

## **Urology Interagency Coordinating Committee Virtual Meeting**

December 11, 2020

9 AM- noon ET

### **Meeting Minutes**

#### **Meeting Participants:**

Kevin Abbott (NIDDK)

Julie Barthold (NIDDK)

Tamara Bavendam (NIDDK)

Sonya Brady (PLUS)

Melissa Constantine (PLUS)

Shayna Cunningham (PLUS)

Emily Duggan (NIDDK)

Bill Elwood (OBSSR)

Lisa Halverson (NICHD)

Bernie Harlow (PLUS - UMinn)

Eleanor Hoff (Office of Scientific Program and Policy Analysis)

Aimee James (PLUS – Wash U)

Ziya Kirkali (NIDDK)

Lisa Kane Low (PLUS - UMich)

Donna Mazloomdoost (NICHD)

Susan Mendley (NIDDK)

Saadia Miran (NIDDK)

Chris Mullins (NIDDK)

Jessie Nodora (PLUS - UCSD)

Jenna Norton (NIDDK)

Matt Oldham (NIDDK)

Mary Palmer (PLUS - UNC)

Leslie Rickey (PLUS - Yale)

Kyle Rudser (PLUS - UMinn)

Marcel Salive (NIA)

Peter Scal (PLUS - UMinn)

Rob Star (NIDDK)

Ariana Smith (PLUS - UPenn)

Siobhan Sutcliffe (PLUS – Wash U)

Roger Weiderhorn (FDA)

#### **Welcome**

Robert Star, MD

Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK

Dr. Star welcomed meeting participants and noted that this meeting will focus on an update from the PLUS Consortium. The Consortium has completed its first five years funding and is now funded through an additional five years. Dr. Star thanked PLUS investigators and NIDDK staff for their important contributions to this consortium.

#### **Introduction to Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium**

Tamara Bavendam, MD, MS

Program Officer, NIDDK

Dr. Bavendam noted that the funding for the first cycle of the PLUS Consortium was funded primarily through NIDDK and received cofunding from the National Institute on Aging (NIA) and the Office of Research on Women's Health (ORWH). Initially, the Consortium numbered over 50 PLUS investigators with the task of establishing a transdisciplinary research approach. While this continues to be an ongoing process, investigators have made tremendous strides to create a new area of science in this field.

As the Consortium continues to move forward, Dr. Bavendam displayed her vision of the long-term potential for the PLUS Research Consortium:

- PLUS 1 (completed): Create evidence for future prevention intervention studies
- PLUS 2: Observational cohort
- PLUS 3: Intervention study; follow up of cohort
- PLUS 4: Follow-up of cohort and intervention study

Dr. Bavendam thanked speakers for their participation and noted the following goals for this meeting:

- Alert Federal partners to PLUS objectives, deliverables, and timeline
- Identify opportunities to collaborate with Federal partners to disseminate PLUS findings
  - Identify areas of alignment of PLUS objectives and agency mission areas
- Provide insights into key lessons from PLUS
  - Using transdisciplinary processes to develop a new area of science
  - Embedding community engagement
  - Committing to diversity and inclusion for investigators and research participants

Dr. Bavendam introduced Dr. Mary Palmer, the PLUS Consortium's Project Scientist.

### **Building a Transdisciplinary Consortium**

Mary H. Palmer, PhD

PLUS Project Scientist/PLUS Steering Committee Chair

University of North Carolina, Chapel Hill

Dr. Palmer thanked Dr. Bavendam for inviting her to speak at today's meeting and opened her discussion with how the PLUS Consortium became a transdisciplinary consortium, charting a novel course with no pre-existing roadmap. While the process was not linear, the group created a consortium including diverse expertise.

Dr. Palmer commented that innovative aspects of the PLUS consortium include using a transdisciplinary approach by engaging multiple disciplines collaboratively to merge into a new field; focusing on prevention and health, using a public-health perspective; and establishing evidence about influences that may affect outcomes, including biology, behavior, and environment. The PLUS Consortium represents almost 35 different disciplines and expertise, including health psychology, behavioral intervention, biostatistics, nursing, and health technology. Additional features that make this Consortium unique include a good working relationship and trust between Consortium members and the PLUS project scientist and frequent in person meetings to build relationships which included planned dinners that combined different members from each site.

