Urinary Stone Disease Research Network

Prevention of Urinary Stones with Hydration (PUSH): A Randomized Adherence Trial

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on behalf of the USDRN Investigators

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FUNDING: NIDDK (U01/U24)

Burden of Disease

- Lifetime prevalence ~10% in the United States
- Recurrence rate up to 50%
- Chronic metabolic condition punctuated by “stone attacks’

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Secondary Prevention of Urinary Stones

- Hydration is mainstay of dietary prevention:
  - AUA guideline recommends sufficient intake to produce 2500 mL urine/24 hours
  - EAU guideline provides same recommendation
  - Hydration supported by single RCT (Borghi et al J Urol 1996)
  - Low certainty evidence: RR 0.45 (95% CI 0.24–0.84)
  - Target urine output (UOP) = 2000 mL (Borghi)

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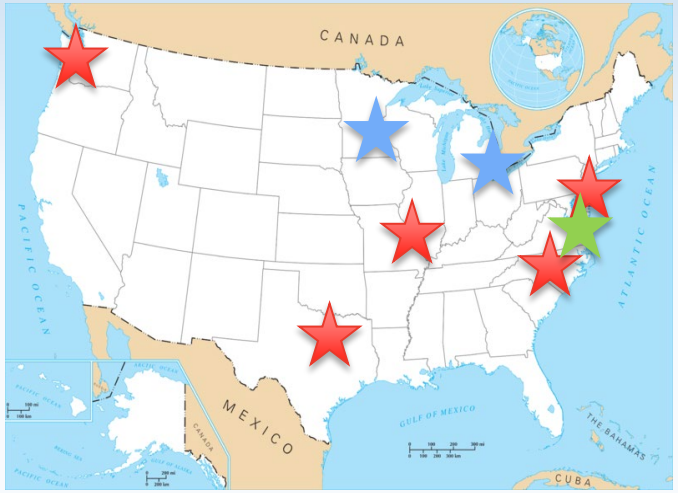

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STUDY DESIGN

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

Design

1,642 participants
≥12 years of age

Symptomatic stone history and low urine volume

Smart water bottle capable of tracking fluid consumption

Randomized

Interventions

Control Arm

Usual care + smart water bottle

Intervention Arm

Usual care + smart water bottle +

Multi-component behavioral intervention:

- Fluid prescription
- Financial incentive
- Behavioral coach

Outcomes

Primary Outcome:

- Symptomatic stone event

Secondary Outcomes:

- New stone formation
- Increase in stone size
- 24-hour urine volume
- Lower urinary tract symptoms

CONCLUSION: Using novel features, the randomized PUSH trial tests if behavioral interventions to increase adherence to higher fluid intake prevent stone recurrence.

Charles D. Scales, Alana C. Desai, Jonathan D. Harper, et al (2020)

@AJKDonline | DOI: 10.1053/j.ajkd.2020.09.016

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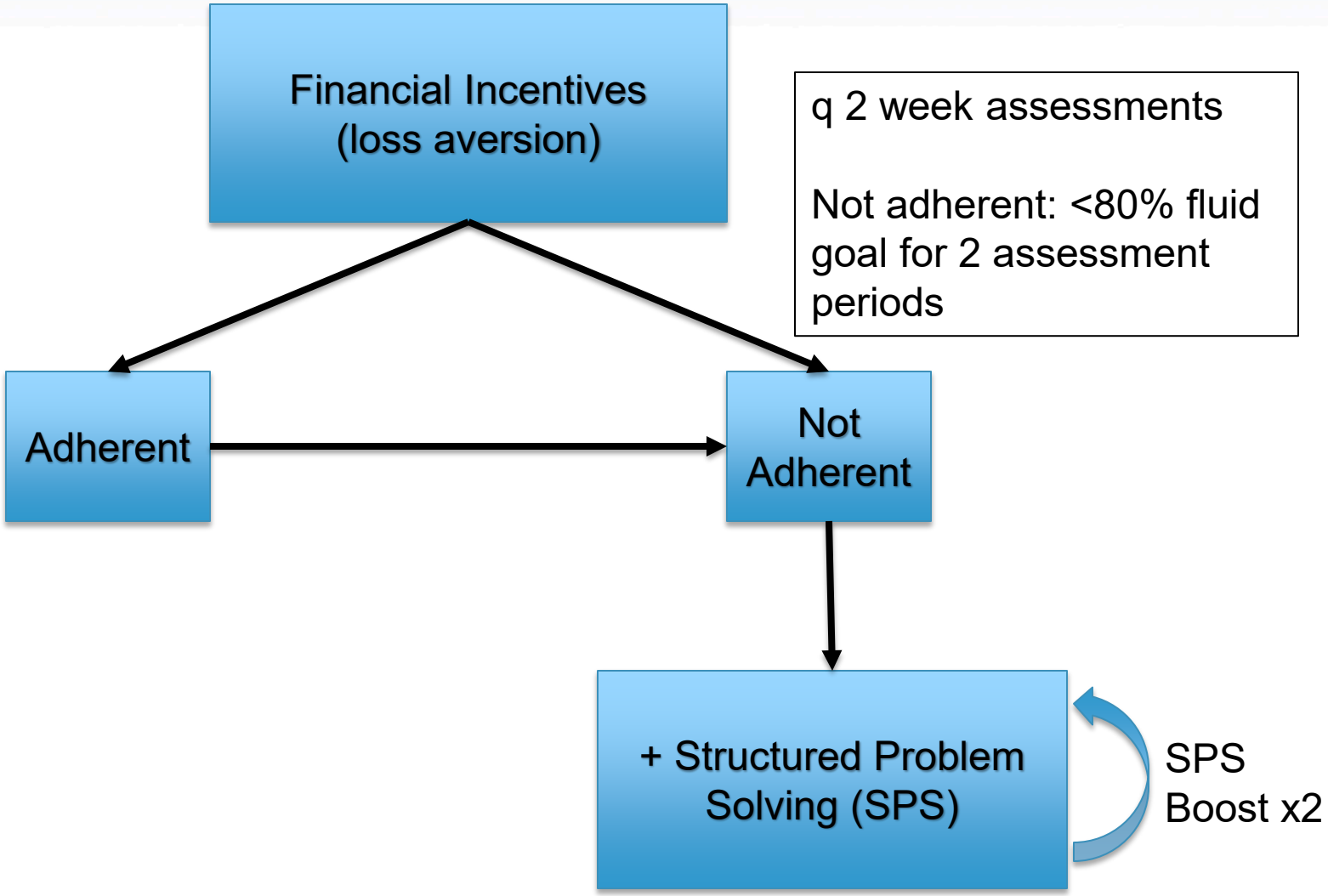
NCT03244189

