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Prevention of Urinary Stones With Hydration (PUSH): Design and Rationale of a Clinical Trial

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Abstract

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Authors' Contributions: research idea and study design: CDS, ACD, JDH, HHL, NMM, PPR, GET, HRA, ZK, HW; data acquisition: ACD, JDH, HHL, NMM, PPR, GET, HW; data analysis/interpretation: CDS, ACD, JDH, NMM, PPR, GET, HRA, ZK, HW; statistical analysis: HRA; Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Trial registration: ClinicalTrials.gov NCT03244189

Rationale & Objective: Although maintaining high fluid intake is an effective, low-risk intervention for the secondary prevention of urinary stone disease (USD), many stone patients do not increase their fluid intake.

Study design: We describe the rationale and design of the Prevention of Urinary Stones with Hydration (PUSH) study, a randomized trial of a multi-component behavioral intervention program to increase and maintain high fluid intake. Participants are randomized (1:1 ratio) to intervention or control arm. The target sample size is 1642 participants.

Setting & Participants: Adults and adolescents ≥12 years of age with a symptomatic stone history and low urine volume are eligible. Exclusion criteria include infectious or monogenic causes of USD and comorbid conditions precluding increased fluid intake.

Interventions: All participants receive usual care and a smart water bottle and smartphone application. Participants in the intervention arm receive a fluid intake prescription and an adaptive program of behavioral interventions, including financial incentives, structured problem solving, and other automated adherence interventions. Control arm participants receive guideline-based fluid instructions.

Outcomes: The primary endpoint is recurrence of a symptomatic stone over 24-months of follow-up. Secondary endpoints include changes in radiographic stone burden, 24-hour urine output, and urinary symptoms.

Limitations: Periodic 24-hour urine volumes may not fully reflect daily behavior.

Conclusions: With its highly novel features, the PUSH study will address an important healthcare problem.

Plain-language summary:

Increasing fluid intake in urinary stone formers with low urine volume is essential to prevent stone recurrence, but difficult to achieve in clinical practice. The **P**revention of **U**rinary **S**tones with **H**ydration (PUSH) study is a randomized clinical trial that uses a “smart” water bottle to track fluid intake and examines whether a combination of behavioral interventions (including a “fluid prescription”, financial incentives, and coaching) improves adherence to higher fluid intake and reduces stone recurrence. We describe the rationale and design of this large multicenter randomized trial currently enrolling 1,642 stone formers, with outcomes including symptomatic stone recurrence, asymptomatic (radiographic) stone disease progression, and urinary parameters associated with disease.

Keywords

urinary stone disease; behavioral intervention; increased fluid intake; randomized clinical trial

INTRODUCTION

Urinary stone disease (USD) is an important medical, scientific, and public health problem. The prevalence of USD in the United States has nearly doubled in the past 15 years[1–3] and health care utilization for treating these patients has risen in parallel.[4,5] USD affects 1 in 11 people in the United States, a prevalence similar to that of diabetes.[1,2] Estimates from the

Urologic Diseases in America project suggest that USD is one of the most expensive urologic conditions.[4]

High fluid intake is a leading intervention for the secondary prevention of USD because it is low-risk, inexpensive, and effective. Current guidelines agree on one fundamental lifestyle change for USD prevention: maintaining an oral fluid intake sufficient to cause urine output (UOP) of at least 2–2.5 L/day.[6,7] Among adults with USD who receive counseling in a stone clinic, the mean increase in 24-hour UOP is only 300 mL/day,[8] suggesting that adherence to increased fluid intake recommendations is low even when the consequences of non-adherence are severe. Barriers to maintaining fluid intake for patients with USD are common, including discounting the probability of a future stone event and forgetfulness. In addition, higher fluid intake may pose specific challenges to patients with lower urinary tract symptoms or overactive bladder, those with restricted access to fluids, or those with limited bathroom access. These patients may require tailored solutions to overcome their specific barriers to increasing fluid intake.[9,10]

Substantial evidence exists for the efficacy of adherence interventions grounded in behavioral economics. Appropriately structured financial incentives can help overcome present bias by helping patients maintain a mental connection between a current behavior, such as fluid intake, and a future event with uncertain probability, such as a recurrent stone episode. Financial incentives have been shown to improve smoking cessation,[11–14] exercise,[15–18] substance abuse management,[19–21] and medication adherence.[22–24] The Prevention of Urinary Stones with Hydration (PUSH) study is a randomized controlled trial that will test a theory-based program of behavioral interventions, including financial incentives, directed towards increasing and maintaining a high fluid intake to reduce USD recurrence.