Dr. Palmer outlined the following PLUS Strategic Priorities and PLUS Consortium Goal Statement:

- continuous refinement of bladder health definition
- identify risk and protective factors for lower urinary tracts symptoms (LUTS) and bladder health
- seed and expand bladder health research
- characterize bladder health in general population through large observational study
- disseminate products to inform future transdisciplinary prevention research

- pioneering community engagement for prevention of bladder conditions in women and girls

Dr. Palmer emphasized the use of transdisciplinary approaches within the PLUS Consortium's goal, noting that the Consortium aims to identify promising strategies for promoting bladder health and preventing lower urinary tract symptoms (LUTS) and conditions in women throughout the lifespan. Using transdisciplinary research approaches, including both qualitative and quantitative strategies, the Consortium will identify protective factors for lifelong bladder health, risk factors for various types and degrees of LUTS, healthy and unhealthy bladder behaviors, and relevant behavioral influences in women and girls at various ages. The focus will be on obtaining the necessary information to plan future interventions to promote bladder health and prevent LUTS.

Dr. Palmer acknowledged the specific transdisciplinary team implemented science processes to support team process such as cross education webinars, online and in person discussions, and readings on transdisciplinary processes. Furthermore, Dr. Palmer discussed strategies to progress through the development phase, which included the generation of a shared mission and valuing of other disciplinary perspectives. The conceptualization phase included generating a shared language and developing a team transdisciplinary orientation. During the implementation phase, the group developed roles and procedures and focused on conflict management. The translation phase included continued refinement of the mission and goals, implementation of research protocols, and robust dissemination of the scientific work products related to bladder health.

Dr. Palmer thanked Dr. Bavendam for the opportunity to present to the group.

### **PLUS Conceptual Framework**

Sonya Brady, PhD  
PLUS Investigator  
University of Minnesota

Dr. Bavendam noted that Dr. Brady was not present for the discussion and discussed the PLUS conceptual framework. The PLUS Consortium framework was developed to provide a visual representation of what is possible to study and to show broad categories or domains of influence on a health outcome. The Consortium's framework was modeled after a framework developed by Thomas Glass and Matthew McAtee (Social Science & Medicine, 2006) and uses a broad framework to identify a comprehensive set of potential risk and protective factors. When prioritizing risk and protective factors for study, the Consortium focused on 44 distinctive influences out of 400 factors such as toileting environment and societal norms and grouped them across eight research themes for bladder health:

- Toileting Environment, Access, Habits, & Techniques
- Physical Health & Medical Conditions
- Pregnancy & Childbirth
- Musculoskeletal Health
- Lifestyle Behaviors
- Biopsychosocial Ecology of Stress & Brain Health
- Infections & Microbiome

- Hormonal Use Across the Lifespan

Dr. Bavendam noted that these subsequent clusterings generated research questions within each theme and commented that teams within the PLUS network then developed 28 research questions for study within the Consortium. For more information about the processes used to refine criteria for study, Dr. Bavendam cited the following manuscripts:

- Brady SS, Bavendam TG, Berry A, Fok CS, Gahagan S, Goode PS, Hardacker CT, Hebert-Beirne J, Lewis CE, Lewis JB, Kane Low L, Lowder JL, Palmer MH, Wyman JF, Lukacz ES; Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. The Prevention of Lower Urinary Tract Symptoms (PLUS) in girls and women: Developing a conceptual framework for a prevention research agenda. *Neurourol Urodyn*. 2018 Nov;37(8):2951-2964.
- B Lewis J, S Brady S, Sutcliffe S, L Smith A, R Mueller E, Rudser K, D Markland A, Stapleton A, Gahagan S, Cunningham SD, Prevention Of Lower Urinary Tract Symptoms Plus Research Consortium. Converging on Bladder Health through Design Thinking: From an Ecology of Influence to a Focused Set of Research Questions. *Int J Environ Res Public Health*. 2020 Jun 17;17(12):4340.
- Schmitz KH, Bavendam T, Brady SS, Brubaker L, Burgio K, Harlow BL, James A, Lukacz ES, Miller JM, Newman DK, Palmer MH, Rudser K, Sutcliffe S; Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. Is the juice worth the squeeze? Transdisciplinary team science in bladder health. *Neurourol Urodyn*. 2020 Jun;39(5):1601-1611.
- Smith AL, Rickey LM, Brady SS, Fok CS, Lowder JL, Markland AD, Mueller ER, Sutcliffe S, Bavendam TG, Brubaker L. Laying the Foundation for Bladder Health Promotion in Women and Girls. *Urology*. 2020 Mar 18:S0090-4295(20)30283-1.

