Laughlin appreciated the comment from Dr. Scherer and noted that things continue to evolve with COVID-19 and this new cohort may present opportunities for ancillary therapeutic trials. In addition, more epidemiological work is needed on the topic as there are as yet no studies on the effects of vaccinations or later SAR-CoV-2 variants on incident diabetes. Dr. Cefalu echoed this sentiment and suggested that therapeutic interventions could be added later. Dr. Snyder asked if samples will be collected.? Dr. Laughlin said that the RFA has not been put out yet, but the plan is to collect samples. Dr. Scherer asked about the status of current initiatives for supplements for clinical trials, or to study the pathobiology of long COVID. Dr. Laughlin said that these are housed at NHLBI, and a decision has not been made yet, but she expects it very soon. Dr. Cefalu noted that when the diabetes phenomena were noted, DEM felt it was essential to develop a time-sensitive DK-lead initiative rather than wait to see how the NIH PASC initiative (RECOVER) focused on patient-reported outcomes worked out before moving forward.. Therefore, this deeper dive into COVID-19 and diabetes was developed.

Stakeholder Engagement (Drs. Artis Dickerson/Broadney)

Dr. Artis Dickerson began by providing some background information on the reasons for the need for stakeholder engagement. She noted that certain members of racial and ethnic groups are at a higher risk of developing type 2 diabetes (or T2D) than other groups. American Indian/Alaska Native adults have the highest rates of diagnosed T2D among all US racial and ethnic groups, followed by Hispanics and non-Hispanic blacks. Adults with less education and family income below the federal poverty level had the highest prevalence of T2D. Racial/ethnic minority populations also experience a higher burden of diabetes-related complications. Data show:

- Non-Hispanic Blacks have a higher prevalence of poor glycemic control

- higher prevalence of diabetic retinopathy in non-Hispanic Blacks and Hispanics compared to Whites
- increased incidence rates of end-stage renal disease in Black, Hispanic, and Asian patients compared to Whites; and
- highest rate of lower limb amputations is among Black people with diabetes

Dr. Artis Dickerson noted that NIH and NIDDK have recently prioritized health equity and health disparities research, which includes & necessitates meaningful and equitable stakeholder engagement. This commitment is specifically highlighted in NIDDK's Strategic Plan for Research. Strategic investments are especially needed to promote and advance health equity in the diabetes community. Next, Dr. Artis Dickerson talked about the rationale and purpose for stakeholder engagement. She noted that T2D research significantly lacks the voices and shared power of underserved individuals, communities, and populations. Stakeholder engagement is an important method to enhance and assess research outcomes - participation goals, health specific outcomes and sustainability. Dr. Artis Dickerson then provided a number of case examples for why field investigators would need stakeholder engagement resources and support to enhance T2D research studies and improve outcomes including:

- research proposal lacking community/patient input, feedback, and or representation on study team
- research design on health disparities projects lacking health equity principles
- investigator team, lacking appropriate expertise, has been unsuccessful or (doesn't know where to begin) to develop an equitable partnership with local community organizations
- research projects lacking sufficient enrollment (e.g., delayed or insufficient recruitment and retention) of under-represented populations and underpowered analyses to draw meaningful conclusions
- study lacking culturally/linguistically appropriate research materials

Then, Dr. Artis Dickerson talked about development of the DEM stakeholder engagement initiative. The concept initiative was approved in Spring 2021 (presented at May Council 2021). The Stakeholder Engagement Innovative Center for Advancing Health Equity in Type 2 Diabetes (NOT-DK-22-020) seeks to 1) accelerate equitable engagement of diverse, multidisciplinary stakeholders, 2) provide investigators with highly specialized research resources – expert consultations and education in principles and methods of community-engaged research, and 3) leverage existing and develop new partnerships across US geographical regions. A T2D Stakeholder Engagement Innovation Center would support T2D investigators with unique research resources to enhance community-engaged methods and approaches, equitable stakeholder partnership development, and diverse participation in clinical studies (recruitment and retention). The Center would establish a network of multidisciplinary research investigators, including from underrepresented groups, with expertise in community engaged, NIDDK research and seek to advance health equity in T2D. To accomplish this, DEM is proposing a general center infrastructure that would consist of a central core of expertise in community engagement in T2D, as well as support for local and regional community partnerships. The expected outcome of this initiative is the creation of a rigorous, center-based, multidisciplinary team and a collaborative network resource. Within which, there will be equitable collaboration with people living with T2D, their families and caregivers, partnerships with diverse institutions and organizations, and extensive knowledge in community engagement methods based on health equity principles and frameworks.

