National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
Optimizing Clinical Trials In Chronic Disease

Virtual Meeting

July 24–25, 2023

SUMMARY REPORT

MONDAY, JULY 24, 2023

Welcome from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Robert Star, M.D., NIDDK

Dr. Robert Star, Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK, welcomed the participants. He noted that the NIDDK has convened a workshop focusing on clinical trials in such specific clinical areas as dialysis, chronic kidney disease (CKD), or acute kidney injury. This workshop, titled "Optimizing Clinical Trials In Chronic Disease," focuses on the larger question of how to best plan and implement clinical trials. This workshop also addresses the broader area of best practices for community engagement throughout the design and implementation phases, with attention to devising the scientific question or the clinical trial hypothesis. Because design and implementation issues occur throughout the trial regarding recruitment, retention, and disseminating data and results, this workshop addresses interventions and improving outcomes for populations.

Dr. Star highlighted that KUH has made "patient engagement," or engaging people with kidney disease, a central part of its culture. The aim has been to include this component in all recent clinical studies and trials—from the early planning phase to implementation and beyond. Continuing that trend, people with kidney disease opened this workshop and participated in the breakout groups and were encouraged to ask questions throughout. The primary goal was to open the line of communication among all people who are interested in participating and conducting clinical trials. The workshop's agenda also featured presentations from other governmental agencies, including the U.S. Food and Drug Administration (FDA), which showcased a suite of planning tools for clinical trials, as well as lessons learned from completed or in-progress trials. In addition, clinical trial professionals provided their perspectives on implementing trials. Last, the workshop included a series of breakout sessions that aimed to start a dialogue extending beyond this meeting. Dr. Star thanked the planning committee—including the patients; the lead organizers, Dr. Kevin Abbott, Program Director, KUH, NIDDK, and Dr. Jenna Norton, Program Director, KUH, NIDDK; and other NIDDK and National Institutes of Health (NIH) staff and external colleagues—for coordinating the workshop.

Welcome from Workshop Planning Committee and Patient Panel Representatives

Glenda Roberts, Kidney Research Institute (KRI); Paul Conway, American Association of Kidney Patients (AAKP), Virginia Renal Disease Council

Ms. Glenda Roberts, KRI, also welcomed everyone to the workshop. As a person living with kidney disease, director of external relations and patient engagement at KRI, and information technology and industry and business leader, she commented on the importance of recruitment, retention, and results of clinical trials and engaging more patients to participate. Data indicate that 62 percent of Americans believe that clinical trials are important, regardless of demographics, political persuasions, or health status; however, diversity in trials is limited. In fact, the majority of participants are White (93%), and most are female (67%). Ms. Roberts hopes that this workshop will address ways to increase diversity in

clinical trials, noting that a key point of recruitment is to "ask" patients to participate. In terms of retention, she noted that keeping participants informed of the trial's progress is critical to success. For results, she emphasized putting the science into clinical practice, resulting in improvements for patients.

Mr. Paul Conway, AAKP, thanked the NIH and NIDDK for sponsoring this workshop and welcomed attendees. From an advocacy community perspective, Mr. Conway noted that in 2019, AAKP declared the Decade of the Kidney™ from 2020 to 2030, aligning with the efforts of the NIH, FDA, and the U.S. Departments of Defense and Veterans Affairs (VA) to include patients' choice for treatment modalities. Such efforts also were observed in Congress and the White House and across several U.S. Administrations. As a result, patients are leading policy changes, are strong partners in research, and are writing editorials and commentaries in medical journals about the burden of kidney disease, as well as the need to have more diverse trials. The advocacy community deploys its resources to be good allies and understands that research shapes not only science and medical practice, but also policy. Advocacy facilitated the 2013 legislation that allowed HIV to HIV-positive kidney transplantations, the 2016 White House conference on organ donation, the 2018 U.S. Department of Labor new Family Medical Leave Act protections for organ donors, the 2019 Executive Order on Advancing American Kidney Health, and the 2020 Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act (commonly called Immuno Bill). Mr. Conway conveyed that future efforts must translate the advocacy community's impact in clinical trials.

Overview and Charge of the Workshop: How Trials Succeed or Fail—Best Practices and Challenges
Kevin Abbott, M.D., M.P.H., NIDDK

Dr. Abbott expressed appreciation to the planning committee for organizing the workshop, thanked everyone for attending, and presented an overview of the problem and charge. Clinical trials are conducted because they are expected to change practice. The consumers, audiences, or customers of these trials are the clinical providers and the lay public, including patients, academia, industry, and the media. Recent reports shed a spotlight on clinical trials and have indicated problems with the way trials are being conducted and results reported. The issue is the need for trials to be conducted well and primary data on the interventional outcomes (positive or negative) to be reported and appropriately identified. An estimated 40 to 50 percent of trials terminate early and never yield a meaningful answer to the research or clinical question.

This workshop focused on recruitment and retention in trials, which are the leading reasons why trials terminate early. Dr. Abbott emphasized that people using trial data want better-performing trials. The ongoing confusion as to which trials are definitive (i.e., causative) and the need for multiple trials of this type to shape practice have damaged public trust and led to disinformation or misinformation. The field needs to better understand how to conduct new, high-quality clinical trials, and focusing on recruitment and retention is a good place to begin. He noted the anticipated outcomes of this workshop: to start a dialogue and conversation and work together to find the answers. Investigators with unanswered questions about submitting clinical trial-related applications were encouraged to contact NIDDK program staff prior to applying.

Dr. Abbott noted the leading reasons why trials do not succeed. In recent years, clinical trials have not reached enrollment for the indicated population by the end of the study, and most had a preventable reason. Trials terminated early for lack of separation procedures or safety reasons. Trials experienced inadequate or delayed reporting of the required research findings. He explained that NIDDK's notices of funding opportunities for clinical trials (e.g., PAS-23-086: Small R01s for Clinical Trials Targeting Diseases within the Mission of NIDDK [R01 Clinical Trial Required]) list contact information for program staff at the end. Dr. Abbott reiterated that investigators should reach out to get their questions

answered prior to a grant submission. In addition, human subjects research resources can be accessed from the NIDDK Human Subjects Research webpage.

The workshop agenda's approach was unique in presenting the problem and then discussing the solution. The invited speakers described the best ways to match research questions with study designs (both adaptive and decentralized). Participants received insight from industry on how to reach out to study enrollees, learned important tips from the FDA on planning ahead for both "unexpected" and expected delays, and gleaned lessons learned from investigators working on NIDDK-funded clinical trials. The workshop ended with breakout sessions, with the goal of identifying strategies for improving the success of clinical trials, including best practices for planning trials. The expected outcome will be a meaningful, complete, and timely reporting of trial results. Dr. Abbott noted that a summary of the workshop will be posted to the workshop website soon after the meeting and that an external publication working group at a future date would submit the workshop's proceedings to a peer-reviewed journal.

Patient Panel Experience in Clinical Trials
Moderator: Janice Lea, M.D., Emory University
Panelists: Paul Conway, AAKP, Virginia Renal Disease Council
Glenda Roberts, KRI
Christine Hernandez, RN, AAKP
Dammeon Marshall, Ph.D., MSW, AAKP

Dr. Janice Lea, Emory University, remarked on the importance of beginning the workshop with the patient's perspective to initiate the discussion of the problem noted by Dr. Abbott. She introduced and invited the panelists to tell the stories of their personal experiences in clinical trials, touching on what has succeeded and the challenges.

Mr. Paul Conway has been living with kidney disease for 42 years and received a kidney transplant 26 years ago. He reported on the AAKP's 2020 survey of clinical trials insights on patient interest and participation. Seventy-nine percent responded that they had not been asked to participate in a trial, and 93 percent of the 21 percent that had been indicated that they would participate in a future clinical trial. Of the 79 percent who had not participated in a clinical trial, 68 percent were interested but would need more information about the trial. This group considered their overall health as the number one risk of engaging in a study, followed by the possibility of side effects. Mr. Conway noted that these responses highlight issues of informed consent and disclosure, which should remain at the forefront of discussions when designing clinical trials and suggests that information privacy is of a lesser concern. In terms of benefits, 41 percent of survey respondents indicated advancing science or treatment of their disease as the primary reason for participating in a trial, and 29 percent felt that participation might help save or improve the lives of patients who have the same type of condition. Collectively, this 70 percent is essentially citing something bigger than themselves and are shedding light on what motivates them, which researchers tend to call "patient idealism." Mr. Conway emphasized addressing and respecting idealism to ensure that research helps prevent suffering and minimizes burdens for people who may never meet, and understanding idealism as a prime motivator for clinical trial participation.

Ms. Glenda Roberts, a kidney disease patient, outlined key points on how patient partners fit into clinical trials, with comprehensive stakeholder engagement as the guiding principle. She emphasized engaging patients early in the process and including them in the trial design, as well as developing simple, easy-to-understand informed consent that clarifies the risks or potential harms. Ms. Roberts encouraged leveraging the NIDDK-sponsored Kidney Precision Medicine Project (KPMP) model of addressing the legal issues in a way that patients feel they understand what they are committing to. For example, investigators can consider providing a no-fault harm insurance policy because participation may require biopsies and may involve adverse events; some may be severe, thus ensuring that patients feel confident.

Investigators should establish an ethics committee to oversee the return of results, which also builds confidence among enrollees. In addition, Ms. Roberts strongly encouraged promoting the concept of "patient partners" versus study participants and engaging them in the research, making the effort to ask people to participate in trials, and recruiting from diverse populations. She noted that patient partners can highlight the needs and help to address concerns or issues. In her final key points, Ms. Roberts encouraged preparing clinicians and practitioners to have conversations with their patients from different cultures and backgrounds and addressing implicit bias appropriately to help overcome barriers to recruitment, establishing community engagement committees or community advisory councils, and expanding community outreach and community engagement.

Ms. Christine Hernandez is a registered nurse, home dialysis patient, and AAKP ambassador (Illinois). She has participated in research studies that revealed she has a rare kidney disease. Ms. Hernandez enrolls in trials to help advance treatment or provide helpful information to similar patients. She has observed some procedures that would discourage kidney disease patients from participating in trials, which she further described. During a COVID-19-related study, the questionnaire links often did not work, and reaching the study leaders after hours was challenging. She noted that these types of issues can be frustrating, especially if a person is answering the questions after completing a dialysis treatment. Another study had what seemed to be never-ending questionnaires that were exhausting to complete accurately. She encouraged condensing such questionnaires so that they would be easier to finish. Ms. Hernandez shared that she participated in a study that required a biopsy that left her in pain for 2 weeks and resulted in a large scar on her forearm. She is expected to return for a follow-up biopsy but is having reservations. Ms. Hernandez has been fortunate to be asked by clinicians or other health care professionals to participate in trials and has been provided detailed information, but she recognizes that this is more the exception than the routine. She emphasized that the approach to discussing what the study entails attracts people to participate in a clinical trial.