### **Building and Operationalizing Community Engagement**

Shayna Cunningham, Ph.D. and Aimee James, Ph.D., M.P.H.

PLUS Investigators

Washington University

To begin the presentation, Dr. Cunningham noted that the community engagement structure within PLUS was developed to conduct responsive research with rigor and integrity; develop the highest quality evidence, grounded in lived experience; maximize research impact; and to meet the consortium's transdisciplinary goals. Because not all PLUS investigators were familiar with engaging the community within a consortium, it was important to work on building a foundation for this effort, which included educating researchers and acknowledging diverse approaches across Centers on this topic. PLUS consortium efforts in this area are guided by the PLUS Community Engagement Toolkit as well as a Strategic Plan. Key PLUS community engagement principles include:

- 1) inclusive, particularly of populations researchers have historically marginalized or exploited
- 2) examination of Consortium's internal practices, processes, and research to promote antiracist practices
- 3) engage in critical reflection, evaluation, and transparent decision making
- 4) build on strengths and resources within each Center and their communities, including power sharing
- 5) foster co-learning and capacity building among partners
- 6) acting with the community rather than on behalf of the community

- 7) universal accessibility, by using plain language, translating materials, holding events in community-preferred locations
- 8) ensuring community feedback is incorporated into all research phases

The PLUS consortium was initiated in 2017 and started by developing a community engagement plan and recruiting the appropriate expertise to facilitate this effort. In 2020 with community engagement expertise firmly in place, this group also advises The Assessments Taken over Time: Relationships Influencing Bladder and Urinary Tract ExperienceS (ATTRIBUTES) group on community engagement features related to research cycles, study design, recruitment and retention, instrument design, data collection, analysis and interpretation, and dissemination. Community engagement accomplishments to date include establishing infrastructure for national engagement strategy, community conversations to initiate this effort, rapid assessment partners which include in-person visits for the ATTRIBUTES study, SHARE Trustworthiness checks, developing a process for reviewing lay dissemination outputs, and an external website.

Dr. Cunningham noted the strategic plan for community engagement in PLUS is aligned to meet PLUS study aims and is needed as:

- Previous “heathy bladder” research is nonexistent and LUTS research has been predominantly provider/researcher-driven and has not included the perspectives of those with lived experience with LUTS. This has created a gap in our knowledge and understanding of bladder health. Incorporating perspectives of non-clinical/research perspectives will help investigators build on our existing knowledge and deepen our understanding of what it means for women to have a healthy bladder.
- The assembly of appropriate evidence of healthy bladder function is contingent on understanding how women and girls experience healthy bladder function. PLUS researchers will need guidance from community experts as to what evidence looks like and how best to collect the evidence.
- Upon assembling evidence, PLUS investigators need guidance from community partners on how to interpret meaning of evidence. This includes guidance on research question identification, data collection instruments. and interpretation of findings.
- Because this is prevention intervention science, engagement should happen at the formative research stages to assure that mechanism of engagement are in place to successfully disseminate findings and set the stage for successful, sustainable interventions.

Drs. Cunningham and James thanked Dr. Bavendam for the opportunity to provide information related to community engagement efforts within PLUS.

### **Voices of Women and Girls (SHARE Study)**

Lisa Kane Low, CNM  
PLUS Investigator  
University of Michigan

Dr. Low discussed the Study of Habits, Attitudes, Realities and Experiences (SHARE) which aims to explore adolescent and adult women’s experiences, perceptions, beliefs, knowledge, and behaviors related to bladder health and function across the life course. Methods for this study included:

- 44 focus groups conducted with 360 participants
- Ages 11 to 93 years
- Six age categories: 11-14, 15-17, 18-25, 26-44, 45-64, 65+
- Purposeful recruitment strategy to include racially, geographically, and culturally diverse participants, including Spanish Speakers.

