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Impact of COVID-19 on Prevention of Urinary Stones with Hydration (PUSH) Study: Challenges and Opportunities for Future Trials

The Urinary Stone Disease Research Network (USDRN) Investigators

Practical challenges to performing randomized clinical trials (RCTs) include difficulty recruiting and retaining participants, enrolling a sample reflecting the source population, and maintaining scientific rigor across large, multi-site trials. Indeed, poor enrollment is the most common cause of failed trials in urology.[1] The success of an RCT hinges on access to the eligible patient population and level of burden on the participants. Access is determined by the methods used to identify, consent, and randomize eligible patients. Study burden reflects the frequency and invasiveness of study procedures beyond routine clinical care, outcome assessment methods, and need for in-person study visits. The COVID-19 pandemic created tremendous challenges to conducting RCTs. We herein review lessons learned from the PUSH trial during the COVID-19 pandemic to provide a framework for successful trial conduct in both traditional and extraordinary environments.

The PUSH RCT (NCT03244189) was developed by the NIH/NIDDK-funded Urinary Stone Disease Research Network (USDRN) to assess the efficacy of education, financial incentives, and coaching to maintain high fluid intake and reduce symptomatic urinary stone disease (USD) recurrence in adolescent and adult stone formers.[2] A total of 1642 participants will be recruited at 6 sites in the US. The primary outcome, symptomatic stone recurrence, will be obtained by adjudicated self-report from participants, with blinded adjudication based upon available evidence and medical records. PUSH includes elements of pragmatic trials such as utilization of 24-hour urine collections and diagnostic imaging obtained for clinical care as secondary outcomes.

When US community transmission of SARS-CoV-2 became widespread in March 2020, 869 participants (53%) had been randomized in the PUSH trial. Most USDRN research activities came to a near complete stop for the safety of study staff and participants. Even as health centers developed protocols to operate safely through the pandemic, hesitation of patients and caregivers to engage in any nonessential activities remained an additional obstacle to PUSH recruitment.

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In early April 2020, the USDRN developed a systematic strategy to overcome these barriers to recruitment. The guiding principle was to increase recruitment and retention while maintaining scientific rigor. To achieve this goal, our aim was to 1) lower barriers to (and the burden of) participation and 2) expand the geographic recruiting pool. The challenges created by COVID-19, the USDRN's responses, and implications for future research are shown in the Table.

The USDRN reduced barriers to study participation by implementing remote recruitment and enrollment of participants via the following steps:

1. *Engagement with the Data Safety and Monitoring Board (DSMB)* – The USDRN worked with the DSMB to secure approval for protocol amendments.
2. *Communication with Institutional Review Boards (IRBs)* – Early interactions with the IRBs at each center included the USDRN's proposal to obtain informed consent remotely rather than in-person. These discussions were successful, and virtual informed consent was ultimately approved, thus enabling remote enrollment and randomization of participants. This transition to remote recruitment was based on the premise that the processes of informed consent could remain robust even if carried out by phone or video.
3. *Review of trial experience* – The original protocol required laboratory testing among a subset of participants for safety concerns, as well as on-study imaging for secondary trial endpoints.[2] Review of participant safety data and power for comparison of secondary endpoints among the 869 participants suggested that waiver of these two requirements would not jeopardize participant safety or scientific rigor. The USDRN requested an *ad hoc* meeting of the DSMB to consider amendments to enable completely remote recruitment, and these changes were approved.

