

A-PRÉP

A Pragmatic Randomized trial Evaluating Pre-operative aqueous antiseptic skin solutions in open fractures

The PREP-IT Investigators

A Program of Randomized trials to Evaluate Pre-operative antiseptic skin solutions In orthopaedic Trauma

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Disclosures

This study was funded by a US Department of Defense grant (WX81XWH-17-1-0702)

The principal investigators report salary support from the grant. No other relevant disclosures.

- Sheela Sprague
- Mohit Bhandari
- Gerard Slobogean

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A-PRÉP trial is very unique

- Full commitment to patient engagement
- Multiple period, cluster randomized, crossover trial
- Results published in The Lancet 2022; 400:1334-44

PREP-IT Investigators

- 30 sites, 300+ collaborators
- 10 papers related to patient engagement, clinical practice patterns, or research methods

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Sites

U Maryland Shock Trauma Center	Wright State University
Indiana University Health	Banner University Medical Center, Tucson
Vanderbilt University Medical Center	UCSF University of California San Francisco
University of Texas Health Center	UF University of Florida
Hamilton Health Sciences	The CORE Institute
Prisma Health Upstate	Vall d'Hebron University Hospital
San Antonio Military Medical Center	Parc Tauli Hospital Universitari

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Committee Members

Jeffery L. Wells C. Daniel Mullins Anthony D. Harris Lehana Thabane Amber Wood Gregory Della Rocca Kyle J. Jeray Robert D. Zura Lucas Marchand Joan N. Hebdén Lindsay M. O'Wara Joseph Patterson Christopher Lee Michael Gardner Stephen Liang Monica Taijaard	Jonah Davies Jenna Blasman Saam Morshed Meir Marmor Jean-Claude D'Alleyrand Jessica Rivera Franca Mussoto Robert O'Toole I. Leah Gitajn Manjari Joshi Diane Heels-Ansdell Gordon Guyatt PJ Devereaux Nathan O'Hara Jeff Friedrich Debra Marvel Jana E. Palmer
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Pre-Op Antiseptic Skin Solutions

Antiseptic skin solutions are a key prophylactic step to reduce bacterial flora and surgical site infections

Alcohol based antiseptic solutions are recommended for surgical skin preparation

- Chlorhexidine-alcohol is believed to be the most effective solution
- Most recommendations are based on clean abdominal / gynec surgery

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Pre-Op Antiseptic Skin Solutions

There are no skin antiseptics trials in fracture populations

Open fractures are particularly challenging and CHG-alcohol has not been tested in in open wounds

Many surgeons have traditionally favored Betadine (10% povidone-iodine) for open fractures

- Prefer to use aqueous-based solutions for open wounds
- Theoretical concern for cytotoxicity and fire risk of alcohol in wounds




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Purpose

To compare the effectiveness of aqueous solutions of **10% Povidone-iodine versus 4% CHG** to prevent open fracture surgical site infection

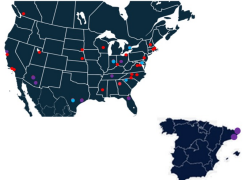




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Population

1683 open fracture patients enrolled at 14 hospitals in USA, Canada, and Spain



Key eligibility criteria:


- Adult patients with open extremity fracture treated with a fixation implant
- Formal surgical debridement within 72 hours of injury
- Up to 3 open fractures per participant were included



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Randomization


Multiple period, cluster randomized, crossover trial



Run-in phase: Orthopedic practice (cluster) → Randomization → Iodophor

Enrollment phase: Iodophor → Chlorhexidine → Iodophor → Chlorhexidine

Practice (cluster) crossover is indicated between Iodophor and Chlorhexidine periods.




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Intervention Fidelity

Protocol

- Last solution used prior to skin incision
- Use the allocated solution for all surgeries
- Analysis based on solution used at fracture fixation surgery

Protocol adherence: 4% crossover rate




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Intervention Fidelity

Adjunctive therapies

- Pre-wash with scrub brush, alcohol, or other steps permitted
- Intrawound antibiotics allowed
- Duration of IV antibiotics and other interventions at discretion of local surgeon



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Outcomes

Surgical Site Infection (2017 CDC)

Unplanned reoperation with 1 year

- Superficial within 30 days, Deep within 90 days of definitive fixation
- Infection, wound healing, fracture healing

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Analysis

Mixed Effects Regression

→ Accounts for clustering, chronologic time, and baseline risk for SSI

Sensitivity analyses:

- SSI within 1 year
- Fracture related infection (FRI) Confirmatory Criteria
- As-treated
- Complete case (missing data)