Dr. Dammeon Marshall is a kidney disease patient and AAKP ambassador (Georgia) who searched websites and consulted with his doctor on ways to change clinical practice. Dr. Marshall has been an advocate for conveying what goes on in the bodies of kidney disease patients like himself, and he readily participates in clinical trials to be that person who makes a difference. He does a plethora of volunteer work with Dr. Lea in communities in Atlanta and was instrumental to Emory University's Patient-Centered Outcomes Research Institute (PCORI) grant, which is investigating patient mentorship and patients with CKD who are on dialysis. Dr. Marshall advocates for self-love and living well.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- When asked about recommendations on recruiting patient partners, Ms. Roberts explained that the aim is to choose someone who is willing to make a long-term commitment (e.g., 5 years or more), is involved early in the process, and is willing to participate in multiple committees and projects, including publication tasks. Many well-known patient advocates (some present at today's workshop), AAKP staff, and the National Kidney Foundation (NKF) can assist with finding patients to participate in studies.
- In response to a question about reimbursing patients for participating in trials, Ms. Roberts first noted that patient partners have a "lived" experience and unique domain expertise and should be recognized and valued as other members of a study. Various studies have different policies, some of which compensate for community engagement, and others (e.g., KRI) offer an honorarium.
- When asked about overcoming the challenge of having adequate diversity in patient partners in trials, Mr. Marshall noted that as a panel member for some pharmaceutical companies, he visits their websites to determine how they define and/or reflect diversity. He suggested connecting

with community partners, agencies, or ambassadors that can represent your company or organization to promote diversity. Mr. Conway emphasized ensuring that research teams reflect the communities being recruited. He suggested reaching out to advocates (e.g., NKF, Home Dialyzors United) that have connections in communities, fostering partnerships to ensure sustainability for a 5-year study, and developing a long-term strategy to ensure that those communities are fully represented. Ms. Roberts added that diversity should be thought of broadly as all the ways people are different (e.g., age, demographics, political preference) and not just consider race and ethnicity.

- Participants discussed surveys from a patient's perspective, including appropriate length and accessibility. An adequate survey is one that engages but does not exhaust the patient and should take 5 to 10 minutes to complete. Electronic surveys are favored over paper versions, but the platform used should be verified as functional and beta-tested with patients. The socioeconomic status of people with kidney disease and their access to various platforms must be considered when developing surveys or questionnaires. Patient engagement surveys to address both the problem to be solved and how the patient's voice would help should be developed. Research Electronic Data Capture (commonly called REDCap) has the capacity to break surveys down into small segments and deliver them via a computer application (app), with reminders to complete the next segment over a period of time. Surveys should include the text messaging feature regardless of the platform used.
- Successful examples of collaborative efforts among industry, academia, and patient advocacy groups and optimizing chronic disease clinical trials include community engagement committees that are composed of scientists, patients and the clinicians, KPMP, and APOLLO (APOL1 Long-Term Kidney Transplantation Outcomes Network).
- The KHI Patient and Family Partnership Council has developed a guideline or template to help organizations design patient engagement committees, and it provides instructions on clinical trial participation.
- Participants discussed distrust from the general population in the scientific community and pharmaceutical industry being a challenge to trial recruitment. Trust is about having a good relationship with the institutions and physicians. Institutional and systemic racism continues to be a problem and a way to improve trust is to develop a working relationship with primary care physicians. Medical and psychological aspects of trust exist. Primary care physicians often do not have discussions with kidney disease patients about their overall health but should consider a holistic approach to their treatment. People are speaking unfavorably of civil service workers, researchers, and scientists who are trying to improve the lives of people with chronic diseases. In a free market health care system, the responsibility exists to call attention to this type of behavior when people are saying things that are not true and are maligning people's motivations for why they conduct science and research. Active engagement and clear communications are essential in the environment in which we operate. Negative messaging can be overcome and this is where trust and personal relationships with principal investigators (PIs), doctors, and study recruiters become fundamentally important.

Matching Study Question to Study Design and Budget
Elizabeth Lorenzi, Ph.D., M.S.P., Berry Consultants, LLC

Dr. Elizabeth Lorenzi, Berry Consultants, described matching the study design to the study question (a reversal of the previous title). Dr. Lorenzi focused her presentation on a recipe for building a trial that includes five steps—understand the science; develop a trial design skeleton; simulate candidate designs; reiterate and adapt one of the rules based on the simulations; and write up the final design—on which she further elaborated.

Understanding the science (step 1) is the most important step. The trial design should be a unique solution to the problem and should have clearly defined goals related to the therapy, disease, endpoints, and constraints, as well as measures of success (e.g., failed or successful trial criteria). An approach to identify the uncertainties also should be established, which, for example, would be the adaptable features of the study for addressing failures. Dr. Lorenzi emphasized that unlike traditional fixed designs for obtaining the results, adaptive clinical trials avoid arriving at the wrong answer and drawing an incorrect qualitative conclusion. They maximize the information obtained and minimize the risk to the study subjects (e.g., enrollees) and sponsor. Moreover, adaptive strategies utilize various tools, including frequent interim analyses, response-adaptive randomization of enrollees, and population enrichment decisions based on responses to treatment.

The trial design skeleton (step 2) for a trial begins with the primary goal of the study and includes the endpoints (primary, secondary, and/or biomarker), study arms (i.e., groups or subgroups) and sample population size, and enrollment. The overall design consists of two parts: part 1, initial enrollment to an interim analysis of *N =100,* and part 2, increased enrollment and analysis of *N =200* and higher until the therapeutic dose futility is reached and/or to the final analysis. The simulation (step 3) encompasses virtual subjects and the execution of variables. Assumptions are used to determine how the trial is running. The output results of the simulated trial often are summarized as operating characteristics, such as power, type 1 error, average sample size, and frequency of selecting the correct dose.

Repeat of the design (step 4) is necessary because the right design is rarely the skeleton design; simulations are utilized to refine a design, and this naturally leads to operating characteristics. The adaptive design report (step 5) provides full details on the design, model, and simulations.

Other tools for improving the success of a trial include linking the decentralized trial design to recruitment, which allows trial-related activities to take place at participants' homes or other convenient locations and reduces barriers to participation, all aiming to increase the breadth and diversity of participants in clinical trials. The Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (commonly called PRINCIPLE) is one such model in which the research comes to the patient.

Evaluating Behavioral Interventions for Chronic Disease: Design, Analytic, And Power Challenges and Resources
David Murray, Ph.D., Office of Disease Prevention (ODP), NIH

Dr. David Murray, Director, ODP, explained that behavioral interventions can be composed of single or multiple components. Intervention can be single-level and delivered to individual participants or multi-level and delivered to groups of participants. Interventions can be delivered in person or via smartphones or apps. Delivery agents are diverse and include clinicians, counselors, teachers, exercise coaches, and teams of agents. Behavioral interventions address two key questions for study design and analysis. First, how are participants assigned to study arms? Second, how is the intervention delivered to participants?

Three types of randomized trials exist: randomized control trials (RCTs), individually randomized group treatment trials (IRGTs); and group-randomized trials (GRTs) or cluster-randomized trials. In RCTs, individuals are randomized to study conditions with no interaction among participants after randomization. No group sessions, virtual interaction, or shared intervention agent occurs. For IRGTs, individuals are randomized to study conditions with interaction among participants or with a shared intervention agent after randomization (e.g., surgical or behavioral trials). In GRTs, groups are randomized to study conditions with interaction among the members of the same group before and after randomization. In parallel GRTs, interventions are similar, with control conditions throughout the trial

and no crossover. Conversely, in stepped-wedge GRTs, all groups start with the control condition, cross over (random and staggered) to the intervention condition, and receive the intervention before the end of the study.

Dr. Murray noted that any trial that randomizes groups or clusters or delivers interventions to groups or clusters through a shared intervention agent experiences unique design, analytic, and power challenges. In fact, the number of units available for randomization may be limited and may constrain the degrees of freedom available to test the intervention effect, thereby limiting power. Randomized trials always involve correlated or clustered data, and that issue must be addressed in the power analysis to avoid an underpowered trial. This issue also should be addressed in the data analysis to avoid an inflated type 1 error rate. This issue is not widely understood by NIH program staff or by extramural investigators. The ODP and Office of Behavioral and Social Sciences Research (OBSSR), NIH, provide resources to help address these issues. Resources include the ODP's Research Methods Resource website; ODP's self-paced online course on pragmatic trials in public health and medicine; and OBSSR's Summer Institute on Randomized Trials Involving Behavioral Interventions, a 10-day in-person (Bolger Hotel and Conference Center in Potomac, Maryland) study for junior investigators.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- When asked what strategies are recommended to ensure that trial results affect in-clinic appointments and providing the results to patients, Dr. Lorenzi highlighted the need to ensure that the results are interpretable to patients and that clinicians understand how to act on the results. In addition, she noted making sure that the study design is answering a question that impacts clinical care and understanding what populations of patients can be affected, as well as the treatment effect. Last, she noted establishing endpoints meaningful to the patient that convey to the patient the effect of a therapy on overall health.
- In response to a question about the cost for attending the ODP and OBSSR courses, Dr. Murray noted that the ODP online courses are self-paced and that those and other resources are publicly available at no cost to the user. OBSSR, with co-sponsor National Heart, Lung, and Blood Institute, incurs the expenses of investigators attending the summer institute program.
- Regarding appropriate control groups for behavioral trials, the panelists clarified that the nature of the intervention largely dictates the appropriate control and depends on the research question being addressed.
- When asked about the responsibility for consenting patients in cluster trials, Dr. Lorenzi explained that consenting requirements vary by setting (school, hospital, worksite, and clinical practices) and depend on the intervention and the related risks. Generally, in a program offered through clinical practices, patients should be informed of the trial options and consent to participate in the study. In addition, consent is required from parents of an intervention added to the standard school curriculum.

Pretrial Planning and Preparation: Stakeholder, Patient, and Community Engagement for Improving Diversity in Clinical Trials
Ashley Moultrie, CCRP, Javara

Ms. Ashley Moultrie, Javara, discussed ways to select sites for trials, noting that the stakeholders are the internal team, selected vendors and materials used, and patients in the communities being served. The internal team evaluates staffing, and the diversity, equity, and inclusion (DEI) teams ensure sufficient training well before trial activation and implement deployment of staff into the community. Vendors

evaluate the equity and inclusivity of trial materials, including the materials for language translation, product accessibility, and inclusive terminology. The community is the location of potential patients and should be made aware of the research organization and the work that they incur. Ms. Moultrie challenged investigators to identify ways to become active members in the communities where they work and where patients are being recruited to help build trust among the community.

In industry, community outreach is one aspect of building community that is done well, but it is just one-way communication that tells community members about an issue, problem, opportunity, or decision. Community engagement, however, is a strategic process that seeks to better engage the community to achieve long-term and sustainable outcomes, processes, and relationships and is best for building community. The community engagement timeline consists of three phases. The first phase is protocol writing and development and provides an opportunity for including patients in the writing and design of a trial and identifying internal and external community champions. The second phase, trial activation, is a time to increase engagement efforts with locally based team members and continue to build awareness. The third phase is post-trial activation and is the time to honor and celebrate participants and maintain relationships built in the second phase through continuous engagement.

