Committee on Energy and Commerce
Implementing the 21st Century Cures Act: An Update from FDA and NIH
November 30, 2017

NIH Questions for the Record

The Honorable Michael Burgess

1. **A goal of 21st Century Cures was to help the transition between research generated by NIH and regulated by FDA. Are there areas where this could be improved? One challenge is that NIH funds new clinical trials that may become difficult to complete because a new drug is approved mid-way through the trial for the condition being researched. Could a "memorandum of understanding" allow for pre-approval data to be shared from FDA to NIH earlier in the process to improve coordination of research and regulation?**

NIH Response:
NIH is committed to speeding the translation of research into improved diagnostics, preventive interventions, and new treatments for patients. The agency works closely with the FDA on improving strategies for doing so through better coordination between the research funded by NIH and the regulatory process overseen by FDA. For example, the NIH-FDA Leadership Council recently established an open access textbook: the Biomarkers, EndpointS and other Tools (BEST) Resource. Biomarkers, or biological markers, are indicators of a condition or disease in the body. These important research tools can be used to measure how well the body is responding to a treatment, for example, and are key indicators used in the regulatory process to evaluate new drugs. The first phase of BEST comprises a glossary that NIH and FDA plan to use when communicating about biomarkers to help ensure a consistent use of terms and a common understanding of issues. In addition, NIH's National Center for Advancing Translational Sciences' (NCATS) Therapeutics for Rare and Neglected Diseases (TRND) program benefits from early interaction and coordination of research with the FDA. A working group of TRND program staff and FDA staff from the Center for Drug Evaluation and Research (CDER) meet on a semi-monthly basis to discuss projects for the TRND program with the goal of an Investigational New Drug Application for each project. TRND staff take FDA/CDER feedback into consideration when developing future project plans, aiming to create a more efficient and successful drug development process.

NIH is exploring mechanisms to enable greater discussion among Federal agencies of upcoming and recent potential regulatory actions and clinical development plans of FDA-regulated products. Such discussions with FDA could include sensitive and proprietary information, although issues around protecting proprietary data, what information can be shared, and when in the process it is best to coordinate would need careful consideration. This type of coordination may prevent investments by government agencies in concepts that have already been studied and could provide key information in developing pre-clinical models for therapy development. Joining FDA data with NIH efforts could produce new opportunities for research coordination and regulation.

2. **As you know, the NIH has made some changes to the definition and requirements regarding clinical trials in order to improve thoroughness and transparency. Can you walk through those changes and the impact on both the patient and the research community? What is the NIH doing to address any concerns and confusion from those in the grantee community who will be impacted by these changes?**

NIH Response:
As the largest funder of clinical trials in the U.S., NIH is dedicated to strong leadership of the clinical trial enterprise. NIH strives to ensure that trials are: relevant to NIH's mission; not duplicative of previous efforts; and, are designed, conducted and reported in a manner that will optimize the likelihood of successfully advancing knowledge and expanding options to improve patients' health. To this end, NIH launched a multi-faceted effort to strengthen how researchers and their institutions develop ideas, design and conduct clinical trials, how NIH chooses which projects to support and oversee progress, and how trial results are shared. The ultimate goal of this effort is to elevate the entire biomedical research enterprise to a new level of transparency and accountability.

These stewardship reforms, which involved extensive public input, include implementation of the NIH definition of a clinical trial among other initiatives such as:

- Dedicated funding opportunity announcements for clinical trials to improve NIH's ability to identify proposed clinical trials, ensure that key pieces of trial-specific information are submitted with each application, and uniformly apply trial-specific review criteria.
- Good Clinical Practice training for NIH-funded investigators and staff who are involved in the conduct, oversight, or management of clinical trials to help assure safety, integrity, and quality.
- Enhanced registration and results information reporting on ClinicalTrials.gov, with the expectation that all NIH-funded clinical trials are registered at, and that summary results information is submitted to, ClinicalTrials.gov for public posting. Increasing the transparency of clinical trial results, among other benefits, will strengthen the design of future clinical trials.
- Use of Single IRBs for multi-site studies to minimize duplicative reviews, allow research to proceed efficiently and expeditiously, and maintain optimal protections for human research participants.
- Development of a clinical trial protocol template and electronic protocol-writing tool to help investigators think through the scientific basis of their assumptions, minimize uncertainty in the interpretation of outcomes, and prevent loss of data.

