July 25, 2022

RE: Application: CLIN2-13267, Wake Forest University Health Sciences
"Phase I Treatment of Urethral Strictures in Humans". PI – James Yoo, MD, PhD

To the Governing Board of CIRM:

We thank the GWG reviewers and patient advocate members for their thoughtful and constructive review. We appreciate their positive feedback with all GWG members unanimously affirming that the review was scientifically rigorous, and that there was sufficient time for all viewpoints to be heard. However, we seek to address the primary areas where the GWG and advocate members felt the DE&I in the Research section was not fully responsive and/or required additional information.

Critique #1: "Does the project serve the needs of underserved communities?"

Reviewer Comment: *I am not aware of the demographics for this condition. Obviously, it affects only males. Both trial sites appear to have well-developed programs, both internally and in terms of reaching underserved populations with urinary tract conditions.*

Response: We address this observation and provide additional information with regard to incidence across diverse populations acknowledging that while data sets suggest that Black Americans are at a higher risk, sample numbers remain too low to draw conclusions.

Urethral stricture is a relatively common disease in men with an associated prevalence of 229-627 per 100,000 males, or 0.6% of the at-risk population, who are typically older men (1). Santucci *et al*. (1) analyzed urethral stricture disease in ten public and private data sets in the United States. They concluded that urethral stricture disease is common in the elderly population with a marked increase after 55 years of age. Data from Medicare and Medicaid Services (for patients older than 65 years) confirmed an increased incidence of stricture disease at 9.0/100,000 for 2001 compared to 5.8/100,000 in patients younger than 65 years. Patients with urethral stricture are considered a vulnerable population as they experience high rates of UTIs (41%) and incontinence (11%) as sequelae of the disease (1,2). Some of the data sets indicate that Black Americans are at a higher risk of urethral stricture disease than White Americans, with sample numbers too low to draw accurate conclusions for Asian, Hispanic, and Native American patients (1).

1. Santucci RA, Joyce GF, Wise M. Male urethral stricture disease. *J Urol* 2007;177:1667-74.
2. Anger JT, Santucci R, Grossberg AL, et al. The morbidity of urethral stricture disease among male Medicare beneficiaries. *BMC Urol* 2010;10:3.

Critique #2: The applicant does not address how the success of the project would lead to a translational advance that impacts underserved communities

Response: As noted and positively reviewed in the proposal, Dr. Benjamin Breyer at UCSF is a renowned reconstructive urologist, and he has access to the optimal patient population with both UCSF and Wake Forest leveraging and developing partnerships with stakeholders across the clinical trial ecosystem (patient groups, community members, clinical research sites, CROs, academia, nonprofit and advocacy organizations, federal and state agencies, industry, etc.) to establish a sustainable, community-based clinical trial infrastructure. It is also notable that both USCF and Wake Forest have NIH CTSI. The CTSI at both institutions provides support and infrastructure for UCSF and WF researchers to diversify their study populations and each offers

expertise and assistance in clinical trial patient recruitment. The CTSI offers consultations, advances critical partnerships and resources, and promotes other initiatives essential activities, and programs in response to FDA recommendations to ensure that the research enterprise more equitably promotes well-being and inclusiveness.

At UCSF, the new Research Action Group for Equity (RAGE) program was created to provide support and infrastructure for UCSF researchers to diversify their study populations. The RAGE offers consultations and resources and promotes other initiatives essential to ensuring that the research enterprise more equitably promotes well-being.

At WF, the CTSI patient recruitment toolbox also includes resources, including consultations for WF researchers to help study teams diversify their study populations and achieve realistic recruitment goals. Emphasis also includes adopting enhanced data collection capabilities to help support the appropriate collection and sharing of racial and ethnic data and real-world data (RWD) through a cloud-based platform.

Studies have shown that older males, those from lower socioeconomic groups, and minority groups are less likely to choose urethroplasty over serial dilation/urethrotomy to treat urethral stricture and may be less likely to seek care at a teaching hospital (3, 4). Dilation and urethrotomy have high failure rates. The patient population for this trial is men that have failed conventional therapy, including dilation and urethrotomy – so those most in need of urethroplasty. This clinical trial can impact underserved communities by offering a no-cost treatment to the participating men in the trial, and, we hope, a safe and effective first-line or second-line treatment option to all men in the future.