Year 1: Form New Habits



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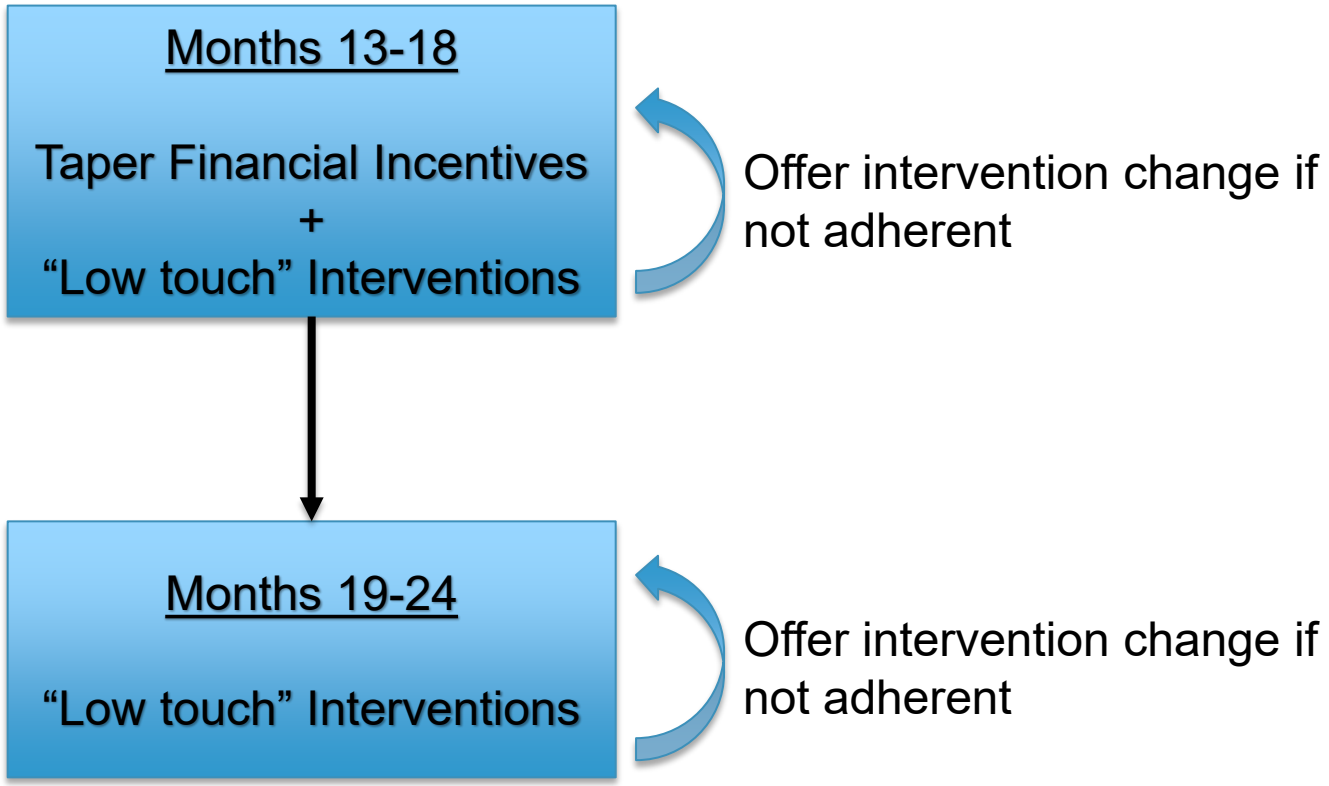
Year 2: Sustain Habits



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Sample Size Estimation

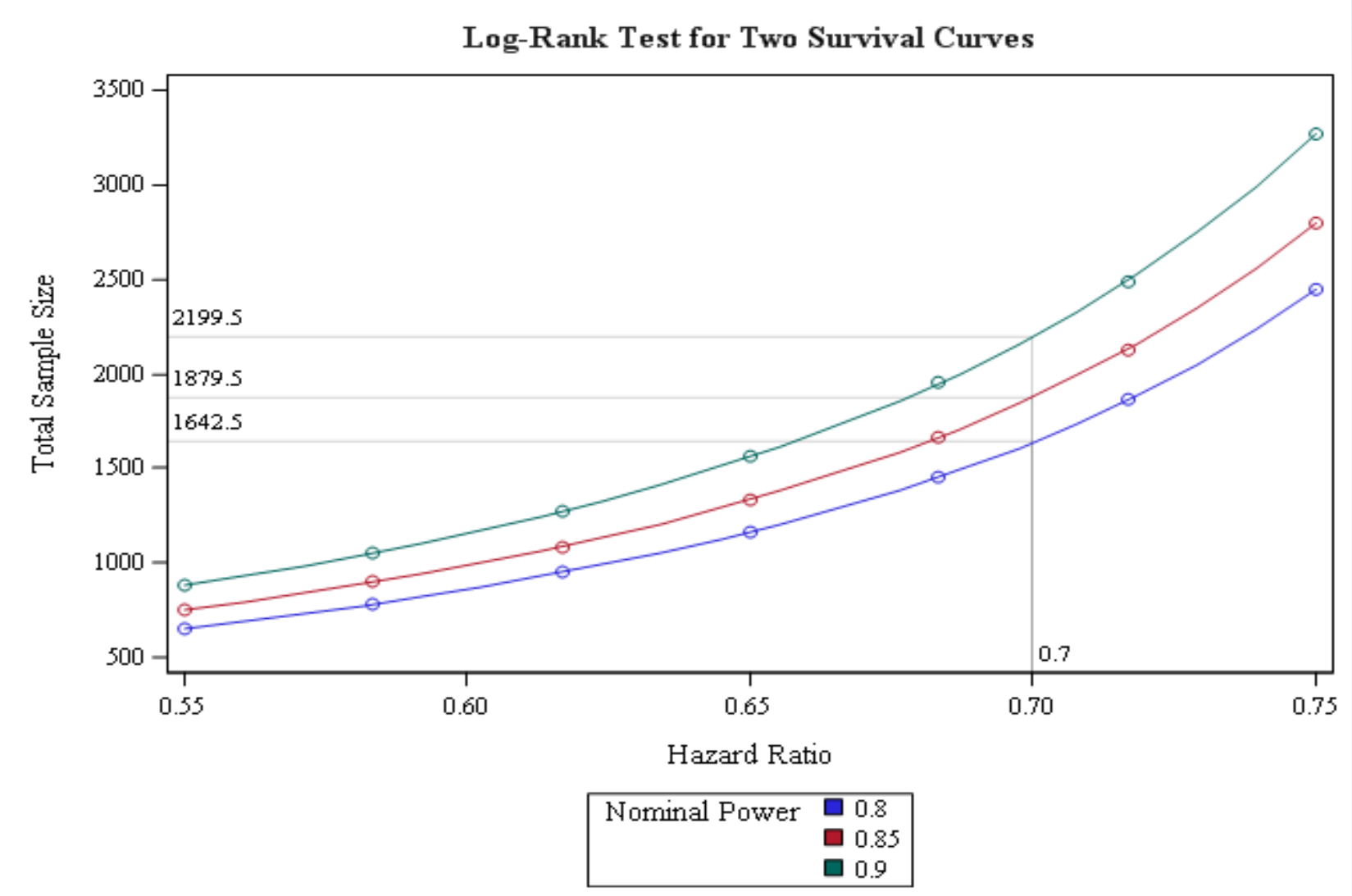
Individual patient randomization (2-arm)