METHODS

Study Design

PUSH (ClinicalTrials.gov identifier: NCT03244189) is a 2-arm, multicenter, randomized controlled clinical trial that incorporates pragmatic features, an adaptable behavioral intervention, patient choice, individualized fluid prescriptions, and automated monitoring of fluid intake through a commercially available wireless smart water bottle that communicates with a smartphone application (Hidrate Spark, Hidrate, Inc., Minneapolis, MN). The study will enroll 1642 participants to be followed for 24 months. Both intervention and control arm participants receive a smart water bottle capable of tracking fluid consumption; usual care, including guideline-based recommendations of adequate fluid intake; periodic 24-hour urine collections; and baseline and end-of-study imaging (Figure 1, Table 1). After enrollment, the majority of the study procedures and interactions between study participants and research personnel will be conducted remotely, with in-person visits occurring only at the beginning and end of the study. Participants will undergo imaging (low-dose computerized tomography [CT] for adults, ultrasound for adolescents) at baseline and 24 months to assess changes in stone burden.

Aims and Hypotheses

The primary aim of PUSH is to assess the effect of a behavioral intervention program on the primary endpoint of symptomatic stone recurrence at 2 years (Table 2). We hypothesize that a multi-component behavioral intervention program will lead to sustained high fluid intake and UOP, resulting in decreased symptomatic stone recurrences compared with usual care.

Secondary endpoints include formation of asymptomatic new stones on imaging, growth of stones present at baseline (by ≥2 mm in any dimension) on imaging, change in 24-hour UOP versus baseline, and change in lower urinary tract symptoms. A composite outcome of symptomatic stone recurrence, formation of new asymptomatic stones, or stone growth on imaging will also be compared between study arms. Finally, costs of study interventions and treatments for USD during the PUSH followup period will be assessed.

Measures

Daily fluid intake is monitored through use of a wireless-enabled smart water bottle and data transmitted daily to the web-based platform for implementation of behavioral economic components at Way to Health (University of Pennsylvania, Philadelphia, PA). Way to Health provides a secure, user-friendly approach to monitoring participation, delivering feedback/communications (email, text, or phone messages using interactive voice response), and administering financial incentives.[25]

Study participants undergo baseline and end-of-study imaging (at conclusion of 24-month follow-up) (low-dose CT for participants aged ≥18 years, renal ultrasound for those aged <18 years at enrollment). In addition, imaging that occurs for clinical care during the follow-up period may also be reviewed for outcome events, such as formation of a new stone. A central committee, blinded to the randomization allocation, will adjudicate the primary and secondary (imaging) endpoints.

UOP is assessed by 24-hour urine collections at baseline and every 6 months during the 24-month study period. Participants are queried every 3 months electronically or by telephone regarding the occurrence of stone events (primary outcome), such as stone passage or procedural intervention for a stone. Supporting details from review of medical records are obtained using standard procedures in the protocol. Lower urinary tract symptoms in adult participants are assessed at baseline and every 6 months thereafter using the Comprehensive Assessment of Self-reported Urinary Symptoms (CASUS) questionnaire.[26]

Setting and Participants

The study is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and conducted at Urinary Stone Disease Research Network (USDRN) clinical centers consisting of the University of Pennsylvania Health System and Children's Hospital of Philadelphia, University of Texas Southwestern Medical Center, University of Washington, and Washington University in St Louis. The Cleveland Clinic Foundation, and the Mayo Clinic were added as recruiting centers in 2019. Duke University serves as the Scientific Data Research Center. The institutional review boards of each institution reviewed and approved the study; participants provide informed consent/assent to participate. Participants receive usual care for their USD clinical centers or at referring institutions.

Eligibility criteria include age ≥12 years, symptomatic urinary stone (stone passage or surgery) within 3 years prior to inclusion or a symptomatic stone event within 5 years if a new stone has been detected on imaging, low 24-hour UOP, and access to a device (smartphone or tablet) compatible with the smart water bottle. For this study, low UOP is defined as <2.0 L/day for participants age ≥18 years or those age 12–17 years weighing ≥75 kg. For participants age 12–17 years weighing <75 kg, the low UOP requirement is <25 mL/kg body weight/day. Exclusion criteria and rationale are listed in Table 3.