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Population

n = 1638

45 Age	62% Male	93% One Fracture	6% Two Fractures
52% ASA I/II	35% Smoker	1% Three Fractures	13 ISS

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Injuries

25%
Upper extremity

75%
Lower extremity or pelvis

Number of Planned Surgeries

Number of Surgeries	4% Chlorhexidine Guconate (n=873)	10% Povidone-Iodine (n=890)
1	66%	65%
2	22%	22%
3	7%	7%
4	2%	2%
5	3%	4%

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Severity

Severity of open fracture

Wound contamination

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Surgical Site Infection

	10% Povidone-Iodine (n=828) number (%)	4% Chlorhexidine Guconate (n=810) number (%)	Odds Ratio (95% CI)	p-value	Risk Difference (95% CI)
Surgical site infection	59 (7)	58 (7)	1.11 (0.74, 1.65)	0.61	0.6% (-1.4, 3.4)
Superficial infection	13 (2)	7 (1)			
Deep incisional	27 (3)	36 (5)			
Organ/space infection	19 (2)	15 (2)			

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Surgical Site Infection

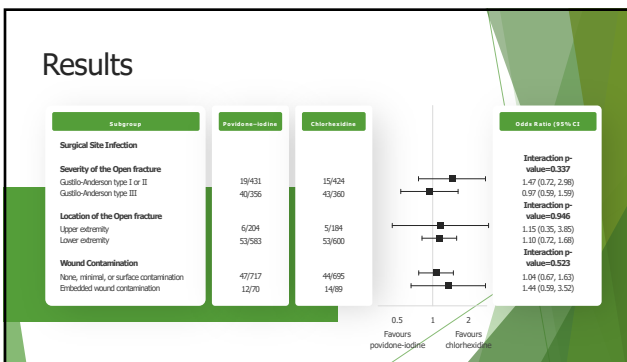
	10% Povidone-Iodine (n=828) number (%)	4% Chlorhexidine Glucosate (n=810) number (%)	Odds Ratio (95% CI)	p-value	Risk Difference (95% CI)
Alternative definitions of surgical site infection	n=735	n=738			
Any surgical site infection by 365 days	97 (13)	88 (12)	1.19 (0.86, 1.64)	0.29	1.7% (-1.3, 5.5)
Fracture-related infection by 365 days	80 (11)	73 (10)	1.18 (0.84, 1.68)	0.34	1.4% (-1.3, 4.8)

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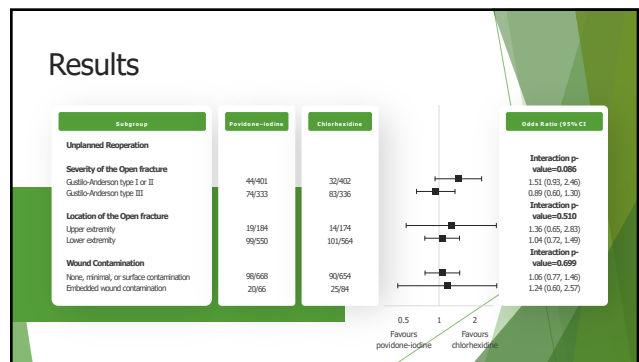
Unplanned Reoperation

	10% Povidone-Iodine (n=828) number (%)	4% Chlorhexidine Glucosate (n=810) number (%)	Odds Ratio (95% CI)	p-value	Risk Difference (95% CI)
Unplanned reoperation by 365 days	118 (16)	115 (16)	1.08 (0.81, 1.46)	0.59	1.0% (-2.5, 5.3)
Unplanned reoperation for infection by 365 days	71 (10)	66 (9)			
Unplanned reoperation for wound healing complications by 365 days	40 (5)	53 (7)			
Unplanned reoperation to promote fracture healing by 365 days	72 (10)	54 (7)			

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Post-Hoc Analyses

Adjuvant therapies did not change the effect of antiseptic solutions

- 63% of participants received alcohol prewash
→ (OR 1.06, 95% CI 0.71-1.57; p=0.79)
- 19% of PVP-I participants received a CHG prewash
→ (OR 1.10, 95% CI 0.72-1.67; p=0.66)
- 35% of participants received intrawound antibiotic powder
→ (OR 1.07, 95% CI 0.72-1.58; p=0.75)

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Discussion

- No prior open wound antiseptic trials
- No differences in SSI or Reoperation detected between aqueous 4% CHG or 10% PVP-I
 - ▶ No subgroup effects detected
- Transportability of prior antiseptic literature?
 - ▶ Abdominal / Obstetrics / Gynecological populations
 - ▶ Often CHG-Alcohol vs Aqueous Iodine