Impact on Patient Community
NIH's efforts to enhance stewardship of clinical trials aim to produce more efficient and higher quality trials, so that scientific knowledge – and ultimately safe and effective treatments – will be available more quickly. The single IRB policy and protocol template address current delays and inefficiencies in trials by streamlining current processes for protocol review and supporting compliance with FDA regulations for Investigational New Drug applications. Dedicated funding opportunities announcements, which include rigorous review criteria for trials, help NIH ensure

only the highest-quality clinical trials are funded, while Good Clinical Practice training holds researchers and NIH staff to a high standard for quality and safety. Finally, increased transparency, achieved through ClinicalTrials.gov registration and results information reporting, will not only help patients and providers identify relevant clinical trials, but also increase public access to the results of clinical trials.

Also, as part of these efforts, NIH is making ClinicalTrials.gov more user-friendly so that patients, family members, and physicians can more easily find clinical trials that may be right for them. In September 2016, NIH formed a partnership with 18F, a digital services consultancy within the General Services Administration, to explore ways to increase the site's usability. Following a series of consultations with stakeholders, updates to ClinicalTrials.gov in 2017 include resizing pages to fit different devices; new fields to refine a search, including by U.S. state; an improved search results page that provides new ways to refine results; and the ability to download search results in various formats. Collectively, these and other changes will enable patients to more quickly navigate the website to find clinical trials relevant to their condition.

Impact on Research Community

Enhancing stewardship of clinical trials and promoting transparency affects investigators and staff responsible for designing, managing, conducting, and overseeing clinical trial research, institutions that are responsible for clinical trials, research participants involved in clinical trials, and NIH staff who are responsible for stewardship of clinical trials. These enhancements will improve the application and award processes, augment NIH's ability to assess clinical trial applications, improve transparency and accountability, and increase sharing of clinical trial results. NIH is committed to continuing to work with the research community to implement these initiatives and engage in discussion with and outreach to stakeholders as needed, or as concerns arise.

Responsibilities of researchers and their institutions include 1) correctly identifying whether their research meets the NIH definition of a clinical trial; 2) applying to the correct Funding Opportunity Announcement and creating applications responsive to the clinical trial review criteria; 3) completing Good Clinical Practice (GCP) Training; 4) complying with the sIRB policy; and 5) registering and reporting results information in ClinicalTrials.gov. NIH is helping investigators and their institutions with these changes through efforts including the following:

- NIH has developed a website with comprehensive information, including case studies and FAQs to help clarify for our research community whether their research study meets the NIH definition of a clinical trial. These resources prompted follow-up questions and suggestions from the research community, which helped NIH refine these documents. NIH considers these informational materials to be living documents, which we will continue to build on and clarify with input from the scientific community.
- NIH has developed tools to help institutions complete their applications, including a video tour of the new Human Subjects and Clinical Trial information form, an annotated application form set, and a summary of changes between the previous and new forms packages .
- NIH is developing a new electronic system to provide more streamlined management and oversight of human subjects and clinical trial information. The system, expected to be

available by summer 2018, will facilitate monitoring and reporting and enhance strategic planning and portfolio analysis.

- In response to input from the scientific community, NIH extended the effective date for the sIRB policy from May 2017 to January 25, 2018 to give investigators and their institutions more time to prepare for the changes. In addition, NIH has developed FAQs on implementation of the sIRB policy, which include links to example standardized agreements that will allow institutions to rely on a single IRB of record for multisite studies.
- Several NIH Institutes have created free online GCP training. Links to these trainings are available on the NIH website. FAQs are available to provide guidance to the research community.
- NIH has developed a decision tree outlining steps to compliance with ClinicalTrials.gov results information reporting and registration requirements.
- Continued outreach and discussion with all affected research communities to support the goals of these initiatives.

The complementary activities described here intend to help fulfill the NIH mission of improving health through scientific discovery, while preserving the public trust in research through efficient and transparent clinical trials. Working together with the public and the scientific community, these efforts allow NIH to enhance scientific stewardship, dissemination of information, transparency, and to excel as a federal science agency.

3. **We've heard a lot about how the 21st Century Cures Act has helped eliminate red tape for extramural researchers, so they can spend less time on paperwork and more time on science. Can you tell us about how these provisions have helped your researchers over the last year?**

NIH Response:
For decades, NIH has focused on reducing administrative burden in various ways including but not limited to, leading efforts within the Federal Demonstration Partnership and supporting efforts coordinated by the Office of Science and Technology Policy. NIH Director Dr. Francis Collins is co-chair of the National Science and Technology Council's Committee on Science, and NIH is a co-chair of the Research Business Models Working Group, an interagency working group under the CoS, formed to facilitate a coordinated effort across Federal agencies to improve coordination and collaboration among research agencies to streamline requirements for the extramural community.