Randomization and Blinding

Study participants are randomized in a 1:1 ratio to 1 of 2 parallel study groups, designated as “intervention” or “control.” Randomization is stratified within clinical centers by adult (age ≥18 years) vs. adolescent (age 12–17 years) and first-time vs. recurrent stone former. Randomization is conducted at the CC level in blocks of variable size to minimize potential confounders related to differences in site-based care practices. Randomization is performed using an internet-accessible integrated randomization module in the trial electronic data capture system to provide concealment of allocation. It was not feasible to blind participants or study coordinators; however, all investigators, clinicians, and outcome adjudicators are blinded to randomization allocation. In addition, the statistical team responsible for analysis of trial endpoints will be blinded to allocation.

Intervention Arm

Immediately after randomization, participants in the intervention arm receive education via a web-based video regarding the rationale for increased fluid intake as a preventive measure in USD. Participants then receive an individualized “fluid prescription,” which is the additional volume of fluid intake needed to maintain the target UOP. The UOP target is ≥2.5 L/day for participants age ≥18 years and those age 12–17 years weighing ≥75 kg. For participants age 12–17 years weighing <75 kg, the UOP target is ≥30 mL/kg/day. The prescription is determined using the following equation: Initial Fluid Prescription = 1.2 × (2.5 L – median UOP on all 24-hour urine collections in the 12 months prior to enrollment). The 20% factor was intended to mitigate, at least partially, insensible losses.[27] Participants are instructed to consume the prescribed additional fluid from the smart water bottle. In addition to the fluid prescription, they are instructed to drink the same volume of fluids they consumed before enrollment using other fluid containers. The fluid prescription is modified, as needed, based on the 24-hour urine volume measurement obtained approximately 2 weeks after randomization. To reduce the risk of unblinding treatment providers, adjustments to the fluid prescription are communicated by the study coordinator. Participants also receive standard clinical care according to American Urological Association guidelines, including general guidance regarding dietary modification.

Adaptable Behavioral Intervention—The intervention arm also includes a behavioral program that consists of financial incentives and, if this intervention is unsuccessful, Structured Problem Solving (SPS) to maintain the recommended fluid intake (Figure 1), to reflect the responsive nature of clinical care and help participants change behavior, and then sustain the change. The intervention period is divided into 6-month phases of “induction,” “consolidation,” “tapering,” and “maintenance.” The induction phase consists of a daily financial incentive ($1.50) for meeting the fluid intake prescription. This daily financial incentive is delivered when the recommended volume of fluid intake is consumed through and recorded by the smart water bottle. During induction, the intensity of the intervention can be increased for those participants who do not consistently meet daily fluid intake goals (defined as at least 80% of days over a 2-week period) by adding SPS to help participants develop feasible solutions to overcoming personal barriers to maintaining the prescribed fluid intake. The consolidation phase also includes financial incentives and SPS (where indicated by the protocol), but the frequency of reward is slightly lower (Table 1). The tapering phase comprises months 13–18, during which SPS is withdrawn, financial incentives are sequentially tapered, and “low-touch” and low-cost interventions (support partners, regular feedback about adherence) selected by the participant are started to help sustain new habits of fluid consumption. In the final 6-month maintenance phase, participants have access only to “low-touch” interventions.

Structured Problem Solving—SPS is an intervention facilitated by a health coach where the solutions to maintaining high fluid intake are identified by and personalized for each participant. Participants randomized to the intervention arm who meet criteria for receiving SPS initially meet with the health coach. The introductory session starts with education about kidneys and USD, the importance of fluid intake, and the prescribed fluid intake regimen. The remainder of the introductory session is devoted to identifying barriers and feasible solutions to maintaining high fluid intake (Methods Supplement). Based on smart water bottle data, participants also receive daily automated feedback of their fluid intake via Way to Health.

During months 1–12, participants who have received SPS but still have fluid adherence <80% of days over two 14-day assessment periods (>3 days where fluid goal was not met during 14-day period), receive up to 2 “booster” sessions, which consist of root cause analysis to identify reasons for failure of the initial approach chosen to maintain high fluid intake. A new solution is chosen and developed by the participants by repeating the SPS process.