In closing, Ms. Moultrie highlighted engagement opportunities and noted that her team frequently attends and sponsors local health fairs and walks. She encouraged thinking creatively about ways to engage communities and to determine the best ways research teams can serve and support the communities they are engaging.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- In response to a question about the hardest challenge of outreach or inclusion, Ms. Moultrie noted the need to overcome being uncomfortable with DEI and to grow to make progress.
- Ms. Moultrie elaborated on outreach to the faith-based community, explaining that this approach can be a deciding or driving factor for some people in thinking about and navigating their health care. Pastors or faith leaders can speak to patients and help them with making decisions, clarify a study process, and provide overall support.
- When asked about an example of a challenging engagement event and how it was resolved, Ms. Moultrie noted that logistically, some of the challenges depend on the community being served. The key is to understand the community landscape (e.g., the accessibility of materials) and to plan ahead but be flexible about changing the original engagement plan, which may not be working.
- Regarding ways to apply an equity and anti-racism lens, Ms. Moultrie explained that during planning is the best time to consider health equity, and from a holistic lens. She emphasized that areas with the greatest need should be equipped with the resources they need prior to starting a clinical trial, as well as addressing all social determinants of health relative to a specific area, such as lack of transportation to visit the clinic.
- A participant asked about the challenges involved with building community connections when you are the PI of a multisite trial and you have not had opportunities to personally connect with each clinical site. Ms. Moultrie responded that you need to ensure that the best teams are in place at each site. She also noted to discuss with the site leaders who coordinate daily activities to convey the study participants' complaints and concerns, as well as those of the staff working with the patients.

- Ms. Moultrie highlighted a Javara collaboration in a recent large-scale respiratory syncytial virus (RSV) vaccine trial (NCT05127434) in adults ages 60 and older as an example of a successful recruitment utilizing a community grassroots approach. Her team determined the knowledge level of the community and RSV status of potential participants 5 to 6 months prior to the trial, which resulted in outcomes of enrollment that surpassed expectations. Participation from underrepresented minorities averaged 21 percent.
- When asked about a radical method for connecting community gatekeepers with clinicians or other recruitment methods, Ms. Moultrie noted one such method: to discuss health care as a career option with high school students and possibly incorporate clinical trial topics into high school curriculums. She emphasized first connecting with community leaders and community health workers, who are well-trusted and well-known, which will be key to establishing these relationships.

NIH Clinical Trial Planning Tools Overview
Salina Waddy, M.D., FAHA, National Center for Advancing Translational Sciences (NCATS)
Paul Harris, Ph.D., FACMI, FIAHSI, Vanderbilt University Medical Center (VUMC)

Dr. Salina Waddy, NCATS, noted that the Trial Innovation Network (TIN) is a collaborative national network that focuses on operational innovation, excellence, and collaboration and leverages the expertise of the Clinical and Translational Science Awards (CTSA) Program. TIN features a single Institutional Review Board (IRB) system, master contracting agreements, and quality-by-design approaches, with a focus on evidence-based strategies for recruitment and patient engagement.

The goal of the TIN is to execute trials better, faster, and more cost-efficiently and to serve as a national laboratory to study, understand, and innovate the process of conducting multi-site clinical trials. The TIN structure consists of Trial Innovation Centers (TICs), a Recruitment Innovation Center (RIC), and more than 60 CTSA Hubs, each with affiliates and other organizations that span the country. TICs focus on trial methodology and the RIC on improving recruitment and retention. The TIN has public-facing resources and can help with multicenter clinical studies. Dr. Waddy highlighted that TIN has developed tools and strategies to assist investigators in successfully conducting their trials. These include tools that focus on design, protocol development, regulatory approvals, startup, and recruitment. In addition, TIN has a Data Coordinating Center and disseminates all the tools that are developed.

Dr. Paul Harris, VUMC, introduced the RIC and discussed service to the TIN and innovative opportunities. Dr. Harris and Dr. Consuelo Wilkins at VUMC are co-PIs of the TIN's RIC. In 2021, the RIC team published the design for the center, which included collecting and harmonizing input from various experts in clinical trial recruitment retention combined with the services the centers would provide—spanning the spectrum from engaging participants to working on research projects. The initial goal was to pair informatics with community engagement across four service domains: recruitment and retention planning, informatics and site assessment tools, community engagement, and recruitment materials.

In 2017, the RIC team developed a Recruitment and Retention Plan to include in grant submissions for multisite trials. This plan aligns with NIH mandates on clinical trials, provides templates to guide the submissions, and includes a feasibility assessment, which is a comprehensive review of a study to evaluate the likelihood that it will meet recruitment goals.

In terms of informatics and site assessment tools, the RIC team has developed TIN Toolboxes and site expression of interest (EOI). The site EOI connects the CTSA Hubs and affiliates with a single request for interest in participating at their site as well as an electronic health record (EHR)–based cohort assessment

via a study-specific phenotype algorithm . A newer tool using ClinicalTrials.gov to identify participation in similar types of trials is being developed as a ”competing trials tool” to facilitate site feasibility.

The TIN Community Engagement Studios (a consultative method that engages diverse groups of stakeholders in the planning and implementation of research) are spearheaded by Dr. Wilkins and have been helpful for obtaining community feedback to influence study activities. CESs have been involved in reviewing recruitment materials that include tailored study flyers and brochures, study websites, social media campaigns, and the Clinician Study app, for over 15 studies that came through the TIN pipeline.

Dr. Harris explained that investigators interested in applying can access TIN from the website landing page and will be guided through an easy process to submit an idea and request a consultation. As of July 24, 2023, TIN has received 401 proposals across 76 therapeutic areas. Sixty-two CTSAs and 31 non-CTSA institutions submitted projects. Twenty NIH Institutes and Centers (ICs) have either engaged with TIN or funded projects in which the NIDDK has supported 31 proposals or studies. The TIN/RIC has supported 365 initial consultations and 83 comprehensive consultations and funded 37 clinical trials.

The RIC developed several community engagement and informatics tools and resources. These include toolkits for development of a study website, study design, and COVID-19 retention and recruitment; a free online training course hosted on Coursera addressing recruitment of minorities in clinical trials; a community-informed recruitment and retention plan and template; and a Perception of Research Trustworthiness scale as a conceptual framework for measuring trust in biomedical research. For informatics, RIC established a free online disease-neutral recruitment platform (ResearchMatch) that connects U.S. researchers to volunteers and REDCap electronic consent and MyCap to collect patient-reported outcomes. In terms of dissemination, TIN platforms, webinars and other presentations, the TIN Toolbox, and publications are widely distributed to the biomedical research community. A RIC community of practice was established as an ongoing communication channel for recruitment and retention experts, as well as ResearchMatch liaisons. Another communication resource is the bimonthly *RIC Download,* which is online bulletin that summarizes the recent news and events being held to support clinical trial recruitment. Dr. Harris acknowledged and expressed appreciation to the RIC team and the RIC Community Advisory Board for their ongoing support.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- Because many people with CKD are not diagnosed and no International Classification of Diseases, Tenth Revision code for CKD currently exists, a participant asked about the approaches used in the EOI site assessment. Dr. Harris pointed out that the EHR cohort assessment serves as a useful preliminary diagnosis that is representative but may not be a definitive diagnosis. Natural language processing will be the focus of future efforts to extract information from clinicians’ notes, which could potentially provide more insight into a diagnosis.
- When asked about the comparison between retention rates using MyCap and research coordinator telephone surveys, Mr. Harris noted that this would depend on the project and the community but that he has not performed such a comparison.
- Dr. Harris clarified that ResearchMatch does not communicate with other registries but is in the process of being launched at VUMC and potentially expanded to other institutions after policy and privacy aspects have been addressed.

Having a Recruitment Plan, A, B, C (and D): How to (Plan to) Recover from a Slow Start, Increased Use of Virtual Interactions/Visits

Health System Interventions to Improve Transplant Equity: The System Interventions to Achieve Early and Equitable Transplants (STEPS) Study
L. Ebony Boulware, M.D., M.P.H., Wake Forest University School of Medicine

Dr. L. Ebony Boulware, Wake Forest University School of Medicine, described the NIDDK and PCORI-funded STEPS Study. The goal is to study health system interventions to overcome systemic barriers to achieving equitable kidney transplant outcomes among diverse populations. The study is being conducted at three clinical sites—Duke University, Geisinger, and University of Mississippi Medical Center—each with diverse populations. English-speaking individuals ages 18 to 74 who qualify for a living donor kidney transplant, have not had a prior transplant, and are not on dialysis are being enrolled and randomized to either intervention or usual care. The STEPS intervention consists of health system surveillance and outreach from a social worker or nurse transplant coordinator. Data are collected via questionnaires and EHRs over 18 months, and the primary endpoint is completion of the transplant evaluation, which also can be measured by patient-reported outcomes. Enrollment is ongoing, and the accrual goal is a cohort of 1,150 patients. A major component of STEPS is to create a patient registry within the EHRs of each of the health systems, leveraging the Epic Systems Corporation EHR infrastructure.

The recruitment strategy and procedures involve randomly selecting a reasonable number of patients to recruit from the eligible STEPS registry population and mailing the potential participants an introductory letter from each of the health systems. Trained interviewers contact all potential participants via telephone, with a 14-day opt-out period. Randomization occurs following completion of the baseline telephone questionnaire. A central recruitment call center coordinates the clinical sites, and since April 2022, accruals have been robust across all sites.

Dr. Boulware noted key success factors in three categories: pre-funding, study launch, and monitoring. The study team (led by Dr. Boulware, the PI) worked with data managers from each health system and collected and verified actual patient data for pre-funding. During this phase, the team also engaged community members and patients to help with recruitment. For the study launch, the team used local area codes to call individuals to enhance trustworthiness and increase answer rates, with follow-up as needed locally by site coordinators. The team established data streams to evaluate contacts with letters and phone calls and focused early on strategies to boost recruitment and understand reasons for refusals. The study team also conducted weekly reporting and assessment and recruitment workforce planning.

Dr. Boulware highlighted insights from the STEPS Study. Health system recruitment can be fruitful but requires attention to detail. Recruitment monitoring frameworks are essential to indicate when recruitment modifications may be needed. Contingency planning is important for managing unexpected recruitment roadblocks. She acknowledged the STEPS team, including the site PIs and collaborators.