Assumptions:

- Unit of randomization - Patient
- Equal randomization ratio 1:1
- 15% event rate over 2 years in the control arm (Rule et al JASN 2014)
- 30% relative risk reduction (RRR) in the intervention arm, i.e. hazard ratio=0.7
- 20% attrition rate (dropouts, lost-to-follow up)
- 80% power to detect a 30% RRR with a two-sided alpha of 0.05
- Duration 2-year follow-up

Power	Total sample size (2-arm)	Intervention arm	Control arm
80%	1642	821	821

Sample size calculations (Primary endpoint: Stone recurrence)



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Secondary Outcomes

- 24-hour urine volume (baseline and 6, 12, 18, 24 months)
- Radiographic outcomes (24 month CT scan v baseline)
  - New stone formation (≥ 2mm)
  - Stone growth (≥ 2mm)
- Composite of primary and radiographic outcomes
- Urinary symptoms (patient-reported, LURN SI-10)
- Safety: hyponatremia requiring hospitalization

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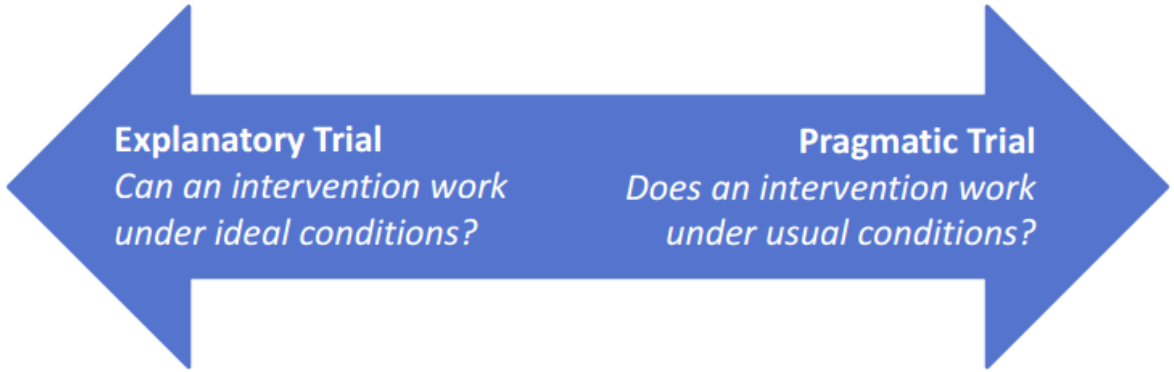
LURN SI-10

Explanatory-Pragmatic Trial Continuum

- PUSH Trial designed as clinical trial with pragmatic features

- PUSH pragmatic features responsive to participant & coordinator feedback



NIH Collaboratory
Health Care Systems Research Collaboratory

Rethinking Clinical Trials

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Pragmatic Features of PUSH

- Clinical care procedures for study data
  - Low-dose CT scan (u/s for adolescents)
  - 24-hour urine collections
- Study procedure data returned for clinical care (clinicians blinded to study arm)
- Remote screening and enrollment
  - 2020 until enrollment closed
- Individualized fluid prescription
- Adaptive features of behavioral intervention

RECRUITMENT & RETENTION

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Initial Recruitment Plan (Plan ‘A’)

Traditional site-based recruitment

1. Four Clinical Centers
2. Screening & Baseline visits
3. Key screening/baseline procedures:
    a. phlebotomy
    b. CT scan
    c. 24-hour urine collections
4. Smart water bottle setup

Initial Recruitment Challenges & “Plan B”

1. Early feedback from study coordinators re: patient reluctance
   a. Burdensome study procedures
   b. Concern re: additional medical imaging (radiation exposure)
2. Modifications
   a. Permitted use of recent 24-hour urine collections & imaging from clinical care, as long as required study data included
   b. Combined screening/enrollment visits for many participants
   c. Focused laboratory testing requirement only for individuals at elevated risk of hyponatremia

Additional Early Modifications

Reducing barriers to study participation:

1. Permit use of 24-hour urine collections from clinical care, within reasonable window & containing required study information
2. Permit use of imaging tests obtained for clinical care, instead of requiring new imaging, within window & containing required information

Lessons Learned

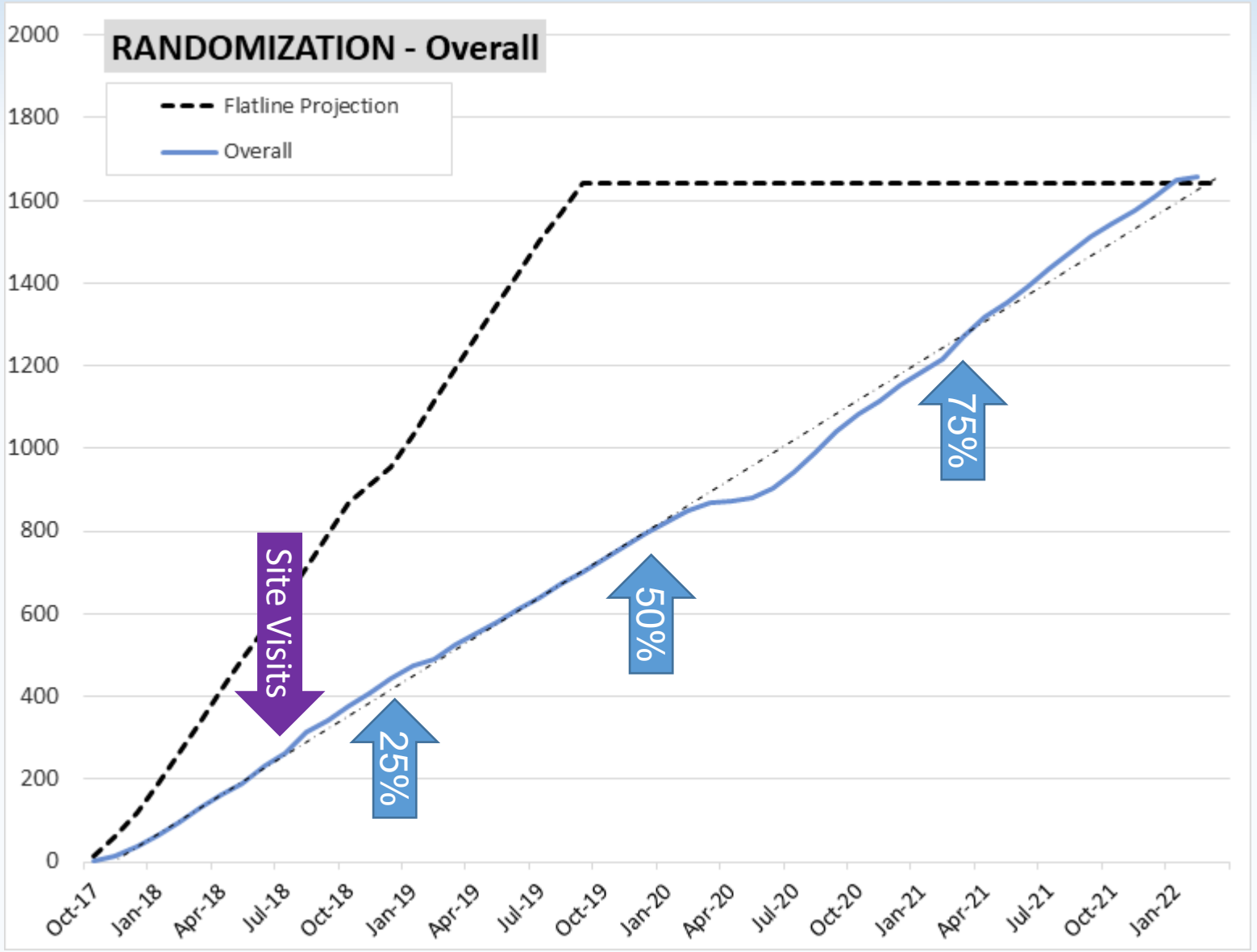
1. Minimize burden of screening/baseline procedures
   a. Incorporate data from routine clinical care
2. Reduce burden of study procedures in follow up
   a. Align with clinical care
   b. Return of results to care team to avoid repetitive testing