As an example of NIH's efforts to reduce administrative burden and in response to the FY15 omnibus report language requiring NIH to initiate an Administrative Burden Workgroup, NIH engaged and was actively involved in a collaborative effort to address the issue of administrative burden with the ad hoc committee of the National Academies of Science convened to study Federal regulations and reporting requirements with specific attention to those directed at research universities. The resulting report, "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century" was issued in two parts: Part I focused on those regulatory issues identified as of most pressing concern to the research

community while Part II contains the analysis of topics that adversely affect the nation's ability to optimize its investment in academic research.

The report recommended harmonizing existing policies and processes across Federal agencies (e.g. uniform format for grant proposals and research progress reporting) as well as reducing the regulatory burden associated with policies for human subjects' research, animal care and use, monitoring of sub-recipients, reporting of financial expenditures, and disclosure of financial conflicts of interest. In addition, the Committee recommended that Congress establish the Research Policy Board (RPB), which would serve as a public-private forum for discussions relating to regulations of federally-funded research. Subsequently, the 21st Century Cures Act requires the Office of Management and Budget to establish the RBP to provide Federal Government officials with information on the effects of regulations related to Federal research requirements.

The 21st Century Cures Act signed into law on December 13, 2016, legislates requirements designed to reduce administrative burden by modifying and harmonizing regulations and policies having similar purposes across research funding agencies to ensure that the administrative burden is minimized to the greatest extent possible while maintaining responsible oversight of federally funded research. NIH has implemented several of these provisions including eliminating Paperwork Reduction Act requirements for scientific studies, and automating the issuance of certificates of confidentiality as a "term and condition of award" for awards involving human subjects so NIH-funded researchers no longer need to request one. Further efforts to streamline applications for clinical trials, effective for due dates on or after January 25, 2018, include a structured data form for human subjects research fields that eliminates duplicate information entries. In addition, NIH and FDA partnered together to develop a clinical trial protocol template[1] with instructional and example text for NIH-funded investigators to use when writing protocols for phase 2 and 3 clinical trials. NIH developed a simplified application appendix[2] to rectify inequities in peer review that arise from submission of inappropriate or excessive appendix materials.

NIH continues to work with DHHS to decrease burden involved in financial conflict of interest reports, reducing audit burden by raising the threshold, waiving the requirement for subrecipient monitoring when the subrecipient is in good standing, and simplifying and harmonizing animal care regulations.

NIH is partnering with ORCID[3] to enable scientists to include additional data fields useful to maintain and update biosketches and CVs across multiple platforms. ORCID is a not-for-profit organization that assigns unique persistent identifiers to researchers that supports automated linkages between researchers and their professional activities with the goal of helping people find information and to simplify reporting and analysis. NIH's eRA Commons, an online interface where signing officials, principal investigators, trainees and post-docs at institutions/organizations can access and share administrative information relating to research

[1] NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials

[2] Updated Appendix Policy Eliminates Clinical Trial-Related Materials for NIH/AHRQ/NIOSH Applications Submitted to Due Dates on or After January 25, 2018

[3] Teaming with ORCID to Reduce Burden and Improve Transparency

grants, is establishing a real-time link with ORCID, which allows users to associate ORCID with their eRA account. Further, NIH and other funders are collaborating on the ORCID Reducing Burden and Improving Impact Tracking (ORBIT) project. This effort will expand the ORCID data model beyond publications to data elements typically found on a CV, such as grants, courses taught, presentations, and other research products. To this end, in 2017, NIH developed guidance on how NIH applicants have the option, for applications submitted for due dates of May 25, 2017 and beyond, to cite interim research products such as preprints in applications.

NIH continues to consider ways to address the recommendations to reduce the administrative burden associated with Federal research funding outlined in the NAS report and 21st Century Cures Act. For some of these recommendations, NIH can take action by implementing changes to grant policies.

Because all of the provisions of the 21st Century Cures Act have not been fully implemented, it is too early to determine the effect on research. However, NIH is diligently working with university faculty and research administration staff to ensure that measures implemented by NIH to reduce administrative burden are effective.