Low-touch Interventions—If after 2 SPS booster sessions, adherence to daily fluid goal is still <80% for subsequent assessment periods, the participant is offered the opportunity to select one or more “low-touch” interventions to continue throughout the remainder of the study period. Examples include activating reminder features on the smart water bottle application, receiving a weekly summary of intake, engaging a support partner, and addition of gamification elements (levels to denote status by consistent adherence). The rationale is that application of an intensive intervention that has not resulted in behavior change is unlikely to do so with continued application and may decrease participant retention. Regardless of whether the participant in the intervention arm has received SPS, they continue to be eligible for financial incentives according to the study schedule.

Control Arm

Participants in the control arm receive standard care instructions according to American Urological Association guidelines to increase overall fluid consumption to achieve UOP of at ≥2.5 L/day[7] or the weight-based fluid-intake goal if they weigh <75 kg, as well as general dietary modification. They also receive the same wireless-enabled smart water bottle with capability to self-monitor fluid intake as the intervention arm participants, although the use of the bottle is optional in the control arm. Approximately 2 weeks after randomization, a 24-hour urine volume measurement is obtained to provide control arm participants with initial feedback as to whether or not they are meeting the UOP goal. Participants in the control arm do not receive an individualized fluid prescription or financial incentives, but do receive monetary compensation for completion of study activities (urine collections, study-related imaging, and study completion).

Statistical Analysis

The primary analysis will be conducted using intention-to-treat principles. The primary endpoint will be analyzed using time-to-event methodology and survival curves will be compared using the log-rank test. For participants who are lost to follow-up or those who drop out of the study without experiencing the primary endpoint, their time-to-event measure will be censored on their last contact date. Safety data will be collected on all randomized participants. All statistical analyses will be tested at a 2-sided nominal significance level of 0.05. If missing data constitute <2% of observations, the analysis will utilize single imputation (mean for continuous variables, mode for categorical variables). If missing data are >2% of observations, then the approach to missing data will depend on checks of the missing-at-random assumption.

The primary outcome of a symptomatic stone event is defined as stone passage, symptomatic stone requiring procedural intervention, or any asymptomatic stone undergoing procedural intervention. A pre-specified sensitivity analysis of the definition of symptomatic stone event will include stone passage, symptomatic stones requiring procedural intervention, and asymptomatic stones undergoing procedural intervention that meet at least 1 of the following criteria: stone size at least 4 mm in any dimension, mobile stone, hematuria, or recurrent urinary tract infection. An additional pre-specified sensitivity analysis will exclude any symptomatic stone events that occur within 30 days of randomization.

Secondary endpoints include asymptomatic stone formation, stone growth on imaging, urinary symptom burden, and a composite outcome of symptomatic stone event, asymptomatic stone formation, or stone growth assessed at study conclusion. These outcomes will be analyzed using a logistic regression model, since asymptomatic stone formation or stone growth are subject to interval censoring (the exact time of occurrence will be unknown).

Other secondary outcomes, including 24-hour urine volume, osmolality, supersaturation of stone-forming salts, and lower urinary tract symptoms, will be compared between intervention and control arms using t-test or Wilcoxon rank-sum test, based on the assumption of normality of the data. The proportion of participants developing symptomatic hyponatremia will be compared in the intervention and control arms using the Pearson's chi square test or Fisher's exact test, as appropriate. All statistical analyses will be conducted using SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

Sample Size and Power

Power calculations were based on symptomatic recurrence rates reported by Rule and colleagues.[28] Power calculations assumed a 15% event rate (symptomatic stone recurrence) in the control arm, and a 30% relative risk reduction (hazard ratio=0.70) for the intervention arm. The attrition rate was estimated at 20% with a 24-month follow-up period. Based on the above conservative estimations (see Methods supplement) and using a 2-sided alpha of 0.05 and a log-rank test for time to first symptomatic stone recurrence, 821 participants per arm (a total of 1642) provides 80% power to detect the pre-specified relative risk reduction. The sample size calculations were performed using PROC POWER in SAS version 9.4. There is no planned interim analysis for efficacy or futility.

DISCUSSION

We designed a multicenter randomized, clinical trial with a pragmatic, adaptable behavioral intervention to increase sustained fluid intake as the primary adherence behavior. This study is expected to provide evidence for the effectiveness of a multi-component behavioral intervention to decrease stone recurrence. Importantly, the primary outcome of symptomatic stone recurrence is a clinically relevant and patient-centered outcome. The study is also expected to contribute evidence to support the role of increased fluid intake with subsequent increased UOP to prevent recurrent USD as well as radiographic disease progression.