Sharing Knowledge

Site visits to Clinical Centers:

1. Share best practices
2. Identify resources & processes to increase recruitment

Cumulative Randomization



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Lessons Learned

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   b. Return of results to care team to avoid repetitive testing
3. Evaluate recruitment practices & share what works

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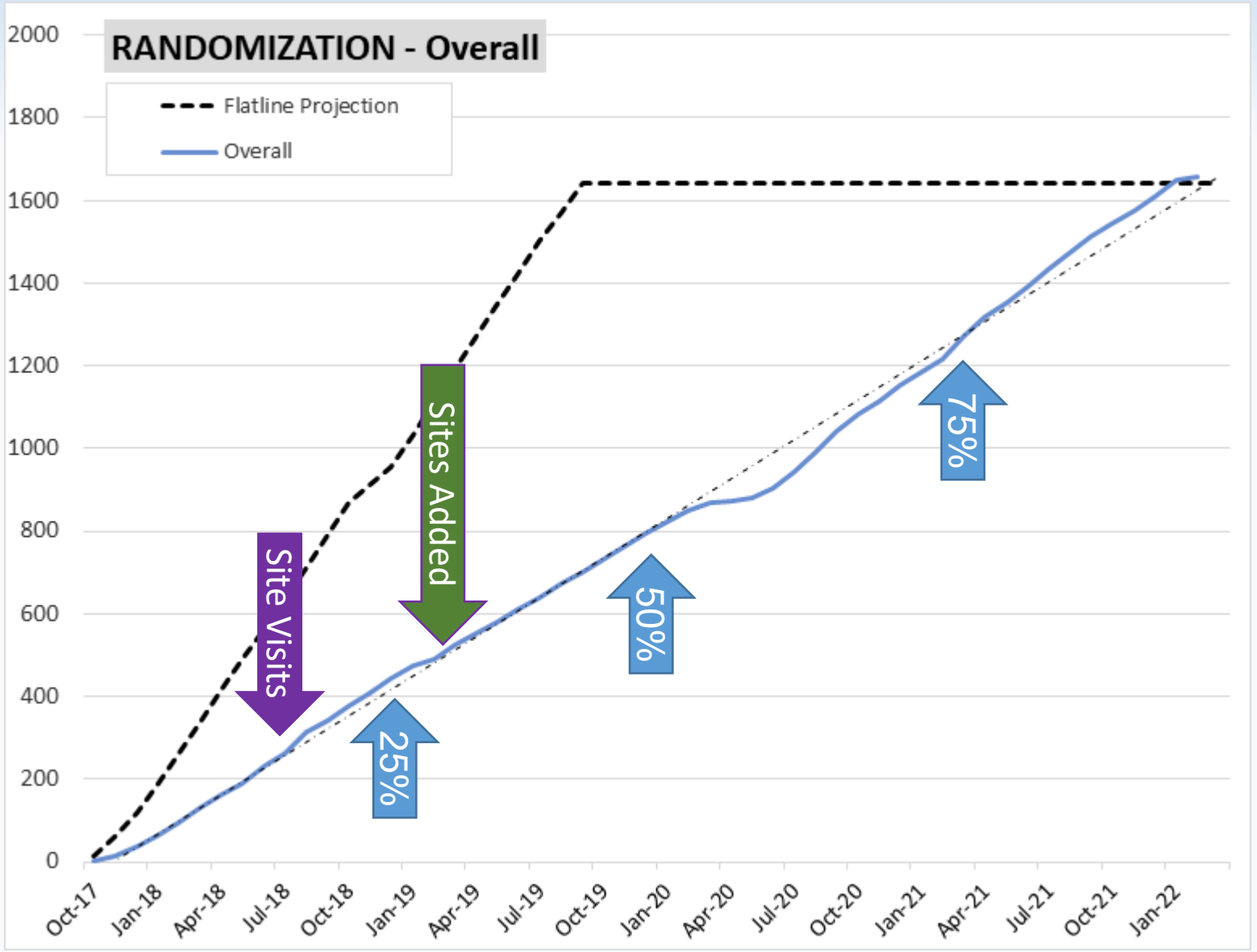
Data Driven Trial Management & “Plan C”

Recruitment projections suggested substantial need for enrolling participants outside of existing patient panels for original centers

Expanded potential pool of recruitment by adding two additional recruiting centers