As a result of these analyses, the team prioritized 4 topics for the first phase of focus group data interpretation:

- Terminology and lay discourse to explore and characterize women’s and adolescents’ lay discourse about bladder health and function, which resulted in a collection of bladder function terms including informal familiar terms used with family and friends.
- Healthy bladder perceptions to explore adolescent and adult women’s perceptions of a healthy and unhealthy bladder, which demonstrated that a healthy bladder is characterized by the ability to not think about the bladder for individuals when no symptoms are present.
- Navigation to explore how adolescent and adult women’s experience accessing and using toilets in schools, workplaces, and public spaces, which demonstrated the influence of “Gatekeepers” who restrict access to toilets across settings such as schools, workplaces, or public spaces.
- Monitoring bladder behaviors to explore the social processes of monitoring oneself and others’ bladder behaviors across social ecology and the life course, which resulted in the observance of three distinct types of monitoring:
  - Monitoring others: Participants engaged in comparative analysis of others in their socio-ecological environment.
  - Individual awareness of being monitored by others: Participants described perceptions of being monitored both explicitly and implicitly by parents, peers, and others.
  - Monitoring oneself: To assess one’s behavior relative to objective/subjective norms. Self-monitoring examples include scrutinizing urine as a health indicator (color, smell, stream).

Based on these observations a crosscutting theme emerged that fear and anxiety were integral to self-monitoring, often rooted in childhood experiences of shame associated with unanticipated leaking of urine or associated social environments that restricted bladder autonomy.

Summary recommendations from this effort include the development of public health programs that may foster bladder health literacy and research focused on understanding the impact inequities in toileting access across the life course on bladder health outcomes in US women, adolescents, and girls, which in turn may help clinicians advise individuals on bladder health behaviors.

### **Development of a Bladder Health Measure**

Leslie Rickey, MD, Yale University

Melissa Constantine, PhD, University of Minnesota

PLUS Investigators

Dr. Rickey began her presentation by noting that the Boston Area Community Health (BACH) was first study to focus on gaps in urologic epidemiologic data from a community perspective, rather than from a physician/patient perspective. As a result of BACH, researchers formed “The Urologic Iceberg” concept,

which shows the visible tip of the iceberg were patient symptoms are present and diagnosed versus the underwater portions of the iceberg were patient symptoms are present but not diagnosed, symptoms that are recognized but not present, and symptoms that were neither recognized nor present. Dr. Rickey commented that prevalence has been underreported as clinicians generally focus on the tip of the iceberg, thus generating evidence that much of the previously reported data has solely focused on this patient population. However, little is known about the prevalence within populations underwater in the iceberg as there are not sufficient measures available to diagnose and treat this population. Dr. Rickey emphasized that the PLUS Consortium focused on shifting from bladder disease to bladder health which aligns with clinical management to prevention.

Dr. Constantine commented that, while there are effective treatment options for LUTS, few incontinence prevention programs have been studied. The transition to focusing on a standardized bladder health definition can aid in identifying factors to promote health as well as factors to modify to prevent LUTS. However, researchers have been unable to identify women who are at the highest risk of developing LUTS to be targeted for prevention efforts due to an underreported prevalence in individuals with few symptoms and in the asymptomatic population. The definition of bladder health used by the PLUS Consortium is: “A complete state of physical, mental, and social well-being related to bladder function, and not merely the absence of LUTS. Function that permits daily activities, adapts to short term physical or environmental stressors, and allows optimal well-being (e.g. travel, exercise, social, occupational activities).” Key bladder health dimensions include functions of the bladder as it relates to the functional impact on the individual’s life. To focus study efforts, researchers developed the Clarification of Language, Evaluation And Refinement of Questions (CLEAR) questionnaire to ensure survey questions could be easily understood by individuals and enhance measure developments for all populations.

Dr. Constantine emphasized the importance of considering the patient population when validating the measure and added that the key to the validation process of any measure is ensuring the measure has been validated in the population that will eventually be studied and that the measured construct matches the intended construct. While there are existing measures for bladder disease, evidence is lacking for certain aspects of bladder health. Dr. Constantine concluded that all research data has been collected and an analysis is underway now. Investigators are currently working toward having validated bladder scale available for ATTRIBUTES or any other studies by January 2020.