Recruitment for the Hemodialysis Opioid Prescription Effort (HOPE) Trial
Laura Dember, M.D., University of Pennsylvania

Dr. Laura Dember, University of Pennsylvania, reported on recruitment in the HOPE trial. HOPE is an ongoing multicenter trial addressing chronic pain among patients receiving maintenance hemodialysis and is evaluating two interventions administered sequentially. The first intervention is a cognitive behavioral therapy intervention known as pain coping skills training (PCST) administered for 24 weeks versus usual clinical care. The second intervention is a pharmacologic intervention administering buprenorphine to a subset of the participants. The PCST intervention consists of two components: 12-week telehealth sessions with coaches and 12-week interactive voice response (IVR) sessions, both conducted via telephone. At week 24, the PCST group and usual care group are assessed for their eligibility for the second intervention, which is buprenorphine and is available only to people who already are using prescription opioids to manage their pain. All groups are followed for 36 weeks. The primary question being addressed is whether the coach-led PCST intervention reduces pain interference at week 12. Secondary questions (IVR enhancements and PCST durability) and exploratory questions (e.g., buprenorphine as an alternative) are answered based on outcomes at either week 24 or week 36. The HOPE consortium comprises eight clinical centers, patient advisors, IRB, and a scientific and data research center. The trial timeline is based on a 4.67-year funding period, extending from September 2019 to May 2024, with no opportunity for an extension. From September 2020 to June 2023, patients were enrolled and randomized at a rate of 5.6 weekly across the consortium. HOPE met its accrual goal of a cohort of 640 in March 2023. The initial slow start to recruitment was attributed to delays in launching some of the clinical sites.

Dr. Dember noted the barriers to meeting the HOPE trial recruitment goals on time, including COVID-19 operational considerations, delays in executing agreements with dialysis providers, a dialysis patient population with high burden from comorbidities and treatment, and a small pool of patients from a VA Clinical Center. Several factors facilitated the HOPE trial's meeting its recruitment goals. These include the large number of dialysis units from which to recruit, efficiencies associated with the dialysis setting, a high level of interest among patients, centralized implementation of intervention and outcomes ascertainment, ability to expand to two new VA enrolling sites, and weekly distribution of recruitment plots and weekly conference calls with investigators and research coordinators.

The HOPE study team (led by Dr. Dember, the PI) developed and implemented other plans to accommodate the trial. Plan B involved expanding to new enrolling sites and enrolling VA patients receiving dialysis care in the community. Plans C and D were not needed but would have extended the enrollment period for an additional 12 or 24 weeks to allow all participants to have the full PCST intervention and maintain the study power for primary and major secondary questions. Dr. Dember expressed appreciation to the HOPE site PIs and patient advisors for their support.

Overcoming Recruitment Challenges: Lessons from the Urinary Stone Disease Research Network (USDRN) Prevention of Urinary Stones with Hydration (PUSH) Trial
Charles Scales, M.D., Duke University School of Medicine (DUMC)

Dr. Charles Scales, DUMC, provided an update on the USDRN PUSH Trial, including study planning and the recruitment strategy. He also reviewed challenges, lessons learned, and insights for future trials. USDRN was established in 2016 and is composed of six clinical sites and a scientific data research center. PUSH is an RCT focusing on encouraging water consumption among individuals who have kidney stone disease. The study is evaluating a "smart" water bottle as a platform that measures fluid consumption. PUSH implements a multicomponent behavioral intervention focusing on increasing adherence to food intake, which is the main dietary measure. The intervention includes financial incentives, structured problem solving, and automated adherence interventions. The control group continues with usual stone

care and a water bottle, without any other support. The primary outcome is symptomatic stone recurrence, and the enrollment goal is a cohort of 1,642 participants. With this accrual, Dr. Scales, who also is the PI, noted that PUSH becomes the largest trial for kidney stone prevention ever conducted at the NIH.

The initial recruitment plan (Plan A) was a traditional site-based recruitment across four clinical centers, with screening and baseline visits and a smart water bottle setup. The key screening procedures included phlebotomy, computed tomography (CT) scan, and 24-hour urine collections. Within 6 weeks of recruitment, PUSH investigators received critically important feedback from study coordinators that individuals with stone disease were reluctant to participate in the study, even with the simple goal of just drinking more water. They expressed new concerns about burdensome study procedures and radiation exposure from the CT scans, which already used a low-dose protocol. The recruitment plan was adjusted (Plan B) to permit use of recent 24-hour urine collections and imaging from clinical care, as long as required study data were included. The modifications combined screening and enrollment visits for many participants and focused laboratory testing requirements only for individuals at elevated risk of hyponatremia. Additional modifications were made with the urine collections and imaging to reduce barriers to recruitment.

Dr. Scales noted some lessons learned: (1) Minimize burden of screening and baseline procedures by incorporating data from routine clinical care and (2) reduce burden of study procedures in follow-up by aligning with clinical care and returning results to care team to avoid repetitive testing. PUSH investigators also shared best practices across clinical sites and identified resources and processes to increase recruitment. The initial projections were to complete enrollment within 2 years, but the actual recruitment took longer. After making initial modifications and implementing a site visit process, recruitment increased. The next lesson learned is to evaluate recruitment practices and share what works within and across study teams. Eighteen months into the study, PUSH investigators determined from data analysis that the original four clinical centers would soon exhaust recruitment from their existing patient panel. The next step was to add two new clinical sites, which averted a decline in recruitment. Another lesson learned is to leverage data to inform planning and trial monitoring.

PUSH enrollment significantly decreased during the COVID-19 pandemic; some sites recovered more rapidly than others. The USDRN developed a COVID-19 response to decrease barriers to study participation and expand the geographic pool of participants. The network implemented remote consent and randomization/enrollment processes, embedded research in clinical care, and reduced the number of study procedures and tests. USDRN incentivized referrals; established new partnerships; and publicized the trial via professional organizations, webinars, and presentations. The implementation process included engaging with the PUSH Data Safety Monitoring Board for approval for protocol amendments; communicating with the individual center IRBs on remote informed consent processes; and reviewing trial experience to safely waiver laboratory testing baselines, as well as imaging for secondary endpoints.

Dr. Scales highlighted that the COVID-19-related implementations resulted in a decentralized-like trial; national recruitment; new collaborations with major health systems with expansive networks (e.g., Mayo Clinic, Cleveland Clinic); and new partnerships with other networks, including the Pediatric KIDney Stone Care Improvement Network (commonly called PKIDS). PUSH recruitment was further accelerated with the virtual site visits. The final follow-up will be complete in February 2024, with results expected in mid-2024. Dr. Scales noted that building capacity of the site team is the foundation of success. He acknowledged the USDRN steering committee and thanked the PUSH team and collaborators.

Rapid Conversion of an RCT of Group Physical-Based Intervention Programs for Older Women with Urinary Incontinence to Remote Platforms: Implications for Engagement of Older Diverse Participants

Alison Huang, M.D., M.Phil., MAS, University of California, San Francisco (UCSF)

Dr. Alison Huang, UCSF, described the rapid conversion of the Lessening Incontinence Through Low-impact Activity (LILA) Study (a.k.a. Yoga to Enhance Behavioral Self-Management of Urinary Incontinence in Women) to remote platforms. The goals were to examine the rapid conversion (without a pilot study) of all study activities to remote platforms during the COVID-19 pandemic; consider the advantages and shortcomings of remote platforms for rescuing trial participant outreach and engagement; and discuss implications for reaching specific populations, including older adults and underrepresented ethnic minorities. LILA was designed to evaluate a complementary behavioral intervention—a pelvic floor yoga intervention in middle-aged and older women with urinary incontinence. Study participants were randomly assigned to either a pelvic floor yoga program involving twice-weekly group instruction and weekly individual practice of a pelvic floor yoga technique or a general physical conditioning program involving time-equivalent instruction and practice of nonspecific muscle stretching-strengthening exercises. The trial endpoints were defined by changes in the (1) frequency and severity and impact of urinary incontinence, (2) quality of life measures, (3) pelvic floor muscle tone, (4) physical performance, and (5) cardiac autonomic function.

LILA investigators, including Dr. Huang, the PI, and other staff were based in academic institutions in the greater San Francisco Bay Area (e.g., UCSF, Stanford University, San Francisco State University), and recruitment initially was of women ages 45 years and higher living in those surrounding communities. Participants with at least daily stress, urgency, or mixed-type urinary incontinence and not already engaged in organized yoga or muscle conditioning activities were enrolled. Initial recruitment approaches included medical center–based enrollment of existing patients, community-based mass mailing to households in the geographic region, and posting flyers in senior and community centers.

When the trial was first launched in 2018, cohort recruitment and screening activities and group intervention sessions or classes were conducted in person. As COVID-19 presented in March 2020, resulting in suspension of research and shelter-in-place orders, in-person activities halted. LILA investigators reorganized the group-based intervention to include shorter intervals (e.g., 2 weeks). After consultations with the IRBs, data safety monitoring board, and the NIDDK, UCSF pivoted to remote operations and resumed recruitment. The transitioning procedures from in-person to remote platforms included implementation of electronic consent, online questionnaires, automated blood pressure monitoring and physical performance assessments during video visits, and guided urine dipstick testing during video visits.

LILA converted group intervention classes to video conference platforms, with participants engaging from their homes. Materials and procedures to teach participants to use video-conferencing technology were developed and represented a fundamental change in the nature of the study interventions and intervention delivery. Many participants, even those who had never used video conference technology before, were successfully retained on the trial, especially after providing the necessary devices.

Overall, the demographics of study participants did not change dramatically after conversion to remote platforms, with minor variations across cohorts. The average age, ethnic background, and educational status were unchanged. Retention was more challenging with the remote platform regarding the 12-week intervention programs, in which the dropout rate increased from 5 to 16 percent but stabilized at 10 to 12 percent with the new cohorts.

The advantages of remote participant engagement include the ability to safely conduct study visits and intervention sessions during the COVID-19 pandemic; decreased burden on participants to travel back and forth to brick-and-mortar facilities; potential to recruit, engage, and retain participants over wider geographic areas; and greater availability of trial staff and intervention instructors working over remote platforms. Clear disadvantages were the inability to administer some types of exam-based and physiologic measures remotely and fewer opportunities for positive social interactions or bonding between study participants and staff.

Dr. Huang summarized that diverse types of routine study measurements were adaptable to remote data collection in trials. The reliance on remote platforms (including video visits) was compatible with promoting diversity in age, race, and ethnicity of participants. The recruitment from wider geographic areas was possible through the use of video visits to promote home-based trial participation. Trial teams were able to create procedures and materials to support participant engagement in physical-based interventions by videoconference. Factors attributing to LILA's success were higher pre-existing penetration of mobile electronic devices use in the study region; overlapping initiatives at the participating institutions to enroll older patients in Zoom; pre-existing emphasis on delivering interventions outside of clinical settings; and supportive IRBs and data safety monitoring board, plus the support of NIDDK, in adapting trial procedures.