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Discussion

▶ Contaminated open fractures:
16% SSI
30% reoperation rate

▶ Type III fractures:
12% SSI
24% reoperation rate

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Conclusion

→ Choice of aqueous skin antiseptics does not alter SSI

→ Results are reassuring for many environments

- Resource constrained
- Patient allergy
- Other traumatic wounds

→ The comparative effectiveness of alcohol-based solutions

- Chloraprep vs Duraprep
- PREPARE-Open: 1,700 patients
- PREPARE-Closed: 6,400 patients

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McMaster University
A-PREP

<https://www.prepiti.com/sites>

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Challenges and Opportunities for Patient Engagement and Novel Study Designs in Pragmatic Trials and Comparative Effectiveness Research

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Department of Surgery
McMaster University

Mr. Jeffrey Wells
Patient Partner
Baltimore, MD

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Disclosures

▶ No Relevant Disclosures

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Patient Engagement

▶ Including patient representatives that reflect the trial population as advisory members and having their lived experience inform the design, conduct, closeout, and dissemination of the trial

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Patient Engagement

- ▶ Involving patients in the design and implementation of clinical trials is necessary to ensure that the research is relevant and responsive to patients
- ▶ Increases the utility of research findings (1)
- ▶ Patient engagement has also been argued to improve recruitment and retention rates
- ▶ Increases the validity of the results of the trial (2)

References:
1. Brett A, Saravanan S, Riddford D, et al. A Systematic Review of the Impact of Patient and Public Involvement on Service Users, Researchers and Contributions. *Patients*. 2015; 5(2):161-81.
2. Robinson A. Patient and public involvement: technology and its impact. *Medical and Educational Research*. 2014; 1(8):133-36.

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Patient Engagement in PREP-IT

10-Step Engagement Framework

- Planning Phase: 3 Steps**
 - Step One: Topic solicitation
 - Step Two: Prioritization
 - Step Three: Framing the question
- Doing Phase: 4 Steps**
 - Step Four: Selection of comparators and outcomes
 - Step Five: Creation of conceptual framework
 - Step Six: Analysis plan
 - Step Seven: Data collection
- Delivering Phase: 3 Steps**
 - Step Eight: Reviewing and interpreting results
 - Step Nine: Translation
 - Step Ten: Dissemination

Source: Ryan BJ, Williams M, Draucker C, Bryant C, Miller CD. Engaging patient engagement in research: evidence, conceptual model and framework. *BMJ Open*. 2015; 9(10):e006776. doi:10.1136/bmjopen-2015-006776

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Patient Engagement in PREP-IT

- ▶ Canadian Institutes of Health Research (CIHR) patient engagement criteria (1):
 - ▶ **Inclusiveness:** integrates a diversity of patient perspectives and research is reflective of their contribution
 - ▶ **Support:** Adequate support are provided to patient participants to ensure that they can contribute fully to discussions and decisions
 - ▶ **Mutual Respect:** Researchers, practitioners and patients acknowledge and value each other's expertise and experiential knowledge
 - ▶ **Co-Build:** Patients, researchers and practitioners work together from the beginning to identify problems and gaps, set priorities for research and work together to produce and implement solutions