Cumulative Randomization



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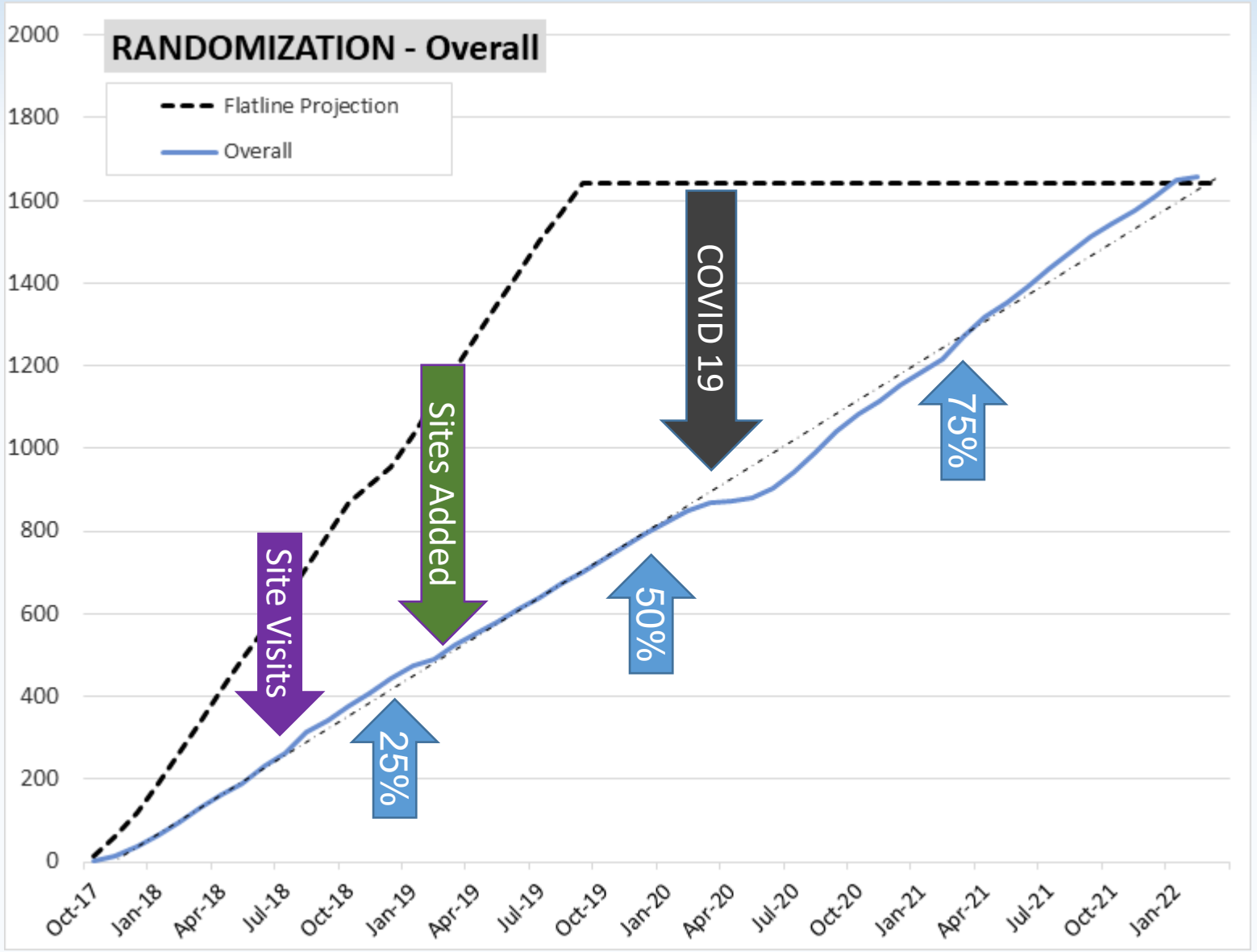
4. Leverage data to inform planning & trial monitoring

Cumulative Randomization



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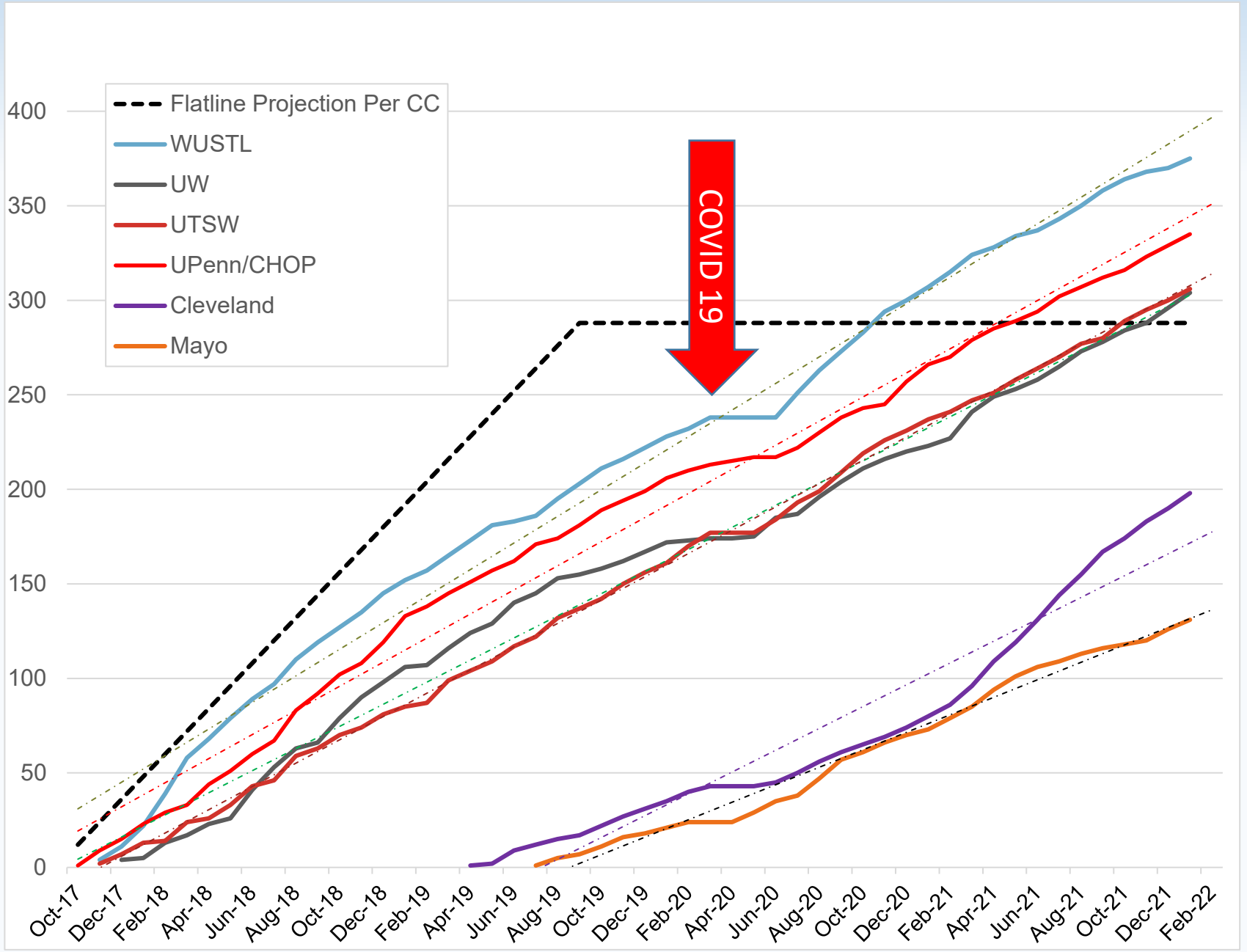
Randomized Participants By Center



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USDRN Response (Plan “Pandemic”)

1. Decrease barriers to study participation
   a. Remote consent process
   b. Remote randomization/enrollment process
   c. Embed research in clinical care
   d. Reduce number of study procedures and tests
2. Expand geographic pool of participants
   a. Incentivize referrals
   b. New network partnerships
   c. Publicize RCT via professional organizations, webinars & presentations

Implementation Process

1. Engagement with PUSH DSMB
   - Approval for protocol amendments
2. Communication with institutional IRBs
   - Remote informed consent processes
3. Review of trial experience
   - Waiver of baseline lab testing based on safety experience
   - Baseline imaging waiver for secondary endpoints