Challenges remain regarding the engagement of participants in the oldest age ranges and with less than a college education. A learning curve for study personnel new to video-based engagement persists. More testing of remote data collection for physiologic measures is needed. Dr. Huang thanked her collaborators for their support of the trial.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- A participant asked about ways to encourage accurate numbers of potential subjects, due to the fact that clinical sites often inflate population numbers. Dr. Boulware emphasized consistently engaging the site, asking increasingly granular questions, and frequently updating the algorithm or equation used to identify potential study subjects or populations.
- When asked about overachievers in the HOPE study sites that recruited much rapidly than other or similar sites and why, Dr. Dember noted that some of the clinical centers likely were recruiting more rapidly than others because of a well-established research infrastructure, extensive experience in trials, and a team of coordinators who could readily pivot from one activity to another. Enrollment had to be completed by June 1, 2023, and sites that were recruiting well were not asked to slow their efforts, but limits were set on the maximum number of participants that any one clinical center could enroll to ensure a geographically diverse population.
- In response to a question about strategies to manage and balance efficiency and also retain a participant pool with complicated morbidities, Dr. Dember emphasized that the HOPE trial was rigid with its eligibility criteria but did not have restrictive exclusion criteria that differed from the overall U.S. dialysis population; an expected rate of withdrawal for illness or death had been incorporated. Flexibility was built into the implementation of the PCST sessions to accommodate patients with comorbidities who had to be hospitalized during the study. The challenge remains to being liberal in terms of eligibility criteria and also having results that are highly generalizable to the overall population of patients with kidney disease and pain.
- All panelists (i.e., the study PIs) highlighted their plans and processes, including individual timelines for providing study participants with updates and general information about the disease after, but not during the trials. They noted that their clinical trial teams made improvements to

provide participants ongoing feedback about their own data and also administered questionnaires and assessments and provided those summaries during follow-up visits to the clinic. Leveraging family and patient collaborators to help increase awareness about the trials and to provide some overall updates about participating are efforts being considered in the future.

- When asked about the budget to accommodate recruitment strategy changes, Dr. Dember noted that in her experience, recruitment takes longer and costs more than expected, and she suggested budgeting liberally for unanticipated expenses and worst-case scenarios. Other panelists noted to balance the costs and benefits of producing materials to promote recruitment engagement with the expenses of trial infrastructure and staffing. They also noted the financial disadvantages of extending the duration of a trial after overspending when the study was smaller during the early phases.
- In response to a question about time for the STEPS team to obtain reliable population numbers when working with candidate enrollment sites, Dr. Boulware responded to plan for several weeks to understand the composition of the study population, which begins during the proposal writing phase. Once the study was funded, Dr. Boulware and her team consistently rechecked the population numbers to predict any mitigation necessary regarding recruitment efforts.
- Dr. Boulware proposed leveraging the CTSAs, other networks, and, broadly, clinical sites on strategies to effectively conduct rare disease trials because this workshop highlighted what has been effective in relatively common diseases. Dr. Scales encouraged reaching out to patient advocacy groups and organizations in the rare disease space and considering decentralization features that could help with these trials. Dr. Dember called attention to two major resources: the NCATS-supported Rare Disease Clinical Research Network and the PCORI-supported National Patient-Centered Clinical Research Network (commonly called PCORnet®), which has a rare disease component.
- Panelists provided suggestions for addressing or mitigating the effects of staff and study coordinator turnover: (1) Develop a transition plan; (2) recruit and hire experienced staff to coordinate the clinical site operations, which has been effective in the HOPE trial and across the USDRN; (3) adopt best practices that have been effective in highly functioning clinical sites; and (4) be proactive in planning clinical research staff support and have procedures, guidance, and trainings in place to address personnel transitions.
- In response to a question about whether feedback on a participant's data/performance during the trial constitutes an intervention, Dr. Huang explained that knowledge of one's own performance on study measures can affect a participant's motivation. Additionally, this information has reflected the reality when interventions are implemented as routine care in the future. Other panelists noted that data are not hidden from study participants but may not be readily distributed to them because of logistical challenges. These can include making clean data available and achieving the necessary clinical conditions that are reflective of clinical practice.

Planning for "Unexpected Delays": Investigational New Drug Applications/Investigational Device Exemptions—and Decentralized Trials
Rekha Kambhampati, M.D., M.H.S., Center for Drug Evaluation and Research (CDER), FDA
Douglas Silverstein, M.D., Center for Devices and Radiological Health (CDRH), FDA
Eric Pittman, M.B.A., Bioresearch Monitoring Division, West, FDA

Dr. Rekha Kambhampati, CDER, FDA, provided as update on the FDA Investigational New Drug (IND) application. She noted that CDER consists of several offices, including the Office of New Drugs (OND), which includes the Division of Cardiology and Nephrology, focusing on drugs and biologics responsive to the treatment of cardiovascular and kidney diseases and conditions. The IND is a request from a

clinical study sponsor to obtain authorization from the FDA to administer an investigational drug or biological product to humans. In general, clinical investigations of drugs that do not meet the criteria for exemption must be conducted under an IND, as required in the Code of Federal Regulations (CFR), specifically, 21 CFR, Part 312. The FDA has two IND categories: commercial and research (or noncommercial). Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, the FDA reviews the IND for safety to ensure that research subjects will not be exposed to an unreasonable risk.

The FDA has several types of INDs, including investigator, emergency use, and treatment. Dr. Kambhampati focused her presentation on the investigator IND. In addition to providing background regarding an IND, 21 CFR Part 312 outlines what should be included in a submission: the cover sheet, the investigator's brochure, the protocol, chemistry manufacturing and controls information, information on animal studies, and previous clinical experience as applicable. An FDA investigator-initiated IND webpage has resources for investigators. Guidance documents represent FDA's current thinking on a topic and describe the Agency's interpretation of policy on a regulatory issue. The FDA has written several guidances related to various aspects of INDs, which can be accessed from the Guidances/Drugs website.

An IND can be placed on a clinical hold, which is an order issued by the FDA to the sponsor of an IND application to delay a proposed clinical investigation or suspend an ongoing investigation. All or some of the investigations conducted under an IND application may be placed on clinical hold. Whenever the FDA concludes that a deficiency exists in a clinical investigation, it may be grounds for the imposition of a clinical hold; the FDA will attempt to discuss and satisfactorily resolve the matter with the IND applicant before issuing the clinical hold order. When a proposed study is placed on clinical hold, patients may not be given the investigational drug. Dr. Kambhampati noted examples of grounds for clinical hold, including cases when patients would be close to an unreasonable and significant risk of illness or injury or when the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives, particularly in phase 2 or phase 3 studies. Further details can be found on the FDA clinical hold webpage.

The FDA also has a webpage dedicated to IND exemption and has a guidance that describes in detail when an exemption is appropriate. The guidance describes two categories of clinical investigations that are exempt from the IND requirements in 21 CFR Part 312, provided the criteria for exemption are met: (1) certain research involving marketed drug products and (2) bioavailability or bioequivalence studies in humans. To request an IND exemption, investigators can contact the Chief, Project Management Staff (CPMS) for the appropriate Review Division.

Dr. Kambhampati explained the FDA requirements regarding INDs and dietary supplements (e.g., insulin). She noted that the Dietary Supplement Health and Education Act of 1994 defines a dietary supplement as "a product taken by mouth that is intended to supplement the diet and contains one or more dietary ingredients." If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. Conversely, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required. In closing, Dr. Kambhampati highlighted that sponsors uncertain whether their proposed investigation meets the criteria for IND exemption can seek advice from the FDA Review Division responsible for the relevant therapeutic area of the proposed trial. Sponsors also can contact the OND CPMS for the appropriate Review Division for additional information.

Dr. Douglas Silverstein, CDRH, FDA, discussed clinical trial design for medical devices and reviewed the FDA Investigational Device Exemption (IDE) requirements. He reviewed the four stages of the CDRH device trial: pilot/early feasibility/first-in-human, traditional feasibility, pivotal, and post-market. An IDE is required per 21 CFR Part 812.3 if a clinical or research investigation of one or more subjects is

determining the safety or efficacy of a device. Medical device types include software as a medical device, mobile apps, and clinical decision support software. A medical device study is exempt from IDE regulations if a legally marketed device is used in accordance with its labeling; is a diagnostic device that complies with the labeling requirements; represents consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed; is a device intended solely for veterinary use; or is a device shipped solely for research involving laboratory animals and not human subjects.

A device classified as a significant risk (SR) will require an IDE. This includes a device that is intended as an implant and presents a potential for serious risk to health; is used in supporting or sustaining human life; is used in diagnosing, curing, mitigating, or treating disease; or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. In addition, SR devices require FDA and IRB review and approval prior to study initiation. A nonsignificant risk (NSR) device (a device that does not meet the definition for an SR device) only requires IRB approval prior to study initiation. IDE submission and FDA approval is not required. If the IRB agrees with the NSR assessment, the study is an abbreviated IDE and must comply with those requirements. If the IRB disagrees with the sponsor-investigator's NSR assessment, the sponsor (sponsor-investigator) must report this to the FDA within 5 working days.

Dr. Silverstein detailed the pivotal study trial design, which is analogous to phase 3 drug studies. Pivotal studies confirm safety and establish efficacy and are statistically driven. The study population should reflect the intended population (i.e., those to whom you want to market your device). This will ensure that the treatment group is appropriate and most likely to benefit, while minimizing risk by excluding patients most likely to exhibit serious adverse events. Inclusion criteria typically include such demographics as age, gender, ethnicity, race, and stage of disease. Exclusion criteria are characteristics that may interfere with the study outcome or expose the subject to unnecessary harm.

The pivotal study endpoints should align with those established in the literature, by expert panels, in society guidelines, or by precedent but ultimately are the decision of the applicant. The FDA may provide an "opinion" about the proposed efficacy endpoints to strengthen a potential future marketing application. A disapproval can be decided if the device involved represents an unreasonable risk to the safety of the individuals who are the subjects of the clinical investigation. The clinical protocol should clearly and prospectively detail (1) the methods for obtaining endpoint data; (2) definitions for what will be counted as a primary event; (3) scenarios in which patient data will be excluded; (4) how missing data will be addressed; and (5) how the impact of covariates will be assessed. Dr. Silverstein reviewed examples of trial design for therapeutic studies and pivotal study endpoints.

Mr. Eric Pittman described decentralized clinical trials (DCTs), including regulation, oversight and execution, and guidance. He explained that a DCT is no different than any other in-person clinical trial and that the same FDA regulations apply. Similarly, DCTs require IRBs and continuing reviews but have added technology different than in other trials. The regulations that govern DCTs include 21 CFR Part 312 and 21 CFR Part 812, as well as 21 CFR Part 11 for EHRs and electronic signatures.

In May 2023, the FDA released a draft guidance document—*Decentralized Clinical Trials for Drugs, Biological Products, and Devices*. This guidance is intended for industry, investigators, and other stakeholders, and the public comment period ended August 1, 2023. The draft was prepared by CDER, in cooperation with CDRH, the Center for Biologics Evaluation and Research, and the Oncology Center of Excellence. The FDA defines a DCT as clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites. DCTs consist of two types: fully decentralized DCT and hybrid DCT. These trials are executed through telemedicine, mobile/local health care providers (HCPs), and mobile technologies.

DCTs utilize digital health technology (DHT), a system that uses computing platforms, connectivity, software, and/or sensors for health care and related uses. DHTs span a wide range of uses, from applications in general wellness to applications as a medical device. They include technologies intended for use as a medical product, in a medical product, or as an adjunct to other medical products (e.g., devices, drugs, biologics). They may also be used to develop or study medical products. DCTs may incorporate component terms and procedures that vary from traditional clinical trials, such as electronic clinical outcome assessment, observer-reported outcome, or performance outcome.