Concurrent with the modifications designed to decrease barriers to participation, we also developed complementary strategies to expand the geographic pool of eligible patients who could participate in PUSH:

1. *National recruitment* – The ability to consent remotely provided a new opportunity to recruit PUSH participants throughout the US. To incentivize physician referral, the USDRN developed criteria to recognize collaborators. These recognitions, which are commensurate with the number of participants who are referred and randomized, range from acknowledgement of the referring site to potential co-authorship of the manuscript that will report the main results of the PUSH trial.
2. *New partnerships* – We leveraged the expansive health systems in the USDRN and their shared informatics structure to identify patients who receive care throughout the care networks. Examples include opening enrollment at Florida and Arizona sites for the Mayo Clinic and in Florida for the Cleveland Clinic. The centerpiece to increasing enrollment of adolescents was establishing a relationship between the USDRN and the Pediatric KIDney Stone (PKIDS) Care Improvement Network, which includes 26 pediatric health

systems. Subsequently, individuals who participated in a PKIDS comparative effectiveness study (NCT04285658) and indicated interest in participating in other research studies on stones were contacted about the PUSH study.

These timely adaptations were motivated by a need to mitigate the impact of COVID-19. Out of necessity, the pandemic greatly accelerated the implementation and acceptance of video and digital technologies for patient contact. The pandemic also accelerated the willingness of investigators, regulatory bodies, and other stakeholders to focus attention on ways to make trial conduct more efficient, without meaningful impact on patient safety. It is important to acknowledge that these adaptations can be adopted even without a pandemic, and thus have theoretical and practical implications for conducting future RCTs. We offer our experience in the USDRN to provide a framework for RCT design and implementation that maintains scientific rigor and reproducibility while reducing structural and attitudinal barriers to study participation. The cornerstone is the remote consent process, which has practical and scientific advantages. Practically, remote consenting allows greater flexibility in scheduling, eliminates the need for clinic research space, increases enrollment speed, and opens up trial participation to individuals living in rural areas or at distance from a site. It also bypasses the need for prolonged face-to-face encounters, which is key when physical distancing is recommended. In addition, video informed consent has been reported to result in inclusion of a more diverse and representative participant population compared to traditional in-person consent.[3]

In addition, we recommend embedding research procedures within clinical care (*e.g.*, using existing clinical data to determine eligibility, using imaging obtained for clinical care purposes within specified windows as trial outcomes) and use of home-based sample collection (*e.g.*, 24-hour urines). Embedding research in clinical care could potentially improve participant recruitment with the secondary benefit of decreasing data missingness. A further goal should be to minimize the number of procedures that do not enhance participant safety, and to limit procedures designed to assess secondary outcomes to the smallest number needed to detect a meaningful difference.

Establishing the appropriate regulatory environment and study design for remote participation creates an opportunity to expand the eligible participant population beyond patients who receive care at clinical trial sites. In addition to the obvious benefits of faster accrual and a more representative patient population, expansion of access to RCTs increases participation of the broad urologic community in research. This improves the generalizability of results and allows institutions to generate knowledge that directly benefits the patients they treat.

As revealed by our experience with the USDRN PUSH trial, the COVID-19 pandemic has created tremendous challenges to conducting trials but has also revealed opportunities to adapt and improve the design and implementation of future RCTs with higher efficiency, broader inclusion, and generalizability.

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Abbreviation Key:

USDRN	Urinary Stone Disease Research Network
RCT	Randomized Clinical Trial
PUSH	Prevention of Urinary Stones with Hydration
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
USD	Urinary Stone Disease
US	United States

DSMB	Data Safety and Monitoring Board
IRB	Institutional Review Board
PKIDS	Pediatric Kidney Stone Care Improvement Network

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Table:

Challenges for conducting RCTs during the COVID-119 pandemic, responses of the Urinary Stone Disease Research Network (USDRN) to mitigate the impact of COVID-19, and the implications for future trials.

National, State, and Institutional Restrictions	USDRN Responses	Implications for Future Trials
Study visits Study coordinator availability Clinical activity Hesitation from patients	1) Lower barriers to participation a. Remote consent process b. Remote randomization c. Embedding research in clinical care d. Reduced number of study procedures and tests 2) Expand geographic pool of participants a. Incentivizing referrals b. New network partnerships c. Publicizing the RCT through professional organizations, webinars, and presentations	Study participants who are more representative of the population Increased engagement of the clinical community in research Faster accrual More appealing for patients to participate in an RCT