Implementation Process

1. National recruitment
   - Incentivize physician referral via collaborator recognition
   - Potential manuscript acknowledgement or co-authorship
2. New partnerships
   - Health systems with expansive networks (Mayo Clinic, Cleveland Clinic)
   - Pediatric KIDney Stone Care Improvement Network (PKIDS) – PCORI
3. Outreach
   - Presentations at virtual national & regional meetings
   - Webinars hosted by national experts (nephrology, urology)

Challenges and Opportunities

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

Impacts from National, State, and Local Pandemic Restrictions:

- Study visits
- Study coordinator availability
- Clinical activity
- Hesitation from patients

J Urol 2021 PMID 33908800

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Lessons Learned

1. Minimize burden of screening/baseline procedures
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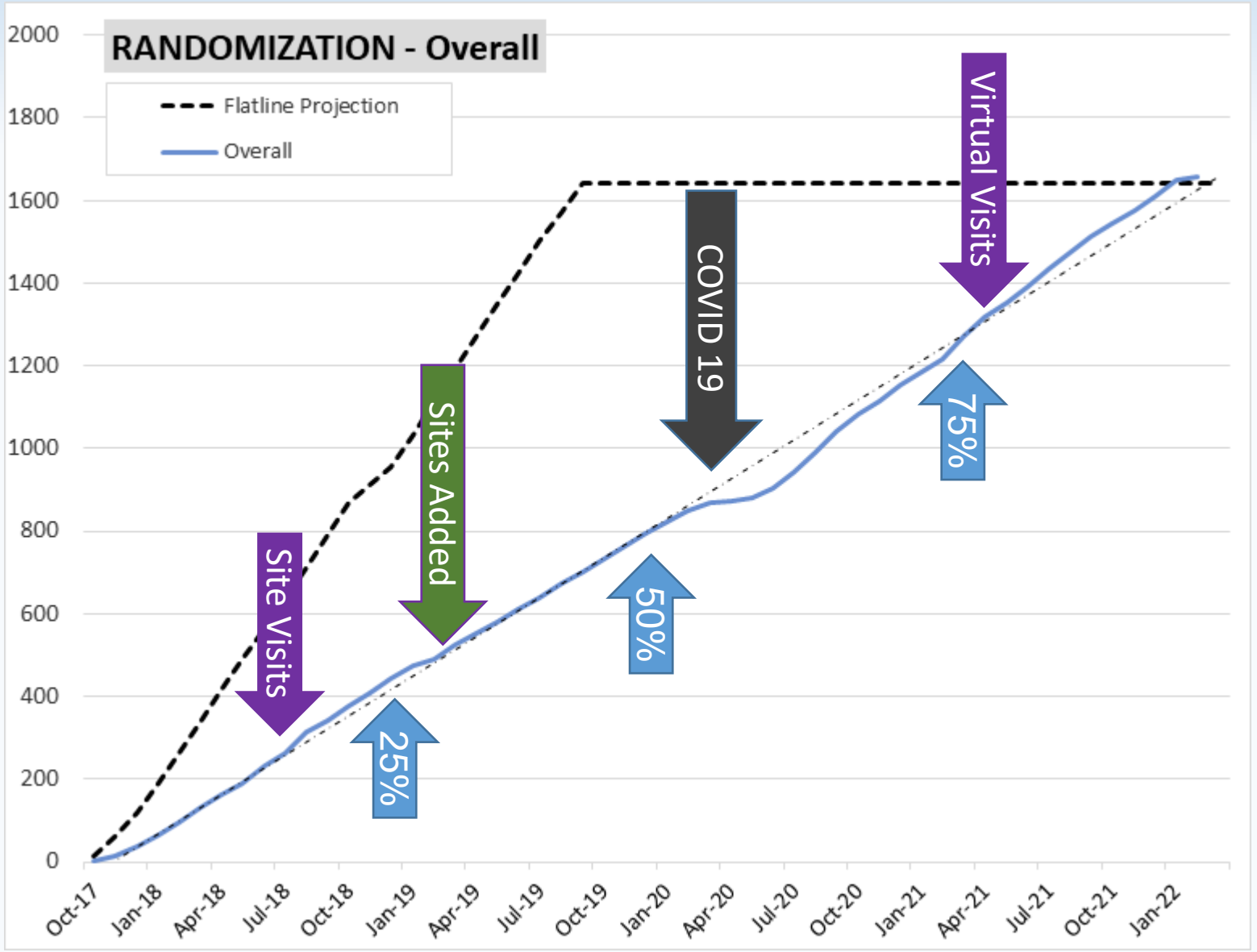
3. Evaluate recruitment practices & share what works
4. Leverage data to inform planning & trial monitoring
5. Every challenge is an opportunity (even a pandemic)
   a. Virtual/remote consent/enrollment feasible and extends study reach

Cumulative Randomization



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Other measures

- Data-driven assessment of recruitment & retention efforts by site
- Sharing successful recruitment & retention practices among sites
- Virtual and in-person site visits focusing on recruitment

Lessons Learned

1. Minimize burden of screening/baseline procedures
   a. Incorporate data from routine clinical care
2. Reduce burden of study procedures in follow up
   a. Align with clinical care
   b. Return of results to care team to avoid repetitive testing
3. Evaluate recruitment practices & share what works
4. Leverage data to inform planning & trial monitoring
5. Every challenge is an opportunity (even a pandemic)
   a. Virtual/remote consent/enrollment feasible and extends study reach
6. Building capacity of the site team is the foundation of success