3. Dornbier RA, Kirshenbaum EJ, Nelson MH, Blackwell RH, Gupta GN, Farooq AV, Gonzalez CM. Socioeconomic and patient-related factors for the management of male urethral stricture disease. World J Urol. 2019 Nov;37(11):2523-2531. doi: 10.1007/s00345-019-02702-0. Epub 2019 Feb 27. PMID: 30810835.
4. Anger JT, Buckley JC, Santucci RA, Elliott SP, Saigal CS; Urologic Diseases in America Project. Trends in stricture management among male Medicare beneficiaries: underuse of urethroplasty?. Urology. 2011;77(2):481-485. doi:10.1016/j.urology.2010.05.055

Critique #3: While the reviewers simultaneously thought the overall DEI section was acceptable, the patient advocate reviewers pointed out a lack of describing or addressing potential barriers to trial participation, so it is difficult to evaluate whether they can achieve inclusive trial recruitment.

Response: We thank the reviewers for acknowledging our clear focus on DEI, as evidenced by our selections of trial sites and our many ties to minority health advocacy and health equity organizations and programming which includes a strong emphasis on achieving diversity, equity, and inclusion in all aspects of research, education, training, and patient health care and clinical trial recruitment. Nonetheless, we agree that we may be relying on the reputation of our institutions and provide our philosophy and approach as related to addressing barriers:

Phase I – Treatment of Urethral Strictures in Humans -- Addressing barriers to DE&I in clinical trials

Racial and ethnic diversity among our 10 clinical trial participants is important to support science-driven strategies aimed at understanding the needs of those who are affected by the disease or condition being investigated. We believe the ability to achieve this lies in our realizing development of an ecosystem with the successful integration of multi-stakeholder partnerships addressing the barriers recognized by both the FDA's guidance on *Enhancing the Diversity of*

Clinical Trial Populations (5) and PhRMA's, *Principles of Conduct of Clinical Trials and Communication of Clinical Trial Results (6).* Our efforts reflect both FDA's and PhRMA's guidance and include: increasing clinical trial awareness and enhancing clinical trial representation across both sites in partnership with the USCF and WF CTSIs, partnerships with stakeholders across the clinical trial ecosystem (patient groups, community members, clinical research sites, CROs, academia, nonprofit and advocacy organizations, federal and state agencies, industry, etc.) and well as leveraging established partnerships with targeted communities through regional HBCUs and HSIs (Winston Salem State University, North Carolina Agricultural and Technical College and City College of San Francisco) recognizing that none of the stakeholders can make sustainable change alone.

As detailed in the proposal, our approach focuses on the topic of building partnerships to improve clinical trial diversity and seeks to address three primary barriers to enhancing clinical trial diversity: 1) Lack of awareness of clinical trials, 2) lack of access, and 3) mistrust by underrepresented communities and populations.

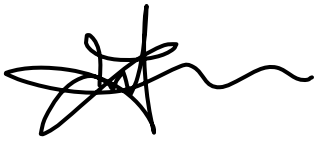
Approach:

- Partnering with USCF and WF stakeholders across the clinical trial ecosystems (patient groups, community members, clinical research sites, CROs, academia, nonprofit and advocacy organizations, federal and state agencies, industry, etc.)
- Leveraging established relationships with the target community through community leaders, Historically Black Colleges and Universities (HBCUs), Hispanic Serving Institutions (HSIs), and other minority-serving institutions Federally Qualified Health Centers (FQHCs), patients, and others to provide outreach, training, and education, and mentorship/job pathways.
- Integrating data collection capabilities to help support the collection and sharing of racial and ethnic data
- Sharing of pre-existing with the ongoing development of educational tools and resources to heighten awareness of clinical trials focused on the pipeline of students as well as patient-friendly resources that address issues of mistrust and make it easier to identify and enroll in relevant clinical trials

5. US Dept of Health and Human Services, Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry, FDA, November 2020. Accessed July 24, 2022 at Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry | FDA
6. Pharmaceutical Research and Manufacturers of America (PhRMA), **"** Principles on Conduct of Clinical Trials & Communication of Clinical Trial Results**",** November 2020. These principles became effective April 2021. Accessed July 24, 2022 at Pharmaceutical Research and Manufacturers of America (PhRMA) and its member companies published the first-ever industrywide principles on clinical trial diversity in November 2020, - Search (bing.com)

We hope that we have addressed the concerns the GWG reviewers and patient advocate members have raised on our application. We are happy to clarify further if additional information is needed.

Sincerely,



James Yoo, MD, PhD.