4. **The 21st Century Cures Act included language addressing medical rehabilitation research at the NIH. The language changed the requirements for this research, including revise the purpose of the National Center for Medical Rehabilitation Research, or NCMRR, and transfer responsibility for developing a comprehensive research plan to NCMRR from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. What steps has the Office of the Director, in coordination with NCMRR, taken to implement the rehabilitation research provisions in Cures?**

NIH Response:
The National Center for Medical Rehabilitation Research (NCMRR) in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development was established to promote rehabilitation research within the National Institutes of Health, coordinate NIH's research efforts across Institutes and Centers, and foster collaboration with other federal agencies. Together, they provide funding for research projects, career development, small business efforts, and research infrastructure. NCMRR oversees implementation of the updated provisions of Section 2040 of the 21st Century Cures Act; implementation is well underway.
A scientific workshop on the state of rehabilitation research was held in the spring of 2016. This widely attended workshop informed the development of the 2016 NIH Research Plan on Rehabilitation, which was published in late 2016. The Plan, which will be next updated in 2021, sets forth NIH's research priorities in five major areas: Rehabilitation Across the Lifespan, Community and Family, Technology Use and Development, Research Design and Methodology, Translational Science, and Building Research Capacity and Infrastructure. The NIH Rehabilitation Research Coordinating Committee, led by NCMRR, coordinates the NIH's efforts in carrying out the Plan's priorities. Most recently, for example, NCMRR has worked with other NIH Institutes and Centers, and other federal agencies, to sponsor research workshops on Clinical Trials in Rehabilitation (2016) and Optimizing the Investment in Medical Devices for Rehabilitation (2017). In addition, NICHD recently awarded new grants to support research

infrastructure in rehabilitation, including biomechanics and modeling of movement, and regenerative medicine. Working with other NIH Institutes, multiple funding opportunities on aspects of rehabilitation research also have been published, seeking grant applications on sleep disorders in the context of medical rehabilitation, and tailoring cardiac rehabilitation to enhance participation of older adults, among others.

The first analysis of the rehabilitation research portfolio at NIH is complete and was presented as part of NCMRR's annual report at the December 2017 meeting of the National Advisory Board for Medical Rehabilitation Research. Additional data tracking the first two years of changes in the portfolio following the publication of the research plan will be provided to the Board at its May 2018 meeting. The reporting of rehabilitation research is consistent with the definition in Section 2040 and, as required, the Director of NIH's Division of Program Coordination, Planning, and Strategic Initiatives is now an active member of the Advisory Board to facilitate coordination with the NIH Office of the Director.

5. **Part of the intent of 21st Century Cures was to support better collaboration in research and further trans-NIH initiatives. One opportunity for such an initiative would be in better understanding how individuals with three copies of chromosome 21, which causes Down syndrome, are protected from certain cancers and heai1 attacks, but are more likely to succumb to Alzheimer's disease, childhood leukemia, and certain autoimmune disorders. It is my understanding that Trisomy 21 is unique in that it is the only genetic condition with these co-morbid condition connections. Do you see any opportunities for enhanced coordination among NIH Institutes to better unlock the secrets of Down syndrome, and in tum identify ways to prevent and treat Alzheimer's? How can precision medicine advance this goal?**

NIH Response:
One benefit of communication and collaborations across NIH Institutes and Centers, and with the Down syndrome community, is increased coordination of research efforts. Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the public-private Down Syndrome Consortium, which includes 11 NIH Institutes and Centers (ICs), 13 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members, provided valuable input to the 2014 revision of the NIH research plan on Down syndrome. *DS Directions: The NIH Down Syndrome Research Plan* has had an impact on the field of Down syndrome research; in submitting grant applications, many researchers have cited one of its objectives, particularly including the call for research on many of the comorbidities commonly experienced by people with Down syndrome (congenital heart disease, leukemia, and intestinal issues, and other developmental disorders). While life expectancy for people with Down syndrome who are living in the United States has increased dramatically over the last 50 years, these coexisting conditions still require more research and, in turn, a wider variety of expertise as represented across NIH.