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RESULTS

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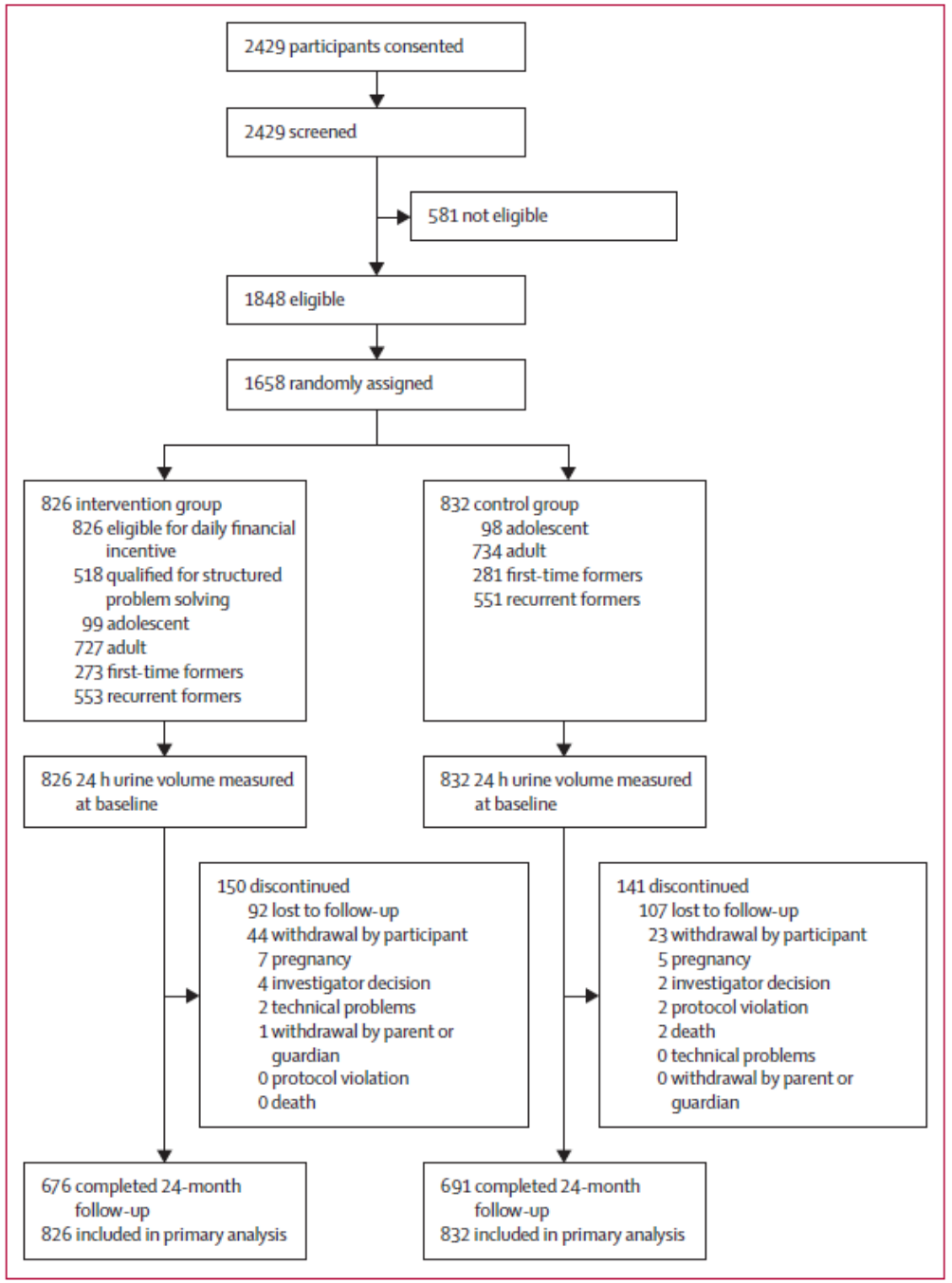
CONSORT Diagram



USDRN PUSH
Prevention of Urinary Stones with Hydration

The Lancet, 407, 1171-81

Study Population

	Intervention (n=826)	Control (n=832)	Total (n=1658)
Age in years, median (IQR)	45 (30 – 60)	44 (27 – 58)	44 (29 – 59)
Age Group – Adult	49 (35 – 61)	48 (34 – 59)	48 (36 – 60)
Adolescent	15 (14 – 16)	16 (14 – 16)	15 (14-16)
First stone former	274 (33.1%)	281 (33.8%)	555 (33.5%)
Recurrent stone former	552 (66.8%)	551 (66.2%)	1103 (66.5%)
Female	469 (56.8%)	477 (57.3%)	946 (57.1%)
Male	357 (43.2%)	355 (42.7%)	712 (42.9%)

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The Lancet, 407, 1171-81

Study Population

	Intervention (n=826)	Control (n=832)	Total (n=1658)
Race			
White	732 (88.6%)	719 (86.4%)	1451 (87.5%)
Black or African Am	55 (6.7%)	58 (7.0%)	113 (6.8%)
Native American	0 (0%)	3 (0.4%)	3 (0.2%)
Asian	22 (2.7%)	25 (3.0%)	47 (2.8%)
Hawaiian or other PI	2 (0.2%)	2 (0.2%)	4 (0.2%)
Other/Unknown	8 (1.0%)	11 (1.2%)	19 (1.1%)
Multiracial	7 (0.8%)	14 (1.7%)	21 (1.3%)

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Prevention of Urinary Stones with Hydration

The Lancet, 407, 1171-81

Study Population

	Intervention (n=826)	Control (n=832)	Total (n=1658)
Ethnicity			
Not Hispanic/Latino	761 (92.1%)	757 (91.0%)	1518 (91.6%)
Hispanic/Latino	46 (5.6%)	56 (6.7%)	102 (6.2%)
Not reported/Unknown	19 (2.3%)	19 (2.3%)	38 (2.3%)
Household Income			
<$90,000	323 (39.1%)	305 (36.7%)	628 (37.9%)
≥$90,000	365 (44.2%)	371 (44.6%)	736 (44.4%)
Other*	138 (16.7%)	156 (18.8%)	294 (17.7%)

* Includes “don’t know” and “prefer not to answer”

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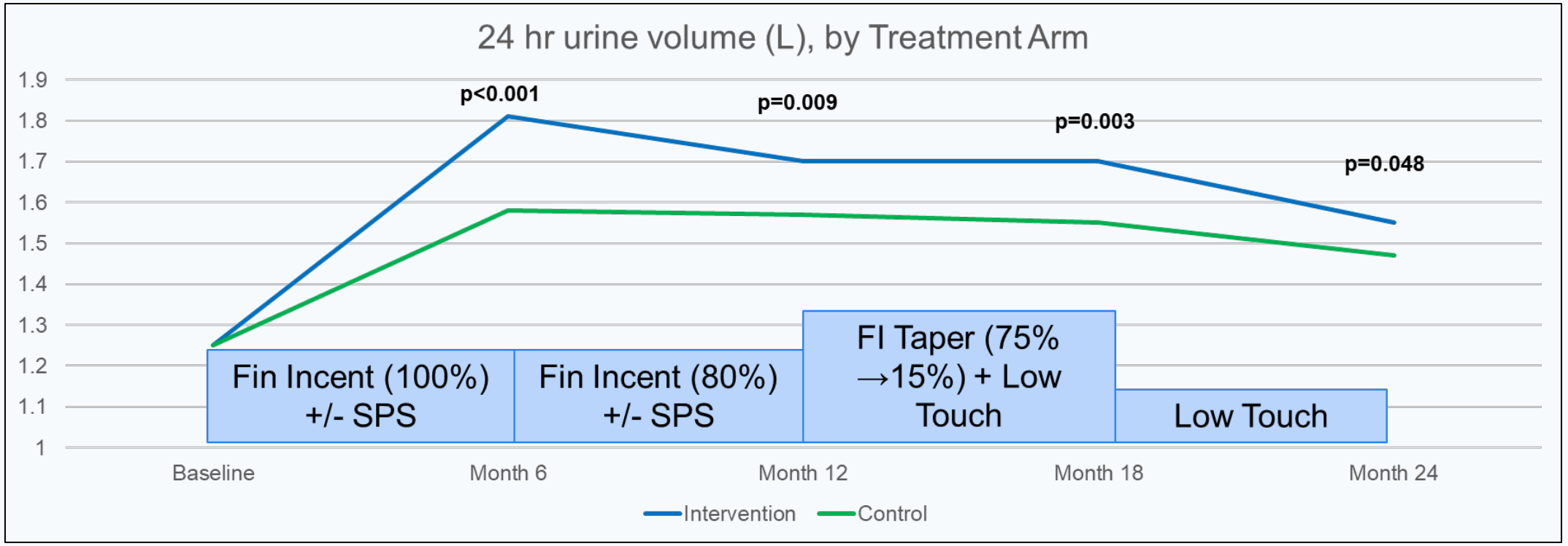
The Lancet, 407, 1171-81