Reference:
1. Canadian Institutes of Health Research. Strategy for Patient-Oriented Research - Patient Engagement Framework. 2010. Available at: [33](http://www.cihr.gc.ca/eng/0,6611,14243_14244_14245_14246_14247_14248_14249_14250_14251_14252_14253_14254_14255_14256_14257_14258_14259_14260_14261_14262_14263_14264_14265_14266_14267_14268_14269_14270_14271_14272_14273_14274_14275_14276_14277_14278_14279_14280_14281_14282_14283_14284_14285_14286_14287_14288_14289_14290_14291_14292_14293_14294_14295_14296_14297_14298_14299_14300_14301_14302_14303_14304_14305_14306_14307_14308_14309_14310_14311_14312_14313_14314_14315_14316_14317_14318_14319_14320_14321_14322_14323_14324_14325_14326_14327_14328_14329_14330_14331_14332_14333_14334_14335_14336_14337_14338_14339_14340_14341_14342_14343_14344_14345_14346_14347_14348_14349_14350_14351_14352_14353_14354_14355_14356_14357_14358_14359_14360_14361_14362_14363_14364_14365_14366_14367_14368_14369_14370_14371_14372_14373_14374_14375_14376_14377_14378_14379_14380_14381_14382_14383_14384_14385_14386_14387_14388_14389_14390_14391_14392_14393_14394_14395_14396_14397_14398_14399_14400_14401_14402_14403_14404_14405_14406_14407_14408_14409_14410_14411_14412_14413_14414_14415_14416_14417_14418_14419_14420_14421_14422_14423_14424_14425_14426_14427_14428_14429_14430_14431_14432_14433_14434_14435_14436_14437_14438_14439_14440_14441_14442_14443_14444_14445_14446_14447_14448_14449_14450_14451_14452_14453_14454_14455_14456_14457_14458_14459_14460_14461_14462_14463_14464_14465_14466_14467_14468_14469_14470_14471_14472_14473_14474_14475_14476_14477_14478_14479_14480_14481_14482_14483_14484_14485_14486_14487_14488_14489_14490_14491_14492_14493_14494_14495_14496_14497_14498_14499_14500_14501_14502_14503_14504_14505_14506_14507_14508_14509_14510_14511_14512_14513_14514_14515_14516_14517_14518_14519_14520_14521_14522_14523_14524_14525_14526_14527_14528_14529_14530_14531_14532_14533_14534_14535_14536_14537_14538_14539_14540_14541_14542_14543_14544_14545_14546_14547_14548_14549_14550_14551_14552_14553_14554_14555_14556_14557_14558_14559_14560_14561_14562_14563_14564_14565_14566_14567_14568_14569_14570_14571_14572_14573_14574_14575_14576_14577_14578_14579_14580_14581_14582_14583_14584_14585_14586_14587_14588_14589_14590_14591_14592_14593_14594_14595_14596_14597_14598_14599_14600_14601_14602_14603_14604_14605_14606_14607_14608_14609_14610_14611_14612_14613_14614_14615_14616_14617_14618_14619_14620_14621_14622_14623_14624_14625_14626_14627_14628_14629_14630_14631_14632_14633_14634_14635_14636_14637_14638_14639_14640_14641_14642_14643_14644_14645_14646_14647_14648_14649_14650_14651_14652_14653_14654_14655_14656_14657_14658_14659_14660_14661_14662_14663_14664_14665_14666_14667_14668_14669_14670_14671_14672_14673_14674_14675_14676_14677_14678_14679_14680_14681_14682_14683_14684_14685_14686_14687_14688_14689_14690_14691_14692_14693_14694_14695_14696_14697_14698_14699_14700_14701_14702_14703_14704_14705_14706_14707_14708_14709_14710_14711_14712_14713_14714_14715_14716_14717_14718_14719_14720_14721_14722_14723_14724_14725_14726_14727_14728_14729_14730_14731_14732_14733_14734_14735_14736_14737_14738_14739_14740_14741_14742_14743_14744_14745_14746_14747_14748_14749_14750_14751_14752_14753_14754_14755_14756_14757_14758_14759_14760_14761_14762_14763_14764_14765_14766_14767_14768_14769_14770_14771_14772_14773_14774_14775_14776_14777_14778_14779_14780_14781_14782_14783_14784_14785_14786_14787_14788_14789_14790_14791_14792_14793_14794_14795_14796_14797_14798_14799_14800_14801_14802_14803_14804_14805_14806_14807_14808_14809_14810_14811_14812_14813_14814_14815_14816_14817_14818_14819_14820_14821_14822_14823_14824_14825_14826_14827_14828_14829_14830_14831_14832_14833_14834_14835_14836_14837_14838_14839_14840_14841_14842_14843_14844_14845_14846_14847_14848_14849_14850_14851_14852_14853_14854_14855_14856_14857_14858_14859_14860_14861_14862_14863_14864_14865_14866_14867_14868_14869_14870_14871_14872_14873_14874_14875_14876_14877_14878_14879_14880_14881_14882_14883_14884_14885_14886_14887_14888_14889_14890_14891_14892_14893_14894_14895_14896_14897_14898_14899_14900_14901_14902_14903_14904_14905_14906_14907_14908_14909_14910_14911_14912_14913_14914_14915_14916_14917_14918_14919_14920_14921_14922_14923_14924_14925_14926_14927_14928_14929_14930_14931_14932_14933_14934_14935_14936_14937_14938_14939_14940_14941_14942_14943_14944_14945_14946_14947_14948_14949_14950_14951_14952_14953_14954_14955_14956_14957_14958_14959_14960_14961_14962_14963_14964_14965_14966_14967_14968_14969_14970_14971_14972_14973_14974_14975_14976_14977_14978_14979_14980_14981_14982_14983_14984_14985_14986_14987_14988_14989_14990_14991_14992_14993_14994_14995_14996_14997_14998_14999_15000</small></p>
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PREP-IT Patient Advisors