Mr. Pittman noted some benefits of DCTs, including more efficient clinical trials and lower cost; accelerated enrollment and increased diversity; more frequent or continuous measurement; fewer participant burdens of time and travel; more representative of real-world administration/use post-approval; and possible advantages in rare diseases, limited populations, and geographically dispersed populations.

Perceived or actual challenges include immature digital infrastructure, limited experience with the approach among clinicians and the FDA, a perception of new regulatory barriers with the FDA, highly varied state laws and regulations, consistency in protocol execution, and data reliability and integrity.

Questions and points sponsors should consider in the oversight and execution of DCTs are whether conducting such a trial is reasonable for a specific context. Can human subject protections be assured? Can the quality and integrity of data be ensured? In the design of DCTs, investigators should consider the technology support for the site and subjects and data flow, as well as access controls. Mr. Pittman highlighted that in April 2023, the FDA released a final guidance document for industry—*A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers*—which discusses remote monitoring. Other factors sponsors should consider include geographical location of trial participants, documentation of monitoring activities remotely, and aspects of risk-based monitoring.

Last, Mr. Pittman reviewed guidance documents the FDA has developed to assist sponsors in conducting DCTs and other remote clinical activities. Further details can be found on the FDA Guidance Document website.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- When asked about suggestions for interacting with other regulatory agencies, Dr. Silverstein explained that the FDA does not regulate trials conducted outside of the United States. Those trials are regulated by whatever regulatory authorities exist in those countries for the devices. He added that sponsors considering trials that will enroll subjects from outside the United States are encouraged to contact the FDA for a discussion on the study design and data collection.
- Dr. Kambhampati commented that the FDA is in communications with the other regulatory agencies outside the United States, including the European Medicines Agency (EMA). Sponsors can request parallel scientific advisory meetings to meet with both the EMA and the FDA if there are issues that affect both agencies.
- Mr. Pittman emphasized ensuring diverse participation of patients (representative of the U.S. population) in trials conducted outside the United States.

Summary of Day 1 and Charge for Day 2
L. Ebony Boulware, M.D., M.P.H., Wake Forest University School of Medicine

Dr. Boulware recapped the presentations and noted some underlying messages. Clinical trials are not useful for answering the research question if they terminate early, which typically occurs for recruitment and retention reasons. Individuals with kidney disease who have "lived" experiences are interested in being involved in studies but often are not contacted. Engaging patients early in the study design and including interventions can assist in the development of more appropriate, reliable, and feasible trials. Capitalizing on the idealism of the patient is essential. Some common themes included employing consistent community engagement, understanding success factors, building trust among communities, ensuring diversity in trials, and understanding recruitment as a key aspect of the study.

Adjournment

Dr. Abbott thanked participants for attending and adjourned day 1 of the workshop.

TUESDAY, JULY 25, 2023

Charge for Day 2
Kevin Abbott, M.D., M.P.H., NIDDK

Dr. Abbott welcomed everyone to the second day of the workshop and touched on the previous day's presentations, noting the productive first day and insightful sessions. In today's agenda, speakers will share their real-world experience from industry and add an important component representing the voice of the CRPs. Panelists who are on the ground doing the research will provide their perspectives and feedback. After the breakout sessions, Dr. Star will summarize and highlight future directions. Dr. Abbott conveyed that the NIDDK recognizes that this workshop will not solve all the problems or questions about optimizing clinical trials but will began the conversations. NIDDK program staff are available to discuss clinical trials research with investigators during the planning stage of a project and can provide information about the NIH and other groups involved in the clinical trial process.

Real-World Trial Experience and Lessons Learned—Inclusion
Barbara Bierer, M.D., Harvard Medical School

Dr. Barbara Bierer, Harvard Medical School, discussed inclusion in clinical trials, in the context of challenges to recruitment and retention and leveraging the efforts of the Multi-Regional Clinical Trials (MRCT) Center. She explained that the MRCT Center is a research and policy center focused on addressing the conduct, oversight, ethics, and regulatory environment of clinical trials. The mission is twofold: (1) Engage diverse stakeholders to define emerging issues in global clinical trials and (2) create and implement ethical, actionable, and practical solutions. Dr. Bierer noted some foundational statements about inclusion. Optimizing for inclusivity will benefit the trial for all participants, extending beyond underrepresented populations. When done well, increasing the population able to participate in a trial can increase the rate of enrollment and decrease the time to completion. This approach often will require a change in practice and investment and always will require planning.

Dr. Bierer highlighted the importance of diversity and inclusion in clinical research. Participation in clinical research should be reflective of the population affected by the condition or disease, or to whom the intervention is intended. Analyses of group differences in outcomes among diverse populations can promote the identification of underlying biological and socially relevant factors that affect health, but only if data exist and are at scale. Diversity in enrollment seeks to achieve fairness in the distribution of direct and long-term benefits of research. Diverse representation in clinical trials is not just a matter of

biology, but also of health equity and fairness. Participation contributes to the development of public trust in research and health care. The demand for a representative population changes over time, from product development to a phase 1 trial and to using an approved medication, all culminating in clinical comparative effectiveness research, observational data, and real-world data.

Over the past 8 years, the MRCT Center has been working on DEI in clinical trials and on the quality and completion of clinical trials. In 2020, the Center published a guidance document on achieving DEI in clinical research, which and includes a toolkit. From 2020 to 2021, the MRCT Center sponsored a webinar series on practical approaches to achieving diversity in clinical research followed by a series on achieving inclusion in clinical research. The Center conducted trainings in recruitment, retention, and DEI considerations in clinical research. Efforts also focused on improving understanding about individuals with impaired abilities decision-making who may benefit from support. In addition, the MRCT Center has developed health literacy tools and resources, a clinical research glossary, and tools for IRBs and human research protections programs. The Center recently completed a large project on inclusion of people with disabilities. All materials can be accessed on the Center's DEI website.

In terms of accountability, everyone (e.g., sponsors, funders, patients, journal editors) has a responsibility to understand DEI and the lack of representation in clinical trials. Furthermore, individuals must be invited to participate in trials. A common thought is that underrepresented populations do not participate in trials; however, a recent report showed that, when asked, the rate of willingness to participate in health research was equal among African Americans and non-Hispanic Whites. Although education, accessibility of the trials, and referral (if necessary) play a role, access is the primary reason people are not participating in trials. Study teams in academic centers have made assumptions rather than asking underrepresented groups to participate in trials. The field needs to confront and address this implicit bias and cultural incompetence.

A clinical trial encompasses early interventions, the study, and end study data analysis and reporting. Investigators should plan for inclusion throughout the patient's journey in a clinical trial. Early interventions include patient and community engagement, education, health, literacy, feasibility, assessments, and an examination of eligibility criteria. The study itself includes standardized data collection, access to medicines, return of results, and ongoing engagement with study participants. The end-of-study activities include data analysis and standards results reporting. In each of these touch points, there is impact and room for improvement.

Dr. Bierer further elaborated on the clinical trial components relevant to inclusion. For participant and community engagement, investigators can focus on the patient, community partnership, input to the study question, conduct, and communications. A traditional, hybrid, or decentralized trial can be considered in the study design plan. Investigators can plan to design the trial for inclusion from the outset, making it accessible, addressing health literacy, increasing eligibility by minimizing the ineligibility requirements, using recruitment navigators, and providing payment for participation. Dr. Bierer emphasized ensuring that the trials have access to digital technology and have financial neutrality, as well as insurance independence. She also noted confidentiality and communications and end-of-study results as other areas for inclusion, pointing out that the return of results, transitions of care, and continued community engagement are necessary. The MRCT Center has developed DEI tools for study-level considerations to encourage investigators to thoroughly review all aspects of trial feasibility and increase the parameters for recruitment and retention.

Investigators perform risk analysis for clinical trials to understand the challenge to participation. Patients are more concerned about the risks than the benefits. They highlight issues of privacy, lost work, uncertainty in the outcome, childcare, travel, discomfort, trust, and costs. The MRCT Center has moved from conducting site-based trials to patient-based trials and using DCTs, HCPs, and remote data

collection. The Center also has begun using data from other sources. Access to data should inform selecting the right populations for a study, but some data sources are not diverse and representative of the U.S. population. EHRs are representative of the insured population.

Dr. Bierer emphasized critically assessing the feasibility prior to starting a trial and noted that site population and catchment area and inadequate resources are challenges to be addressed. She detailed several approaches to alleviating burden and described the plan for inclusion, including addressing health literacy and communications and costs and payments to patients.

Lessons from Industry
Shawn Paladini, Bayer Pharmaceuticals

Mr. Shawn Paladini, Bayer Pharmaceuticals, described lessons learned and best practices in the field from his perspective as a clinical study manager with more than 20 years of experience. He highlighted that approximately 80 percent of clinical trials fail to meet enrollment timelines, and approximately one-third of all phase 3 study terminations result from enrollment difficulties, suggesting room for improvement in designing and conducting trials.

Mr. Paladini detailed several key factors contributing to success and failure in trials. The critical first step of the clinical trial process is to clearly define the study objectives, which includes the research questions and endpoints and well-defined primary and secondary outcome measures. At this phase, a concise clinical development plan that includes key elements of the study protocol, as well as a well-conducted feasibility study, should be in place. Pragmatic approaches, such as DCTs, should be considered to address recruitment and retention. Investigators should develop a study design that minimizes bias and considers such factors as sample size calculation, randomization and blinding, and a control group. Efforts should focus on developing well-thought-out inclusion and exclusion criteria for full participant selection and be suitable for enrolling patients in the respective setting. The population being studied should be clearly defined and also reflect the real-world patient population. Properly powered statistics are needed and require advance planning. Studies must adhere to all local and country ethical guidelines and regulatory requirements and must obtain informed consent from participants.

Mr. Paladini strongly emphasized developing a detailed, comprehensive study protocol that outlines the study objectives, methodology, participant selection details, intervention, outcome measures, and statistical plan. The protocol is maintained during the trial and will be a roadmap of procedural guidance to investigators and study personnel. Four areas of insight for the protocol are (1) investigators who provide feedback on the previous high-performing studies; (2) experts who provide unbiased review of the study concepts; (3) patients who provide feedback on aspects of the study related to the disease; and (4) data, which can be internal and from third-party vendors. A data management plan that incorporates standardized data collection and utilizes electronic data capture is essential. A quality monitoring plan should be implemented in advance of the trial to ensure compliance with the protocol. Last, regular communication (both internal and external) will be critical to the success of the trial and includes effective communication among all study team members.