Clinical Surrogate, Total Urine Volume (24 h)



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Primary Outcome

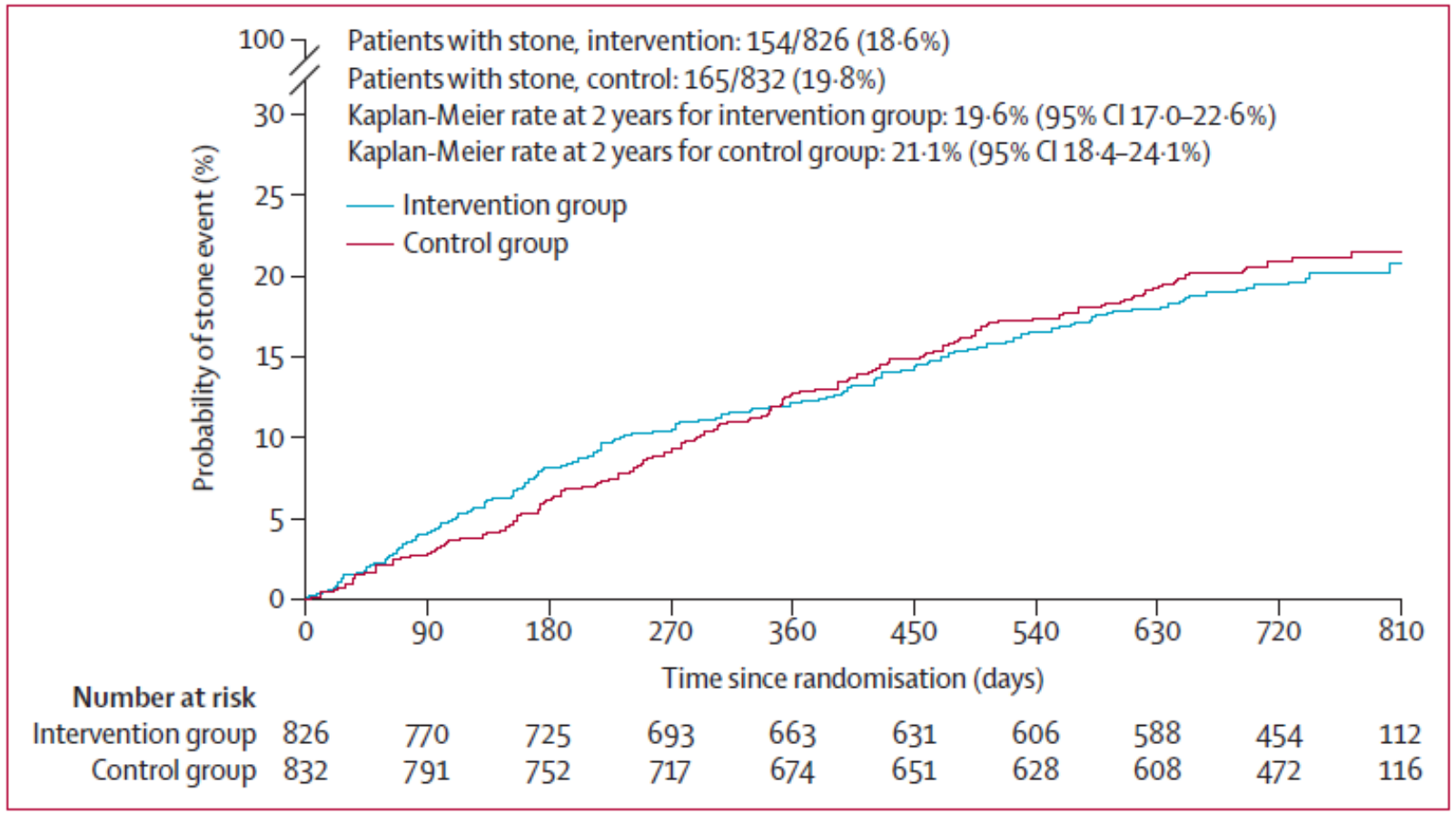

Figure 2: Symptomatic recurrence of urinary stones

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The Lancet, 407, 1171-81

Primary Outcome Events (Confirmed Clinical + Participant-Reported)

	Intervention N=826	Control N=832	HR (95% CI)	P value
Participants with ≥ 1 stone event	154 (18.6%)	165 (19.8%)		
Time at Risk for Event [subject-years]	1372.73	1416.05		
Incidence rate (participant with event/100 yrs at risk)	11.22	11.65		
			0.96 (0.77, 1.20)	0.729

Protocol assumptions required a total of 283 participants with at least 1 stone event (primary), with 80% power. Event rate exceeded this requirement.

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Andersen-Gill Model for Primary Endpoint

	Intervention N=826	Control N=832	HR (95% CI)	P value
# Participants with ≥ 1 stone event (total events)	154 (239)	165 (250)	0.98 (0.75,1.27)	0.8733

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Win Ratio Analysis

	Analysis Result
All Participants, N	1658
Treatment A, N	826
Treatment B, N	832
All unmatched pairs, N	687232
Wins for A/B, N	122331
Tier 1: symptomatic stone	111885
Tier 2: New stone formation	837
Tier 3: Stone growth	9609
Losses for A/B, N	117322
Tier 1: symptomatic stone	108477
Tier 2: New stone formation	786
Tier 3: Stone growth	8059
Ties, N	447579
Win Ratio estimate (95% CI	1.043 (0.781,1.166); p = 0.709

Secondary Outcome Events - Stones

	Intervention N=826	Control N=832	OR (95% CI)	P value**
New asymptomatic stone	19 (2.3%)	23 (2.8%)	0.83 (0.45, 1.53)	0.548
Stone growth ≥ 2 mm	39 (4.7%)	25 (3.0%)	1.60 (0.96, 2.67)	0.072
Composite*	196 (23.7%)	196 (23.7%)	1.01 (0.80, 1.27)	0.935

* Composite of primary outcome, new asymptomatic stone, or stone growth of ≥2mm
** Logistic regression

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Where do we go from here?

1. Long-term adherence to hydration is very challenging – can we achieve precision prevention?
2. Secondary analyses
    1. 24-hour urine data (Urine osmolality)
    2. Adolescents with urinary stone disease
3. Design of future behavioral intervention trials
    1. Important to follow to patient-important outcomes
    2. Consider SMART trial designs
    3. Incorporate patient preference assessments

USDRN PUSH Biorepository

Sample Type	# Participants	# vials
Whole Blood (DNA)	368	717
Blood – Serum	383	3769
Blood – Plasma	384	1778
Urine – Pellet	402	752
Urine – Supernatant	397	2305
Urine – Native	393	1945
Urine – Acidified	341	678
Urine – Alkalinized	340	678
Stool	30	59

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