- ▶ Jeff Wells
- ▶ Jana Palmer
- ▶ Debra Marvel

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PREP-IT Patient Advisors

- ▶ Jeff, Debra, and Jana participated because they would like to give back to their healthcare professionals and help future patients
- ▶ Were involved from start to finish
- ▶ Initial grant development meeting in 2017
- ▶ Trial results meeting in May 2023
- ▶ Multiple meetings in-between

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Initial Planning Meetings

- ▶ Grant planning sessions
- ▶ Protocol development meetings
- ▶ Protocol review investigator meeting
- ▶ Meeting with Research Coordinators to review the case report forms and data collection procedures

PREP-IT Protocol Review Meeting Agenda
Wednesday, November 29th, 2017
9:30 AM - 11:35 AM
Westminster Hall
520 W. Fayette Street
Baltimore, MD 21201

9:30	Welcome Coffee Reception
9:50	A Patient's Experience
10:00	Patient Engagement in Research
10:20	Patient Oriented Question Research (POQR)
10:25	Welcome and Opening Remarks
10:30	Think Bigger, and Smaller
10:45	Pre-Operative Antiseptic Skin Solutions
10:55	55 in Orthopaedic Trauma
11:05	Overview of the PREP-IT Program
11:15	Research Questions
11:30	Cluster Randomized Cross-over Design
11:40	Benefits and Challenges of Cross-over Study Design
11:55	Participating Clinical Sites

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Patient Centered Advisory Core Meetings

- ▶ Bi-monthly meetings
- ▶ Update on the trial activities
- ▶ Challenges being faced by the investigators and clinical sites
- ▶ Knowledge dissemination activities including videos and manuscripts

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Informed Key Aspects of the Protocol

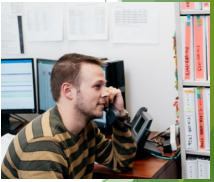
- ▶ Eligibility criteria
- ▶ Outcomes
- ▶ Follow-up schedule
- ▶ Language (e.g., avoid abbreviations, define complex terms, etc.)



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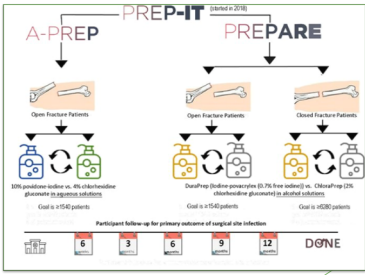
Informed Consent Form Development

- ▶ Discussed the purpose of informed consent
- ▶ Patient partner shared their experience as a study participant during the consent process
- ▶ Reviewed timing of the consent
- ▶ Simplified the language in the informed consent form
- ▶ Informed the use of telephone consent




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Development of a Trial Visual



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Development of a Clinical Site Posters



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Clinical Site Initiation Visits

- ▶ Allowed for bidirectional learning
- ▶ Patient partners learned about the trial logistics at the different clinical sites
- ▶ Clinical site personnel learned about the trial from a patient-perspective and maintained a patient focus



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PREP-IT Educational Rounds

PREP-IT ROUND
PREP-IT ROUNDS
PREP-IT ROUND

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Annual Investigator Meetings

- Meetings began with a patient focus
- Topics relevant to patient partners
- Guest speakers
- Discussions of challenges faced during the trial
- Celebrations of successes

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Newsletters

PREP-IT NEWSLETTER | February 2021
PREP-IT Spotlight
PREP-IT Monthly Enrollment 20/21

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Engagement Manuscripts and Sub-Studies

- Contributed to multiple manuscripts and sub-studies
- Included as co-authors or contributors on all publications

THE ORTHOPAEDIC FORUM
Contemporary Clinical Trials Communications
Journal of Comparative Effectiveness Research

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Engagement Manuscripts and Sub-Studies

Pragmatic Design and Inclusion of Patient-Partner Representatives Improves Participant Experience in Clinical Research

David Pogorzalski, Jeffrey L. Mills, Debra Maxwell, Lisa E. Palmer, C. David Mullis, Michelle Rodomo, Joel L. Eldred, Ella Sporer, Patrick F. Bergin, I. Leah Gagli, Devin S. Mullis, Craig E. Gask, Robert Hynes, Sofia Bovevay, Garrett P. Stangor, Shua Sprague, the PREP-IT Investigators