Mr. Paladini encouraged learning from your mistakes by reviewing previous high-functioning clinical trials, understanding the challenges confronted by similar studies, and identifying potential risks of the study to proactively develop strategies to resolve them. He also emphasized being flexible to pivot when needed and noted supporting quick turnaround of data and reporting. Mr. Paladini highlighted several pros (e.g., access to cutting-edge technology) and cons (e.g., lack of communication and cost) of third-party trial support.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- When asked how the NIH and/or FDA can help change the culture among industry sponsors opposed to moving to a participant-friendly study culture, Dr. Bierer remarked that this question rests upon a supposition that industry and other sponsors are resistant to decentralized or hybrid clinical trials; she is not convinced that this is the case. She explained that the issue is not about the control of the data, but of privacy and confidentiality. The field, in general, is learning how to conduct these trials well, and the recent FDA draft guidance on DCTs for sponsors and investigators, which she recommended reviewing, is very helpful.
- In response to a question about workforce, Dr. Bierer underscored that the workforce should reflect the communities that clinical trials serve, as well as the U.S. population. Investigators can focus on equally diversifying the clinical research workforce.
- When asked for advice on incorporating DEI for recruitment in smaller trials, Dr. Bierer explained that limitations exist for using this approach in smaller trials. She noted that smaller trials can be appropriate if they answer the study question, and that question can be answered by a specific small population. The study also would need to be statistically powered.
- In response to a question about examples of how patient insights from the study ambassadors improved the conduct of the study, Mr. Paladini explained that ambassadors help with patient engagement to maintain the focus of the overall study team, reduce misconceptions regarding aspects of the trial, and provide real-world perspectives of what the research is helping to accomplish. Ambassadors also assist with enrollment and set the basis for what the patient population could be facing in terms of burdens, which informs the design of the study.

Clinical Research Professionals (CRP) Panel
Moderator: Jeri Burr, M.S., RN, PED-BC, CCRC, FACRP, University of Utah
Panelists: Ashley Moultrie, CCRP, Javara
Edwina McNeill-Simaan, M.S.H.S., CCRC, CCRP, VUMC
Mary Pautler, M.P.H., CP, University of Utah
Krista Ellis, M.S., CCRC, University of Utah

Ms. Jeri Burr, University of Utah, opened the discussion and introduced the panel. She noted that CRPs are composed of clinical research coordinators (entry-level positions), CCRAs, trial monitors, project managers, clinical directors, and directors of research. Ms. Burr explained that today's presentation will focus on the feedback on CRPs' perspectives as a result of an Association of Clinical Research Professionals (ACRP) survey sent to the ACRP membership soliciting input on the major challenges encountered when implementing clinical studies. Ms. Burr and other panelists also forwarded the survey to their colleagues at the University of Utah, VUMC, and Johns Hopkins University. In addition, Ms. Burr, past Executive Director of the University of Utah TIC (NCATS TIN), and now Program Director of the University of Utah Data Coordinating Resource Center (DCRC) (funded by NCATS), and her DCRC colleagues interviewed research coordinators from the university's Clinical Trials Office and met with the University of Utah Data Coordinating Center (DCC) project managers. Collectively, this panel represents more than 105 years of clinical trial experience.

Study Startup—Processes and Timelines

Ms. Burr highlighted study startup processes and timelines, which CRPs responding to the ACRP survey ranked as the second-largest problem contributing to unsuccessful clinical trials. Setting realistic timelines and expectations for starting a study is critical. Most grants include timelines for startup and enrollment of

3 to 6 months. Most CRPs have reported that 3 months is not reasonable. Funding or notice of grant award (NOGA) is needed to begin working on projects, but NOGAs require IRB approval. This provides a challenge to meeting enrollment goals. How can you meet enrollment goals if you are already behind before you start?

Ms. Burr next reviewed examples of clinical trial startup challenges, some from the survey interviews and her research and provided suggestions for improvements. In one example, a group working on an R34 project sought IRB approval for its protocol, as well as FDA approval for their research. They needed Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Reliance from all the sites participating in the study and required a data safety and monitoring plan. All these items were points of discussion prior to the NIH Just-in-Time request for the grant application. The University of Utah, like most academic institutions, does not allow staffing a project prior to a NOGA. An NIH program officer suggested that during grant development, sites can document that they have signed the SMART IRB agreement and have experience working in the IRB Reliance Exchange (commonly called IREx) platform or an equivalent platform being used to document reliance. The sites also can include in their letters of support that they will rely on the single IRB selected for the study. Ms. Burr emphasized the importance of becoming acquainted with and communicating early and often with the IRBs.

In another example, a newly funded R01 investigator had received IRB approval prior to the NOGA but experienced a series of miscommunications. The NIH program officer requested clarifications on 21 sites that were in the grant application. A revised NOGA was issued 6 months later, approving only 5 of the 21 sites, citing the need for other required information. The granting officer subsequently requested sending all communication in a written form from the institutional official. Eight months after the original NOGA, a communication was received from the IC's project officer, noting the misunderstanding about approved versus accepted. All 21 sites were accepted, but only 5 were approved. The remaining sites were pending IRB approvals. The study team did not know the sites had been accepted so they could assist them with obtaining IRB approval. This is an example, Ms. Burr noted, of how miscommunication can delay a trial.

Many coordinating centers have accelerated startup programs. They have demonstrated sites can be ready in 90 days, but delays often result because of issues at a central level. For example, a researcher at an academic center reported spending an average of 6 to 8 months activating the sites in a large trial. After implementing their accelerated startup program, the researcher discovered that sites finished their tasks and were ready to enroll well below the 90-day goal. Delays at the central (not individual site) level delayed activation to enrollment. These were attributed to things like the addition of new consent forms, unavailability of the drug being evaluated, revisions to training materials, and use of new technology. In addition, DCCs, clinical coordinating centers, and statistical coordinating centers collaborate to run trials, and this approach can be productive. One advantage is the shared accountability, but one disadvantage is that the split between activities and shared staff and services is not always efficient. With three times as many staff to deal with, this model requires dealing with more people, which takes more time and more levels of agreement. Lessons learned from using this model is that there is a learning curve and things will not initially go smoothly. Ms. Burr summarized that if the startup process can be streamlined to 3 months, it frees up another 3 to 4 months to spend recruiting and executing the protocol, which, in a 5-year trial, is a significant amount of time. The enrollment time can be increased by more than 10 percent using this approach.

DEI and Community Engagement—Recruitment and Retention

CRPs responding to the ACRP survey ranked recruitment and retention as the number-one problem contributing to unsuccessful clinical trials.

Ms. Moultrie noted that in 2020, the times of crises (health, social, economic) revealed the inequities in the health care industry, including access to care, resulting in a drive to increase diversity among clinical trial participants and clinical trial professionals. Before this can be achieved, the existing inequities and determining how they developed need to be addressed. The decisions and required changes to address those inequities need to be made known. The major factor to increasing diversity of clinical trial participants lies in activating our communities. One approach is to engage with community health workers, who have knowledge of the communities they serve. Connecting with community leaders is the best strategy for reaching underserved populations. The key is to spend time in the community, reach out to the patients and their families, listen, have those uncomfortable conversations about DEI as applicable, and be a part of the solution.

Although discussions in the field suggest that DCTs could be the solution for improving diversity in clinical trials, Ms. Moultrie emphasized the importance of carefully ensuring equity and access to those trials, as well as the availability of the necessary tools and equipment to successfully conduct those trials. She noted to not shift but rather solve the problem.

Site Resources—Investigator Engagement and Involvement

CRPs responding to the ACRP survey ranked investigator engagement and involvement as the third-largest problem contributing to unsuccessful clinical trials.

Ms. Edwina McNeill-Simaan, VUMC, described challenges at the site level she has observed in her 20 years of coordinating and leading clinical trials. Ms. McNeill-Simaan noted that PI oversight can be limited and that as an experienced coordinator on some trials, she searched charts and clinics for patients, compared their charts to the trial's eligibility criteria, and then approached patients independently about the studies. She was knowledgeable in clinical trial work and could identify when the research was out of the scope of her discipline and when to reach out to medical residents to answer questions about study participants. Her role was to consent, randomize, and set up patients on studies. She also prepared all the paperwork and documents for signature. Although she was knowledgeable about most trial aspects related to the studies, she could have performed some aspects of the work better with more PI guidance, coaching, and guidance related to discussions about the study drug.

Another challenge at the site level is not having adequate staff and resources to support the trial. Coordinators often work across studies and sites, and PIs are not always aware of the available resources. Ms. McNeill-Simaan explained that research funding can be limited and, combined with high personnel costs, is a factor contributing to the reduced staff and heavy workloads for existing coordinators. She highlighted the importance of investigators assessing what tasks are necessary, what resources are needed, and how many person hours are needed to adequately resource their clinical trials.

Ms. McNeill-Simaan highlighted other challenges. Dedicated academic and administration time of faculty and time for clinical research are ongoing battles at most academic institutions but are vital to the success of clinical trials. Study feasibility assessments are often conducted by the industry partners. PIs can consider performing these assessments internally to better assess the sites and the capacity for new studies. In addition, PIs should define study roles in advance when the protocol is being written and should have a plan to accomplish the work for any particular study.

Protocol Design—Protocol Complexity and Hurdles

CRPs responding to the ACRP survey ranked protocol complexity and hurdles as the fourth-largest problem contributing to unsuccessful clinical trials.

Ms. Mary Pautler, University of Utah, noted that a common theme among research coordinators and project managers interviewed for the survey is the impact that protocol design has on the success of a trial. Ms. Pautler highlighted two key factors to consider for protocol design: involve the study team and reduce the complexity of the protocol. She further elaborated on these factors. Investigators are encouraged to solicit input from their study team (research coordinator and/or research nurse) on whether the design of the protocol is feasible for assisting the patient's journey over the course of the trial, can make a difference regarding participant retention, and is effective for study coordinators. Multiple coordinators report not having dedicated research space to complete procedures, which poses a challenge. Research coordinators can offer valuable input on the patient's journey—from navigating through a facility to each step of the schedule of events of the trial.

Protocol designs are becoming more and more complex, and the burden to study participants should be considered. One approach for beginning to reduce this complexity is to be strategic about the data being collected and only focus on what is needed for the study. In addition, a demanding protocol with a complex schedule of events creates a heavy participant burden and could lead to incomplete visits, missing data, and loss of follow-up. Simpler protocols increase patient engagement and site enrollment.

Ms. Pautler closed with some key takeaways of protocol design to improve the likelihood of success in trials: Understand the patient journey and how that journey might transpire at the study site, and be mindful about the data collection.

Site Selection—Site Related Challenges

CRPs responding to the ACRP survey ranked site-related challenges as the fifth-largest problem contributing to unsuccessful clinical trials.

Ms. Krista Ellis, The University of Utah, explained that site selection for a trial can significantly impact the success of a study and can affect study startup time. A slow or delayed study startup will negatively affect enrollment numbers and patient recruitment. A site that does not have the needed population related to the inclusion/exclusion criteria or where the diversity of the geographical areas of recruitment have not been considered will not meet its diversity goals. The process of selecting sites can be daunting, and highly qualified research teams can assist with site selection. PIs should not rely on friends and family to participate in studies without considering objectively what makes a study site successful.