Dr. Bavendam thanked Drs. Rickey and Constantine for their participation in the meeting and introduced Dr. Sutcliffe at Washington University.

**Longitudinal Cohort Study (ATTRIBUTES)**

Siobhan Sutcliffe, PhD, Washington University

Ariana Smith, MD, University of Pennsylvania

Jesse Nodora, PhD, University of California San Diego

PLUS Investigators

Dr. Sutcliffe noted that the ATTRIBUTES study is a large, longitudinal observational study of bladder health in women across the life course and detailed the two major objectives for ATTRIBUTES:

- Identify risk and protective factors for bladder health and lower urinary tract symptoms (LUTS) in women across the life course
- Estimate the distributions of bladder health and bladder health knowledge, attitudes, and beliefs in women across the life course.

The ATTRIBUTES study aims to identify risk and protective factors across eight themes: toileting environment/access/habits/techniques, personal physical health/medical conditions, pregnancy and childbirth, musculoskeletal function/pelvic floor health/muscle awareness, lifestyle behaviors (e.g., fluid intake, dietary factors), stress and mental health, infections and microbiome, and hormonal status across lifespan. Dr. Sutcliffe detailed that the goal within this study is to obtain nationally representative estimates regarding racial/ethnic diversity, socioeconomic diversity, and geographic diversity. The study design balances regional samples and national samples by obtaining a regionally-representative sample of women recruited from the population surrounding the seven clinical research centers (CRCs) as well as a nationally-representative cross-sectional sample of women recruited from areas outside the CRCs to estimate (together with participants from the regional sample) national distributions of bladder health and bladder health knowledge, attitudes, and beliefs.

The sampling plan will identify eligible households from the USPS Delivery Sequence File (DSF, list of valid addresses in the US) and households selected by multi-stage sampling such as counties surrounding the CRCs. Regarding eligibility, households selected by multi-stage probability sampling will be mailed an invitation and questionnaires and females 18 years or younger will be eligible. Dr. Smith noted that data collection efforts will include self-reported information from participants on bladder health and bladder health knowledge, attitudes, and beliefs and depending on the results of the pilot study, participants may also be asked to provide biologic specimens. In addition, regional cohort participants will be asked to provide information on additional candidate risk and protective factors and will be followed longitudinally with periodic questionnaires. In-person visits will collect clinical data such as participant height, weight, musculoskeletal and pelvic floor muscle assessments, and a urine sample. Currently, a pilot study is underway to collect biospecimens using a home shipped protocol method to increase the number of samples available. If this pilot study is successful, it may be included in within the full scope of the ATTRIBUTES study.

Dr. Nodora noted that another component of the ATTRIBUTES study will feature a XRA-Latinx cultural adaptation to ensure the study measures established are also appropriate for the Latino community. Dr. Sutcliffe thanked meeting participants for the opportunity to provide information about the ATTRIBUTES study. Dr. Bavendam thanked Drs. Sutcliffe, Smith, and Nodora for their participation.

### **Keeping Our Focus on Adolescents: Progress and Plans to Launch Adolescent ATTRIBUTES**

Peter Scal, MD  
PLUS Investigator  
University of Minnesota

Dr. Scal presented a summary of adolescent-focused research from the PLUS 1 and commented that PLUS researchers collaborated to create a definition of bladder health that is applicable across the life course: “A complete state of physical, mental and social well-being related to bladder function, and not merely the absence of LUTS.” To date, researchers have completed 27 focus groups with

socioeconomically and racial/ethnic diverse samples of 11- to 17-year-old adolescent women across the United States. The data will inform the development of a novel adolescent bladder health instrument that will be used in a future observational study, as well as measures of knowledge, attitudes and beliefs, toileting practices and behaviors, and toileting environment.

Secondary data analyses of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, also from PLUS 1, have focused on bullying, school environments, and sexual health behaviors and their relationship to bladder health. The Young Women's Health Council has met monthly for 1 year and has helped provide feedback on the measurement study specifically.