Dr. Broadney then focused the discussion on T1D. She noted that T1D also requires attention and resources for improved participation, reach, and health equity. Dr. Broadney mentioned that over the last decade demonstrate that the incidence of T1D is disproportionally rising within minority populations. T1D outcomes are significantly disparate. Minorities living with T1D have worse glycemic control, increased acute complications (e.g., diabetic ketoacidosis), increased chronic complications (e.g., neuropathy, cardiovascular disease), and less diabetes technology use. She noted that stakeholder engagement is an important step toward improving health equity in T1D because T1D research significantly lacks the voice and participation of underserved individuals. The following critical needs quintessential as we aim for racial and ethnic health equity in T1D:

- meaningful stakeholder participation in T1D clinical studies
- improved Recruitment and retention of people with diverse backgrounds
- accelerated use of community-driven and community-engaged methods and approaches

NIDDK is vigorously working on opportunities in the T1D space similar to this stakeholder engagement resource described to the Diabetes Mellitus Interagency Coordinating Committee in March 2022.

Dr. Haire-Joshu said that there was a lot of excitement when the notice came out. She has heard from many community organizations, such as churches, who wondered if they will have a role in the programs to strengthen efforts by academic institutions? Dr. Artis Dickerson said that the hope is for the new initiative to create equitable partnerships with community partners having a seat at the table. Dr. Haire-Joshu said that having community partnership is a good way to focus on community development and equity. She was hopeful that these organizations can have a real leadership role and advance the work in a meaningful way. Ms. Johnson mentioned that having community engagement is very ideal. Potentially having leaders of these organizations as a PI or Co-PI is an important step.

Special Council Review (SCR) (Dr. Haft)

Dr. Haft started by talking about changes to NIH's policy on Special Council Review of research applications. She noted that the threshold of PI other support that triggers a SCR has been changed from $1M direct costs per year to $2M total costs per year. The change is effective with the FY22 May Council round. All other elements of the policy remain unchanged.

Next, Dr. Haft talked about the outcomes analysis requested by Council members of the DEM SCR >$1M applications recently considered. She noted that since 2017, 38 applications were brought to Council where the PI had greater than $1 million of other NIH support. 32 of these applications were ultimately funded with the majority receiving administrative cuts that were larger than the standard pay line R01 cuts. Three of the applications were not funded right immediately but were ultimately funded once issues such as available PI effort were resolved. Of the 38 applications, 16% were not funded for reasons such as overlap with funded work, limited PI effort and low scientific priority.

Dr. Snyder found the analysis very helpful. He asked if it was possible to determine if there were appropriate outcomes when an additional project was funded. Dr. Haft said that determining what the appropriate control group should be and what constitutes "appropriate outcome measures" is quite challenging due to numerous factors. Therefore, what we do assess are the publications that result and their impact.

DEM Meetings and Workshops (Dr. Cefalu)

Dr. Cefalu presented information on upcoming DEM workshops. Council members did not have any questions/comments on the workshops.

Concluding Remarks (Dr. Cefalu)

Dr. Cefalu asked Council members to let DEM know what they would like to have presented during future meeting to help their work moving forward. Dr. Seaquist said that she would like to know the outcome of the new training programs and symposia- Are they having an impact in bringing people in and increasing diversity? Does participation in these lead to job offers?
Dr. Cefalu then thanked the sub-council members and NIH staff for their presentations and comments.