Ms. Ellis noted objective criteria to consider when choosing a site: Select the population of interest, not just the general disease, and include a major review of inclusion/exclusion criteria using EHR data; review the population diversity of the site, and determine how that will contribute to the overall diversity goals of the study; identify the resources that will be required, including the research staff, equipment, and space and how they will contribute to the success of the study; identify any competing trials at the site selected; and set expectations for startup and enrollment goals.

ACRP Survey Results and Summary

Ms. Burr highlighted that the ACRP is the only nonprofit organization solely dedicated to representing, supporting, and advocating for CRPs. The Association is well-known for its outstanding training programs and is leading in workforce development in clinical research. She explained that from June 5, 2023 to June 30, 2023, ACRP, in advance of today's NIDDK webinar, conducted a brief survey in the CRP community and reiterated the purpose—to solicit perspectives on the challenges related to implementing clinical trials. One-hundred CRPs completed the survey and primarily consisted of clinical research coordinators, who worked in academic institutions. Of the 100 CRPs responding, 50 percent had more than 11 years of experience, 23 percent had 6 to 10 years of experience, and 66 percent had been

involved in planning and implementing studies. Dr. Burr reviewed the remaining problems contributing to unsuccessful clinical trials, including communication and collaboration and budget and contracting. She summarized the suggestions for improvements, of which key areas included investigator cooperation and support, training and oversight, and streamlined decision-making.

Questions and Answers
Moderators: Shannon Givens-Bradley, M.P.H., NIDDK; Kevin Abbott, M.D., M.P.H., NIDDK

- When asked how to identify and locate community health workers, Ms. Moultrie noted that community health workers are usually employed by community-based hospitals, nonprofit organizations, or community free clinics.
- In response to a request for recommendations on weighing each study when it comes to comparing the study coordinator's workload, Ms. McNeill-Simaan proposed (1) increasing the knowledge among investigators and research administrators to educate them on the work that coordinators do in support of trials regarding the time it takes and the skills needed; (2) speaking up for the coordinators, or research associates who are interacting with the study participants; and (3) bringing in additional resources when needed.
- The panel provided their perspectives on changing the industry model on start-up payments and reimbursements when enrolment or randomization of study participants is ongoing at a site. Provide incentives to accelerate achieving pre-milestones at sites, which can free up funds for other activities. Begin with what the study will cover and then determine the costs for completing the research.
- When asked about ways to help investigators better estimate startup times and with grant applications or study planning, the panelist called attention to the NCATS TIN Toolbox described earlier in the meeting and suggested streamlining workflows, reaching out to experienced CRPs in the local institution, and contacting TIN leadership for assistance if not located near a CTSA Hub.

Concurrent Breakout Groups—Putting It All Together in a Sample Study Design

Workshop participants were invited to choose a breakout session on one of four topics: pretrial planning, outreach, recruitment, or documentation. The planning committee, external collaborators, and other NIH staff moderated the discussions. Guiding questions were provided to frame the discussions.

Group 1: Pretrial Surveillance Planning, Defining, and Selecting Eligibility and Inclusion/Exclusion Criteria
Group Facilitators: L. Ebony Boulware, M.D., M.P.H., Wake Forest University School of Medicine
Douglas Silverstein, M.D., FDA
Leigh Ann Williams, M.S., M.P.H., AAKP
Debbie Gipson, M.D., M.S., NIDDK

Guiding Questions:
What strategies, approaches, and tools can help us best optimize pretrial planning?
What is the hardest part of achieving this today?
How does this process inform site selection (and vice versa)?

Group 2: Outreach (Feasibility Assessment, Venues)
Group Facilitators: Vanessa Marshall, Ph.D., National Institute on Minority Health and Health Disparities
Raquel Greer, M.D., M.H.S., NIDDK
Richard Stacewicz, AAKP

Guiding Questions:
What strategies, approaches, and tools can help us best optimize outreach?
What is the hardest part of achieving this today?
How does this process inform site selection (and vice versa)?

Group 3: Recruitment (Looking for Best Practices, How to Plan for B, C, and D)
Group Facilitators: Janice Lea, M.D., Emory University
Precious McCowan, M.S., AAKP
Jenna Norton, Ph.D., M.P.H., NIDDK

Guiding Questions:
What strategies, approaches, and tools can help us best optimize diverse recruitment processes?
What's the hardest part of achieving this today?
How does this process inform site selection (and vice versa)?

Group 4: How to Document/Indicate/Measure Clinical Trial Primary Results Publications/Trial Success
Group Facilitators: Elizabeth Lorenzi, Ph.D., M.S.P., Berry Consultants, LLC
Kevin Abbott, M.D., M.P.H., NIDDK

Guiding Questions:
How important do you think this is as a problem?
What potential solutions would you recommend?

Report Back and Discussion

Dr. Abbott invited the breakout group leaders to report the results of their discussions.

Group 1

Dr. Boulware summarized the group's discussion of pretrial surveillance planning and defining and selecting eligibility and inclusion/exclusion criteria. The group listed several tools and approaches to help optimize pretrial planning, including careful consideration of which groups will be included in studies, as well as the ability to balance inclusion criteria with the need for more inclusive studies. Strategies should be implemented to avoid overly restrictive participant criteria. Investigators should be encouraged to justify their criteria for inclusion/exclusion, which will aid with pretrial planning and preparing for assessment by study sections. Pretrial planning also would benefit from data harmonization and readiness efforts, robust clinical development plans, and engagement with sites to develop strong relationships and a full understanding of their clinical trial capabilities. Inclusion criteria, feasibility evaluations, and existing technology and resources should inform pretrial site selection. The group discussed barriers to pretrial planning. For example, clinicians must engage with participants, communities, and sites well in advance of trials, but these efforts often are not well funded. Smaller institutions that are interested in

engaging in clinical trials require seed funding, even for smaller efforts (e.g., Small Business Innovation Research award applications).

Group 2

Dr. Raquel Greer, NIDDK, reported on the group's discussion of optimizing outreach to ensure diverse representation in clinical trials. Additional analysis of given populations is required before studies are conducted. To ensure diverse representation, this analysis should involve more depth than merely collecting EHR data and include connecting and establishing relationships with community organizations to learn more about potential study participants (and maintaining those relationships beyond the duration of a single study). The group discussed the meaning of diversity, which does not only encompass race and gender but also includes age, language, sexual and gender identity, and other categories. Additional resources and funding are required for effective community outreach and engagement, especially for recruitment efforts in what some consider "nontraditional" locations. Investments in community outreach should be provided by institutions, study sponsors, and federal funding sources. Awareness should be raised regarding available tools to support community outreach efforts, and investigators should be trained in using these tools. A centralized repository of such resources would be valuable to the community. The siloed nature of investigator communities and ICs must be overcome and integrated to ensure that best practices and knowledge in this area can be shared widely. Site selection should be informed by the availability of resources for a particular study and the nearby location of a population of interest (to minimize transport and childcare costs and improve study participation). Other key considerations related to community outreach and site selection include study team diversity and past performance.

Group 3

Dr. Lea described the group's discussion of best practices for recruitment efforts and approaches and tools to support pretrial planning for recruitment. She noted that a patient participant shared helpful information with the group. The group discussed the need to leverage health information technology capabilities in pretrial recruitment efforts. Databases should be queried to ensure that goal numbers and diversity of study participants can be recruited. Patient advisory boards should be convened to guide transparent study planning efforts and ensure that participants are knowledgeable about the risks and rewards associated with study participation. Populations of interest should be surveyed about study practices and sites that are most preferable or convenient for their needs. Members of populations of interest (especially study participants) must trust investigators. Community groups should be leveraged to build trust and support improved health literacy and education efforts related to clinical trials. The group agreed that establishing trust was the greatest challenge associated with recruitment. Because of prior experiences, many people carry negative associations with certain clinics and institutions (or the health care system as a whole). More effort is required to recruit such people into clinical trials. Clinical trial professionals should be involved early in trial planning to address foreseeable concerns, limitations, and barriers. Adequate funding is needed to retain research staff, educate them on properly conducting research, and support their community outreach efforts. Investigators should partner with industry to develop more robust advertisements for participating in clinical research. To ensure success, trial sites should consider and support the needs of all participants.

Group 4

Dr. Lorenzi summarized the group's discussion of documenting clinical trial results and measuring trial success. Clinical trial results should be definitive and influence clinical practice. The group discussed trial readouts that most benefit patients and how to measure the success of a clinical trial (e.g., full enrollment, meeting of early goals, statistically significant results, generation of evidence to support clinical practice

guidelines). Publications associated with clinical trials should include these primary results in their abstracts, and primary analysis readouts from trials should be more readily available (possibly on a website, such as ClinicalTrials.gov). Measurements of clinical trial success should be considered during workshops and standardized across the field; the NIH and scientific journals should support these efforts. Statistical analysis plans should guide study results so that outcomes are prespecified and more trustworthy. The group acknowledged that varying requirements for success would be associated with different phases of a study.

Conclusion—Closing Remarks and Future Directions
Robert Star, M.D., NIDDK

Dr. Star thanked the participants, including Dr. Abbott, the planning committee, and the patient participants, for their contributions to the workshop. He highlighted an emerging theme of the workshop—the need for successful clinical trials that adequately address scientific questions—and crosscutting topics associated with this theme:

- **Culture:** Patients and participants must be at the center of clinical trial efforts. Attention paid to ethics, safety, and burdens associated with trial participation will help establish trust with patient populations.
- **Diversity:** Diverse scientific and administrative teams, as well as diverse patient populations, improve the quality of studies, build trust, and lead to more fair and equitable health outcomes.
- **Communication:** Key partners must be involved early and continuously throughout all phases of a study. This includes patient partners and study participants—who should be included on all committees and papers associated with the study and be honored and reimbursed for their involvement—as well as clinical research coordinators, anyone interacting with participants, trial sponsors, and NIDDK staff.

Dr. Star emphasized that the design phase of a study is critical. Investigators must ask whether the trial protocol is feasible in a real-world setting; map out and optimize all study procedures for coordinators and participants; ensure that the burden associated with trial participation does not reduce inclusion and decrease trial success; develop a clear and realistic study protocol and timeline; consider inclusion and exclusion criteria for the population of interest, including real-world EHR data and their limitations; select an appropriate site based on data rather than personal connections; and leverage new tools, checklists, and third-party contractors where beneficial. Continuous measurement of data quality and trial fidelity was necessary for the implementation phase of studies. Investigators must acknowledge their mistakes and constantly improve their methods.

Dr. Star reviewed novel study design concepts and tools that were shared during the workshop. Decentralized study designs involve patient-centered study operations. This form of design reduces the burden on patients but might lead to missed outcomes and does not guarantee equitable results. Dr. Star urged workshop participants to promote new tools and best practices developed by NCATS TIN and other organizations. He encouraged researchers to develop methods to more easily identify the key publications resulting from clinical trials and to use lay language when communicating with study participants.

Adjournment

Dr. Abbott thanked the participants and noted that presentations and a summary report of the workshop will be posted on the NIDDK workshop website. Dr. Abbott added that he can be reached via email (kevin.abbott@nih.gov) if anyone has additional comments or suggestions. He adjourned the meeting.