The multi-component intervention offers an important extension of the use of financial incentives to motivate behavior change. As implemented in the PUSH trial, a loss-framed financial incentive acts to counter present bias, wherein an individual at risk for recurrent USD discounts future risk and does not engage in preventative behavior, such as increasing fluid intake. The loss-framed incentive moves the adverse consequence of non-adherence into the present, thereby counteracting an individual's tendency to overlook future consequences. Prior randomized trials leveraging this principle support the efficacy of financial incentives for smoking cessation, increased physical activity, and weight loss.[13,29,30] However, not all participants are able to achieve the desired behavior change, and other trials of financial incentive structures have not demonstrated efficacy.[31] These variable results suggest that adaptability of an intervention, particularly if financial incentives do not appear to result in the desired behavior change, may be important to achieving success.

As implemented in the PUSH trial, the financial incentives are intended to focus the study participant's attention on fluid intake. We note that the initial financial incentives rely on an individual's insight and self-efficacy in identifying and overcoming specific barriers to fluid intake. However, some participants may not achieve fluid intake goals as a result of financial incentives alone. PUSH was therefore designed to offer participants not able to adopt new behaviors based on financial incentives an additional supportive intervention, namely health behavior coaching in the form of structured problem solving. The SPS intervention is designed to provide guidance in identifying each patient's specific barriers and solutions to increased fluid intake. The final part of the multi-component intervention is grounded in the assumption that financial incentives and adaptable implementation of SPS will permit formation of new habits, which ideally will be sustained through the nudge of "low-touch" interventions. Thus, the PUSH trial will offer evidence regarding whether an adaptable intervention built on the foundation of financial incentives can be effective in supporting behavior change.

A second key feature of the PUSH study is the clinically important and patient-centered endpoint of symptomatic stone recurrence. Many behavioral intervention trials focus on surrogate endpoints, such as increasing step counts as a measure of physical activity, or medication adherence, which have validity as health behaviors but are not health events *per se*. In addition, stone prevention likely requires durable behavior change over a relatively long period (years). In the PUSH trial, the initial interventions (financial incentives and SPS) will taper or end well before the end of the 24-month study follow-up period. The PUSH trial will add evidence to help answer the important question of durability of behavior change, as well as whether a multi-component program to support behavior change can result in a reduction of a clinically relevant health event.

Finally, the PUSH trial attempts to address another important unanswered question in the science of behavior change, namely that of cessation of financial incentives. Very little evidence exists to guide cessation or tapering of a behavioral incentive, although sudden cessation appears deleterious.[32] The financial incentive in the PUSH trial is tapered over time, along with introduction of either social incentives (support partner) or low-cost interventions (text message reminders). Observing how adherence to increased fluid intake changes as the nature of the incentive changes over time will provide valuable insight into this question, particularly in the context of a substantial lag between the end of the financial incentive and SPS components and the final outcome assessment

If the behavioral interventions described herein decrease the symptomatic stone recurrence rate in the intervention arm, the study findings will have important implications for the secondary prevention of a highly painful condition associated with a number of long-term negative health effects.[33] The multi-component intervention could readily be adapted for remote delivery or in generalist care settings. In a value-based care setting, health systems may see a strong economic rationale to reduce recurrent USD, and thus could consider investing resources into a financial incentive or health coaching program. While some patients with specific causes of stones would still likely require specialist care, an effective prevention program readily delivered to the general population of idiopathic stone formers could substantially reduce the burden of this very common disease.

The PUSH trial has some design limitations. Incorporation of 24-hour urine volume as a secondary outcome reflects current clinical practice, yet may not be reflective of daily urine volume if participants purposely increase fluid intake only during the 24-hour collection period. While it is possible for participants to meet daily fluid goals by consuming fluids without bottle use, they are instructed to use the bottle for their fluid goal and for self-monitoring; they also do not receive financial incentives if not using the bottle. Likewise, the study relies upon participants to supplement their usual fluid intake with the prescribed amount, although the risk of participants decreasing other sources of fluid intake exists.