Members of the Trans-NIH Working Group meet regularly about the wide-range of investigator-initiated research projects and other NIH-supported efforts to improve the health of people with Down syndrome, including those with co-existing conditions. Studies show that virtually all middle-aged adults with Down syndrome exhibit the neuropathological hallmarks of Alzheimer's

disease: amyloid senile plaques and tau-containing neurofibrillary tangles. The Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS), funded collaboratively by the National Institute on Aging (NIA) and NICHD, provides an exciting opportunity to improve our understanding of Alzheimer's disease among people with Down syndrome, 50 percent or more of whom develop brain changes associated with Alzheimer's by age 40. This initiative seeks to identify biomarkers and track the progression of Alzheimer's in people with Down syndrome, using brain imaging, as well as fluid and tissue biomarkers, to help us understand progression of the disease. In addition, NIH's Alzheimer's research agenda continues to be informed by the recommendations of the April 2013 workshop "Advancing Treatments for Alzheimer's Disease in Individuals with Down Syndrome," which was co-sponsored by NICHD and NIA, as well as the National Institute of Neurological Disorders and Stroke (NINDS), the Down Syndrome Research and Treatment Foundation and Research Down Syndrome (now merged and known as the LuMind Research Down Syndrome Foundation). To that end, NIA is supporting a Phase I clinical trial of an anti-amyloid immunotherapy for cognitive impairment in adults aged 35-55 with Down syndrome. The NIA also funds a project investigating the natural history of amyloid deposition in adults over the age of 30 with Down syndrome. This longitudinal study investigates the progression of amyloid deposition using brain imaging, while cognitive function of study participants, at the time of imaging, is also assessed to determine if there is a predictable trajectory toward clinical AD.

In addition, NIH assists the research community by providing research resources that might otherwise prove cost prohibitive for them to support individually. To advance research on Down syndrome, NICHD supports a contract for the leading repository of mouse models for Down syndrome. The Cytogenic & Down Syndrome Models Resource at Jackson Laboratory maintains and distributes mouse models for Down syndrome, as well as the study of chromosomal aneuploidy, and has recently funded a new research project to develop new mouse models for Down syndrome. The NICHD Brain Bank for Developmental Disorders at the University of Maryland, which was first funded in 1991, is now a tissue collection site (including Down syndrome). The site is part of the NIH NeuroBioBank, a partnership involving NICHD, NINDS, and NIMH, to enhance nervous system tissue collection across sites and disorders, including control samples, with a centralized IT platform and shared protocols. Efforts to promote collection of brains from adults with Down syndrome through the NIA-funded Alzheimer's Disease Centers also are being explored.

Together with NIMH and NINDS, NICHD encourages studies that develop, validate, and/or calibrate informative outcome measures for use in clinical trials for individuals with intellectual and developmental disabilities, including Down syndrome. And *DS-Connect®*, a Web-based DS patient registry that was established in 2013 and now includes about 3,700 participants, provides researchers with a tool to recruit for their research studies. The registry benefits families, too; ultimately, the registry will link to biorepositories of tissue samples and other resources, making it easier for participants to take part in clinical studies for new medications and other treatments for Down syndrome and its coexisting conditions.

Current efforts include ongoing discussions with member organizations of the Down Syndrome Consortium to help determine which objectives identified in *DS Directions: The NIH Down Syndrome Research Plan* should be prioritized, as well as efforts related to brain and

biospecimen banking. NIH IC leadership and leaders of several of the Down syndrome organizations also met in December 2017 to explore public-private partnerships to promote research interests related to Down syndrome.

The Honorable Cathy McMorris Rodgers

The 21st Century Cures Act improved upon the National Pediatric Research Network Act, which was initially crafted in 2013 with the intent to address the shortfall in pediatric biomedical research using the well-proven network model to foster greater collaboration, coordination, and sharing of resources. As an author of the underlying statute, I can tell you that our vision was that each consortium would be investigator-initiated, consist of multiple institutions in a "hub and spoke" arrangement and be competitively selected through a rigorous review process. My understanding is that the NIH maintains it has implemented the NPRNA by establishing the IDeA States Pediatric Clinical Trials Network. I suppmi your current efforts, but am concerned about the geographical limitations on the network as well as precluding funding for all phases of scientific research other than clinical trials.

1. **Do you have plans to further implement the full scope of the NPRNA, and if not, why?**

NIH Response:
Pediatric research has been and continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas. In Fiscal Year (FY) 2017, the NIH funded approximately $4.1 billion in research grants and projects directed specifically at pediatric research, an increase of $220 million over FY 2016 spending. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funds the largest portion of pediatric research among the 27 NIH Institutes, Centers, and Offices (ICOs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, all of the ICOs support various aspects of pediatric research, such that the NICHD alone accounts for only 18 percent of the total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

The NIH intends to meet the goals of the National Pediatric Research Network Act through four networks: the Environmental influences on Child Health Outcomes (ECHO) program IDeA States Pediatric Clinical Trials Network, the Pediatric Trials Network, the Neonatal Research Network, and the Rare Diseases Clinical Research Network.