BACKGROUND	OBJECTIVE	RESULTS
<ul style="list-style-type: none"> Meaningful patient engagement in the design of randomized controlled trials is an essential component of a high-quality trial. The PREP-IT trials followed the patient-centered outcomes research (PCOR) approach, which involves allowing patients voices to be heard and focuses on outcomes that are relevant to patients and their caregivers. The PREP-IT trials involve different care preparation sessions in patients with fractures. These data aim to improve orthopaedic fracture research through greater engagement with patient partners and to identify ways to better engage with study participants. 	<ul style="list-style-type: none"> To explore participant experience with clinical research and participation in the PREP-IT trials. At the trial kickoff up until 12 months after final patients participating in the PREP-IT trials were invited to participate in the sub-study. After providing informed consent, participants completed a questionnaire that asked about their experience and satisfaction with participating in the PREP-IT trials. Descriptive statistics were used to summarize the findings. 	<ul style="list-style-type: none"> Demographics: 402 participants were included in the sub-study. The mean age of the participants was 53.3 years (SD 18.3 years) and 57% were female. Reasons for Participation in Clinical Study: 88% of participants indicated that PREP-IT was the first research study that they had taken part in and 87% indicated that they were participating in another study at the same time as PREP-IT. Reasons for Participation in PREP-IT: 66% of participants indicated that they wanted "to help future patients with broken bones" and 60% indicated that they wanted "to contribute to science". When participants were asked to select all items associated with the trial design that influenced their decision to participate, 40% reported at least one item. This included no extra clinic visits (20%), limited time commitments (13%), no additional medications (20%), low questionnaire (20%), and no additional tests (20%). Satisfaction with Participation in PREP-IT: 87% of participants indicated that their experience in the trial was excellent or good. No participants indicated a poor or very poor experience. 83% of participants felt that their participation was appreciated by at least one person and 81% of participants indicated that they would voluntarily or proactively participate in another clinical study.


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Knowledge Dissemination of Primary Results

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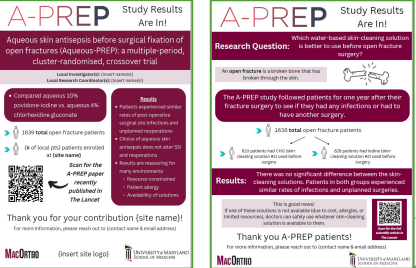
Knowledge Dissemination of Primary Results

- ▶ Critical review of the primary manuscripts
- ▶ Included as co-authors on the primary manuscripts



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Knowledge Dissemination of Primary Results



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Support Provided to Patient Partners

- ▶ Meetings prior to and after key meetings
- ▶ Investigators were available to address any questions and remind presenters to use appropriate language
- ▶ Discussed trial in relevance to patient partner's experiences

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Key Points

- ▶ Followed the 10-step patient engagement framework
- ▶ Followed CIHR's engagement recommendations
 - ▶ Inclusiveness
 - ▶ Support
 - ▶ Mutual Respect
 - ▶ Co-Build

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Key Points

- ▶ Patient partners can easily be integrated into the study team
- ▶ Successfully contribute to all aspects of the trial, from start to finish
- ▶ We have learned a lot from our patient partners
- ▶ Established long-term collaborations with them, similar to those with our clinician co-investigators

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Allowing Co-Interventions in Pragmatic Clinical Trials



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Outline

- ▶ What were the major infection prevention co-interventions occurring in the PREP-IT trials
- ▶ Analysis strategies used
 - ▶ Large RCT sample size...
 - ▶ Would we achieve balance and could treatment interactions exist?

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SSI Prevention

- ▶ Pre-operative
 - ▶ Emergency department, floor nursing care
- ▶ Intraoperative
 - ▶ Prior to incision
 - ▶ During surgery
- ▶ Post-operative
 - ▶ Floor nursing care

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Preoperative Co-Interventions

- ▶ Emergency department
 - ▶ Prophylactic antibiotics upon diagnosis
 - ▶ Type and time to first dose of antibiotics
 - ▶ Iodine-soaked open wound dressing
- ▶ Floor nursing care
 - ▶ Normoglycemic, normothermic, clean dressings, preoperative antibiotics
 - ▶ Chlorhexidine bathing

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Intraoperative Co-Interventions

- ▶ Anesthesia provider administrated
 - ▶ Prophylactic antibiotics 30 minutes to incision
 - ▶ High intraoperative FiO₂
- ▶ Surgeon antisepsis steps
 - ▶ Mechanical scrub brush
 - ▶ Alcohol pre-wash
- ▶ Topical open wound antibiotics
 - ▶ Antibiotic-eluting PMMA cement
 - ▶ Vancomycin and / or other topical antibiotic powders prior to wound closure