Also developed from PLUS 1 was the Adolescent Bladder Health Instrument, which included the ability for the instrument to be self-reported, reflects the lived experience of adolescents, focused on health, and aligns with the adult bladder health instrument where possible.

Dr. Scal commented that the overarching goal of the adolescent ATTRIBUTES study was to understand the current state of bladder health and its determinants among adolescent women in the United States and he detailed the following potential research aims:

- Describe the distribution of bladder health among US Adolescents and examine the relationship between bladder health and sociodemographic characteristics
- Examine the relationship between the timing of life course developmental events and bladder health
- Examine the relationship between health related behaviors, general health, and bladder health

Dr. Scal thanked Dr. Bavendam for the opportunity to participate and invited questions from participants.

### **Questions and Answers with PLUS Investigators**

Moderated by Tamara Bavendam, MD, MPH

Dr. Bavendam thanked all the PLUS presenters and consortium members and requested that participants introduce themselves.

- Dr. Weiderhorn queried if there are any hard data points that the group will explore such as any studies of any type related to bladder changes, aging, studies using patient reported outcomes as an endpoint, and queried if there are any genetics data that are measurable. Dr. Smith noted that the group is working on developing an in-person measure for genetic data and added that the group is also focusing on microbiome analysis. In addition, the group collects urine and vaginal swabs which can provide additional analyses. She noted that most measures are biological, but others are self-reported questions and commented on PLUS validation versus FDA validation methods. Dr. Constantine noted that measured responses to therapy will evaluate responsiveness with PLUS and ATTRIBUTES data. Dr. Bavendam noted a high level of interest in collecting specimens for use in analysis and added that the group does not have plans to collect blood or saliva.
- Dr. Harlow noted that participants will receive long-term follow-up as the group is interested in collecting more samples and added that more infrastructure will be in place to aid recruitment and retention efforts for these patients.

- Dr. Weiderhorn queried how one phenotype may predict changes and commented that a longitudinal follow-up study might be helpful to observe these changes. Dr. Smith noted interest from a PLUS PI to conduct a cluster analysis that will create a phenotype related to bladder health and added that there will be various data points of work to be completed which may allow the group to look at data similar to the MAPP network. Dr. Scal commented that the experiences of young individuals may not show dysfunction of bladder health and added that it is important to understand current and potential long term influences.
- Meeting participants queried if participant related data from the COVID-19 pandemic will be included in the ATTRIBUTES study. Dr. Sutcliffe noted the group is also interested in capturing COVID-19 related changes from participants. Dr. Cunningham noted that community engagement efforts are underway to maximize data collection related to the pandemic. Dr. Bavendam commented that the pandemic has impacted consortium work but added that PLUS PIs were able to make modifications fairly quickly for participant recruitment.

### **Round the Table**

- Dr. Norton queried if other agencies are able to help NIDDK strategize on how to disseminate PLUS findings. Dr. Weiderhorn commented that the FDA looks at measurable endpoints as treatments and added that these are not changes FDA would evaluate as it is focused on changes in behavior. Dr. Weiderhorn suggested the development of patient-reported outcomes, hard data to predict syndromes, and recommended that PLUS investigators consider how to measure prevention efforts and consider if any surrogates that could be used.
- Dr. Norton queried participants what future interventions could developed for the PLUS Consortium. Dr. Barthold commented that identifying subpopulations of individuals may clarify which interventions should be in each group. Dr. Barthold queried if there is clustering in the data analysis, and what other factors could be considered that affect syndromes in healthy individuals besides genetic. In addition, Dr. Barthold queried if the group would consider microbiome changes within urologic systems as an opportunity for an area of study. Dr. Mullins commented that would be valuable to study in this population.

### **Agency Updates**

- Dr. Salive noted the NIA has funded several urologic studies at the University of Pennsylvania and the University of Pittsburgh as well as a pelvic research society meeting grant. In addition, NIA is funding up to two applications related to the Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) program for bladder research/urinary incontinence.
- Dr. Wiedernhorn noted the FDA has published a request for comments related to a guidance document for Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS): Establishing Effectiveness of Drugs for Treatment Guidance for Industry and added that comments are now being assessed.

Dr. Bavendam noted that the next UICC meeting will focus on Neurology in urology and adjourned the meeting.