The IDeA States Pediatric Clinical Trials Network (ISPCTN) provides medically underserved and rural populations with access to state-of-the-art clinical trials, apply findings from relevant pediatric cohort studies to children in IDeA state locations, and build pediatric research capacity at a national level. Funding for this new network also supports professional development of faculty-level researchers and their support teams in the conduct of clinical trials research. The awards are a component of the ECHO Program, which is investigating how exposure to a broad range of environmental factors in early development, from conception through early childhood,

influences the health of children and adolescents. It is important to note that the ISPCTN funds research centers in States where there was little to no pediatric research capacity prior to its creation.

ISPCTN consists of multiple institutions arranged in a "hub and spoke" model, with each of its 17 clinical sites in a separate IDeA state and its central Data Coordinating and Operations Center located at the University of Arkansas for Medical Sciences. ISPCTN uses this network model to foster collaboration, coordination, and sharing of resources not only within the Network but also to partner with other NIH networks focused on pediatric biomedical research to increase representation of children from beyond the IDeA states.

The Pediatric Trials Network (PTN) is comprised of over 100 clinical research sites across the U.S with over 7,000 children enrolled. The PTN provides evidence for the formulation, dosing, efficacy, and safety of medications and medical devices in infants and children. The PTN conducts pediatric clinical drug trials in a variety of therapeutic areas, including but not limited to cardiovascular diseases, cancer, infectious diseases, gastroenterology, respiratory diseases, neonatology, and medical devices. Current studies include research on the pharmacokinetic and pharmacodynamics properties of antipsychotic drugs in children and adolescents, a study on the effectiveness of sildenafil to decrease the risk of pulmonary arterial hypertension in preterm infants, and research on the pharmacokinetics of methadone to treat opioid withdrawal in children.

The NIH also supports a national network focused on neonatal research. The Neonatal Research Network (NRN) is a collaborative network of neonatal intensive care units across the United States, comprising 18 clinical centers and a data coordinating center. Focused on newborns, particularly extremely low-birth-weight infants, the NRN conducts clinical trials and clinical studies in such areas as sepsis and other infections, bronchopulmonary dysplasia and other lung conditions, and necrotizing enterocolitis, a condition in which the intestines lack oxygen or blood flow.

Finally, the NIH prioritizes research into rare diseases that affect children. The Rare Diseases Clinical Research Network (RDCRN) program, led by the National Center for Advancing Translational Sciences (NCATS) in collaboration with other NIH Institutes, is a model designed to advance medical research on rare diseases. The RDCRN currently includes 100 institutions and clinical sites in 33 States examining over 6,000 children each year. Several of the Rare Diseases Clinical Research Consortia (RDCRC) focus on or include rare diseases that affect children, including brittle bone diseases, mitochondrial diseases, immune deficiencies, Rett syndrome and Rett-related disorders, sterol and isoprenoid conditions, urea cycle disorders, genetic disorders of mucociliary clearance, developmental synaptopathies, and lysosomal storage diseases, among others.

Collectively, these networks support research capacity across the U.S. to address unmet pediatric research needs. NIH fully expects these networks to continue to expand and will continue to seek out partnerships with all stakeholders and other pediatric research consortia.

The Honorable Marsha Blackburn

2. **Children sometimes fail to benefit from NIH's research because there is no existing mechanism to collect and report the ages of patients enrolled in trials, meaning we have no idea how many children participate in NIH studies. That is why I worked with Rep. Capps to include our bill, the Children Count Act, in the Cures Act to require NIH to collect this critical information. Can you please update us on how NIH plans to implement this provision and when NIH will require the information to be collected for all studies?**

NIH Response:
For nearly 20 years, it has been the policy of NIH that children must be included in all NIH-supported research involving human subjects, unless there are scientific or ethical reasons not to include them. The NIH is committed to the inclusion of all relevant age groups, including children and older adults, in the clinical research studies and clinical trials it supports. Age-appropriate inclusion leads to better science and ultimately informs how interventions affect us all.