The PUSH trial evaluates a multi-component behavioral intervention to increase adherence to fluid intake as a means to prevent recurrent USD. The study design is anticipated to contribute to clinical knowledge regarding lifestyle prevention of USD. In addition, this study is expected to make an important contribution to understanding the impact of behavioral interventions by evaluating not only the change in the targeted behavior, but also the associated and patient-centered health outcome of recurrent symptomatic stones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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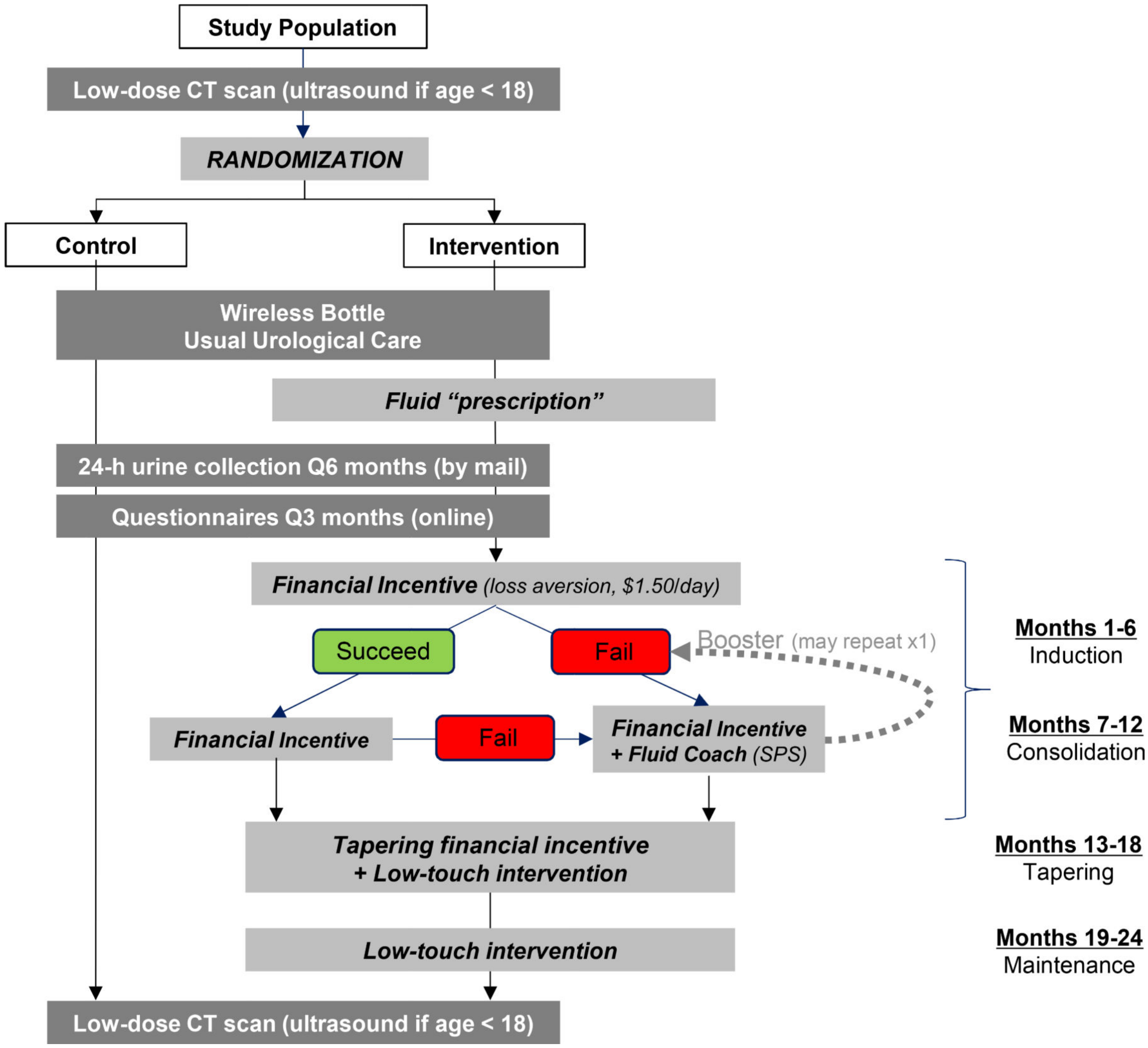

Figure 1.
PUSH study schema.

Table 1.