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Postoperative Co-Interventions

- ▶ Anesthesia provider administrated
 - ▶ Prophylactic antibiotics 30 minutes to incision
 - ▶ High intraoperative FiO₂
- ▶ Topical open wound antibiotics
 - ▶ Antibiotic-eluting PMMA cement
 - ▶ Vancomycin and / or other topical antibiotic powders prior to wound closure

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General Strategies

- ▶ Multiple 2-month periods
 - ▶ Balance changes in co-interventions overtime
- ▶ Record and monitor common co-interventions
- ▶ Statistical analyses
 - ▶ Chronologic time within the trial lifespan as a fixed effect variable
 - ▶ Sensitivity analyses:
 - ▶ Key co-interventions added as covariates
 - ▶ Key co-interventions added to test treatment interactions

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Incidence of Key Co-Interventions

Cointervention	Iodine (n=828)	Chlorhexidine (n=810)
CHG bath	259 (31.3)	272 (33.6)
Alcohol	531 (64.1)	532 (65.7)
Intra-wound antibiotic powder	228 (27.5)	245 (30.2)

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"Alcohol pre-wash" Example

- Rationale why it was included
 - 63% used it
 - No alcohol antiseptis on intact skin did not follow clinical practice
 - Alcohol is a potent antiseptic
- Test for effect as covariate and interaction
 - (OR 1.06, 95% CI 0.71-1.57; p=0.79)
 - Test for interaction p=0.21



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Co-Interventions as Covariates

	Incidence of Predictors (%)	Event (% within predictor)	Odds Ratio (95% CI)	p-value
Model with CHG Bath				
Randomized to Iodine	787 (50.1)	59 (7.5)	1.07 (0.72, 1.59)	0.722
Randomized to CHG	784 (49.9)	58 (7.4)	Ref	
Model with Alcohol				
Randomized to Iodine	787 (50.1)	59 (7.5)	1.06 (0.71, 1.57)	0.786
Randomized to CHG	784 (49.9)	58 (7.4)	Ref	
Model with Intra-wound antibiotic powder				
Randomized to Iodine	787 (50.1)	59 (7.5)	1.07 (0.72, 1.58)	0.749
Randomized to CHG	784 (49.9)	58 (7.4)	Ref	

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Summary

- There are numerous SSI co-interventions
- Pragmatic clinical trial must mirror real-world practice
- Multiple period, cluster randomized crossover trial design balanced important co-interventions
- PREP-IT analysis approach is to monitor for imbalance and explore effects of co-intervention on primary intervention

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Design and Analysis Considerations when using the Multiple Period, Cluster-Randomized, Crossover Trial for Comparative Effectiveness Research

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Disclosures

- No relevant disclosures.

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Cluster Trials

- ▶ Characterized by their multilevel nature (i.e., grouped observations)
 - ▶ Patients within hospitals
 - ▶ Children within schools
- ▶ Cluster (i.e., group) is the unit for randomization

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Type of Cluster Trials

- ▶ Cluster Randomized
- ▶ Cluster-Crossover
- ▶ Multiple-Period, Cluster-Crossover

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Cluster Randomized Trial Design

The diagram shows a grid of 6 clusters (rows) and 6 months (columns). Clusters 1, 2, and 3 are assigned Treatment A, represented by lightbulb icons. Clusters 4, 5, and 6 are assigned Treatment B, represented by person icons. A legend at the bottom identifies the icons for Treatment A and Treatment B.

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Cluster-Crossover Trial Design

The diagram shows a grid of 6 clusters (rows) and 6 months (columns). A vertical line separates the first 3 months from the last 3 months. Clusters 1, 2, and 3 receive Treatment A (lightbulb icon) in months 1-3 and Treatment B (person icon) in months 4-6. Clusters 4, 5, and 6 receive Treatment B in months 1-3 and Treatment A in months 4-6. A legend at the bottom identifies the icons for Treatment A and Treatment B.

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Multiple-Period, Cluster Crossover Trial Design

The diagram shows a grid of 6 clusters (rows) and 6 months (columns). Clusters 1 and 2 receive Treatment A (lightbulb icon) in months 1 and 2, and Treatment B (person icon) in months 3, 4, 5, and 6. Clusters 3 and 4 receive Treatment B in months 1 and 2, and Treatment A in months 3, 4, 5, and 6. Clusters 5 and 6 receive Treatment A in months 1 and 2, and Treatment B in months 3, 4, 5, and 6. A legend at the bottom identifies the icons for Treatment A and Treatment B.