NIH has taken several steps to implement provisions in the 21st Century Cures Act requiring NIH to publish data on relevant age categories, including pediatric subgroups. These steps include:

- In April 2017, NIH announced its new FORMS-E grant application forms, required for applications submitted on or after January 25, 2018. This forms package requires investigators proposing human subjects research specify the minimum and maximum age of participants in the proposed study.
- In April 2017, NIH issued a Request for Information (RFI): Invitation to Comment on Inclusion in Clinical Research Across the Lifespan (NOT-OD-17-059) to solicit input from the scientific community and general public regarding appropriate inclusion of pediatric and older populations in research studies involving human subjects. In the RFI, NIH requested stakeholder input on age-related data, statistics, and reporting.
- On June 1-2, 2017 NIH held a workshop on Inclusion Across the Lifespan, which brought together experts in clinical research to discuss barriers and opportunities for participation of children and older adults in clinical research studies. Among the topics discussed was the need for better data on clinical research participation for children and older adults.
- At the December 2017 Advisory Committee to the Director meeting, NIH presented a proposed Inclusion Across the Lifespan policy, including a plan for collection of de-identified individual-level data on participant sex/gender, race, ethnicity, and age at enrollment.
- In December 2017, NIH revised the NIH Policy and Guidelines on the Inclusion of Children. The policy, now titled the NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects, applies to individuals of all ages and requires NIH-supported clinical research studies submit de-identified individual-level data on participant sex/gender, race, ethnicity, and age at enrollment in progress reports. This policy applies to applications received on or after January 25, 2019.

NIH looks forward to the availability of additional data on the age of participants in clinical research studies. Information on the proposed age range of participants and individual-level data on age at enrollment of clinical research participants will help NIH consider and monitor the appropriateness of participant age distribution in the context of the scientific question proposed. Individual-level data on age at enrollment and other demographic variables will allow NIH maximum flexibility and detail for analyses of participant age in the NIH portfolio.

The Honorable John Sarbanes

The 21st Century Cures Act seeks to accelerate the development of new antibiotics as part of our national effort to address the increasing threat of antibiotic resistant organisms. This threat, combined with the dwindling pipeline of novel antibiotic research, requires policies that prevent inappropriate use of antibiotics.

One potential way to do that is to increase the use of penicillin allergy testing. While about 10 percent of the population reports a history of penicillin allergy, studies show that approximately 90 percent or more of these patients are actually not allergic to penicillin and are able to take these antibiotics safely. If these individuals are tested to verify they are truly allergic, they may be able to prevent the unnecessary use of broader spectrum antibiotics.

1. **Has the NIH initiated research in this area with the goal of changing the behavior of patients and providers?**

NIH Response:
NIH has encouraged the development of research proposals on drug allergy through funding initiatives (see response to Question 2). NIH is not funding research to determine the role that confirming an individual's historical penicillin allergy may play in the prevention of inappropriate antibiotic use.

NIH continues to prioritize research to address the increasing threat of antimicrobial resistance and is an important partner in implementing the *National Action Plan for Combating Antibiotic-resistant Bacteria*. Current NIH efforts to address antimicrobial resistance and to prevent the inappropriate use of antibiotics include the investigation of the mechanisms of drug resistance and pathogenesis via foundational basic research and cutting-edge genomic sequencing technologies; detection and tracking of pathogens with simple and accurate diagnostics; development of next-generation vaccines to prevent bacterial infections; and identification of novel antibacterial drugs and treatment regimens. The NIH also is collaborating with other HHS partners on the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the global public-private partnership dedicated to the preclinical development of new antibiotics.

2. **What initiatives has the NIH undertaken to implement the research agenda developed by a workshop on drug allergy held in 2013?**

NIH Response:
In addition to the 2013 workshop on drug allergy, which brought together U.S and international experts in the field of drug allergy, NIH held a second workshop on drug allergy in 2015. Based on the research agendas developed during these workshops, the NIH developed a drug allergy-related initiative. This effort includes two companion NIH-wide initiatives titled "Serious Adverse Drug Reaction Research" (PAR-16-274 and PAR-16-275) to stimulate new research on drug reactions, including research on drug allergy. In addition to these NIH-wide efforts, research on drug allergy also has been a focus of the NIAID initiative "Asthma and Allergic Diseases Cooperative Research Centers" (AADCRCs; RFA-AI-16-065). The AADCRC program promotes multidisciplinary basic and clinical research on the immunological basis, pathobiology, diagnosis, treatment, and prevention of asthma and allergic diseases.