Overview of intervention and control arms in the PUSH study

	Control	Intervention
Platform	• Participants provided a wireless-enabled smart water bottle. • Participants are allowed, but not required, to use or sync the water bottle with their mobile device.	• Participants provided a wireless-enabled smart water bottle and taught how to use it. • Participants must sync water bottle with their mobile device daily.
Fluid Goal	Usual care (sufficient fluid intake to achieve UOP ≥2.5 L/day or 30 mL/kg/day for participants <18 years and <75 kg)	120% of baseline UOP deficit via the water bottle, with modification possible at Week 2.
UOP	24-hour urine volume check at 2 weeks, 6 months, 12 months, 18 months, and 24 months.	24-hour urine volume check at 2 weeks, 6 months, 12 months, 18 months and 24 months.
Behavioral Intervention Program	None	<u>Months 0–6 (Induction):</u> • Daily financial incentive for success at meeting fluid intake goal via water bottle (financial incentive possible 100% of days) • SPS ◦Non-adherence trigger if fluid goal was achieved <80% of days over 14 days (>3 days where fluid goal was not met during 14-day period) for two 14-day assessment periods. • SPS “Booster” (intensified counseling)
	Control	**Intervention**
		◦Non-adherence trigger if fluid goal was achieved <80% of days over 14 days (>3 days where fluid goal was not met during 14-day period) for two 14-day assessment periods following initial SPS. <u>Months 7–12 (Consolidation)</u>: • Daily financial incentive for success at meeting fluid intake goal via water bottle possibility of receiving incentive for 80% of days in a 1-month period. • SPS ◦Non-adherence trigger if fluid goal was achieved <80% of days over 14 days (>3 days where fluid goal was not met during 14-day period) for two 14-day assessment periods. • SPS “Booster” (intensified counseling) ◦Non-adherence trigger if fluid goal was achieved <80% of days over 14 days (>3 days where fluid goal was not met during 14-day period) for two 14-day assessment periods following initial SPS. <u>Months 13–18 (Tapering)</u>: • Gradual tapering of daily financial incentive (75% of
	Control	**Intervention**
		days at month 13 and 15% of days at month 18) • Self-selected/low-touch intervention(s): ◦Text/phone reminders ◦Commitment contract ◦Social intervention (e.g., team) <u>Months 19–24 (Maintenance):</u> • Self-selected/low-touch intervention(s) : ◦Text/phone reminders ◦Commitment contract

		◦Social intervention (e.g., team) ◦Feedback of adherence
Stone-directed pharmacological or urological care	Per primary stone treating provider	Per primary stone treating provider

SPS indicates structured problem solving; UOP, urine output.

Table 2.

Primary and secondary endpoints in PUSH study

Endpoint	Definition/Assessment
Primary endpoint	
Symptomatic stone recurrence	Stone passage Procedure for symptomatic stone Urological procedure for removal of an asymptomatic stone
Secondary endpoints	
1. Asymptomatic formation of new stone	Detected on imaging
2. Increased stone size by ≥2 mm (any dimension)	Detected on imaging
3. Composite of primary endpoint or secondary #1 and 2	n/a
4. 24-hour urine total volume	Home 24-hour urine collection
5. Presence of lower urinary tract symptoms	Comprehensive Assessment of Self-reported Urinary Symptoms questionnaire

Table 3.

Study exclusion criteria and rationale

Criterion	Rationale
Spinal cord injury	Increased stone risk, impaired sensation
Undergoing active cancer treatment	Potential limited life expectancy
Known infectious or monogenic cause	Therapies other than high fluid intake may significantly alter disease course
History or presence of hyponatremia	Minimize risk of symptomatic hyponatremia from higher fluid intake
Comorbid conditions precluding increased fluid intake	Physiologic barrier to adherence
Comorbid condition with GI fluid loss	Pathophysiologic barrier to adherence, difficulty achieving goal urine volume with usual fluid intake
Pregnant or planning pregnancy	Higher fluid intake recommended during pregnancy and breastfeeding; bioethical consideration
Renal transplant recipient	Altered renal colic sensation
History of recurrent UTI (>3/year)	Risk for infection-based stones
Medication use increasing stone risk	Stone-provoking medication is typically stopped. Potential lack of hydration effectiveness
Less than 2 year life expectancy	Ability to complete follow-up period
Non-English speaker	Ability to utilize smart water bottle app
History of SIADH	Increased risk of symptomatic hyponatremia
Anatomic urologic abnormality (e.g., ileal conduit)	Impaired/altered sensation
Psychiatric condition impairing study compliance	Potential poor compliance to follow-up
Vulnerable population	Bioethical consideration
Unable to participate per investigator	Investigator’s discretion for protection of safety and welfare of study participants

GI indicates gastrointestinal; SIADH, Syndrome of Inappropriate Antidiuretic Hormone Secretion; UTI, urinary tract infection.