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Design and Analysis Considerations

- ▶ Number of clusters
- ▶ Size of each cluster (i.e., number of patients per cluster)
- ▶ Observations within a cluster (and within a cluster's period) are usually correlated
- ▶ Therefore, cluster designs are typically less statistically efficient than individual patient RCTs
 - ▶ Between cluster correlation
 - ▶ Between period correlation
 - ▶ Within period correlation
- ▶ The structure of these correlations will impact your design and analysis.

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Resources

RESEARCH METHODS AND REPORTING

Use of multiple period, cluster randomised, crossover trial designs for comparative effectiveness research
 Karla Hemming,¹ Monica Taljaard,^{2,3} Charles Weijer,⁴ Andrew B Forbes⁵

IEA International Journal of Epidemiology, 2023, 52, 00
doi: 10.1093/ije/dyad001
 Advance Access Publication Date: 23 February 2023
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Statistics in Medicine Research Article
 Received 18 March 2022 | Accepted 23 August 2022 | Published online 29 September 2022 in Wiley Online Library
WILEY
 DOI: 10.1002/sim.9727

Methods
A tutorial on sample size calculation for multiple-period cluster randomised parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator
 Karla Hemming,^{1,2*} Jessica Kwan,³ Richard Hooper,⁴ Andrew Forbes,⁵ and Monica Taljaard^{6*}

Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome
 Katy E. Morgan,^{1,2*} Andrew B. Forbes,³ Ruth H. Kough,⁴ Vipul Jairath,⁵ and Brennan C. Kahan⁶

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Benefits of Multiple-Periods

- ▶ Reduces chance imbalance of time-invariant or time-varying characteristics
- ▶ Improved statistical efficiency relative to trials with a single crossover (including decreasing the number of clusters required)
- ▶ Ability to stop sites (i.e., clusters) early for underperformance with less impact on treatment group balance

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Reasons to Avoid Multiple-Period Designs

- ▶ Interventions have carry-over effects
- ▶ Switching interventions is anticipated to be burdensome or error-prone

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Temporal Effects in Cluster Crossover Trials

- ▶ Intervention involves a learned behavior that can't be undone
 - ▶ Consider a cluster randomized or stepped-wedge design
- ▶ Contamination between periods
 - ▶ Consider a washout in-between periods
- ▶ Interventions and temporal changes that differentially affect interventions (e.g., new infection control policies, pandemic)
 - ▶ Increase the number of periods

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Mitigating Temporal Effects (Design)

- ▶ Concurrent start for clusters (recommended, but often impractical)
- ▶ Equal representation of clusters under treatment groups in each period
- ▶ Switches should be based on calendar time, not the number of patients enrolled
- ▶ Considering seasonal balance within the cluster if enrolling over multiple years

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Incorporating Temporal Effects (Analysis)

- ▶ Is period a fixed effect?
- ▶ Alternative specifications
 - ▶ Categorical, linear, or spline function
 - ▶ Interaction with treatment or cluster
- ▶ Coding
 - ▶ Categorical
 - ▶ Continuous calendar time

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Bayesian Analysis for Comparative Effectiveness Research

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What is Bayes an Alternative To?

- ▶ Frequentist Statistics
 - ▶ Each question has a fixed, constant (unknown) answer
 - ▶ This unknown truth will be uncovered through replicated experiments
 - ▶ P-value – probability of data compatibility with the null hypothesis

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Bayesian Statistics

- ▶ Developed in 1700s
- ▶ Gaining popularity with advances in computing power
- ▶ Probabilistic view
- ▶ As we gain more evidence, we update our probabilities

Prior Evidence × Observed Data = Posterior Probability

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CLINICAL
TRIALS ARTICLE

Clinical Trials 2012; 9: 37-47

Bayesian approaches for comparative effectiveness research

Donald A Berry

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Comparative Effectiveness

- ▶ Direct comparison of existing health interventions to inform healthcare decisions
- ▶ “The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care” – Institute of Medicine (2009)

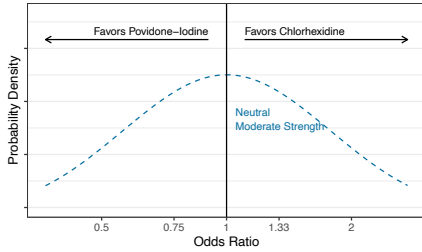
83

Comparative Effectiveness

- ▶ Direct comparison of existing health interventions to **inform healthcare decisions**
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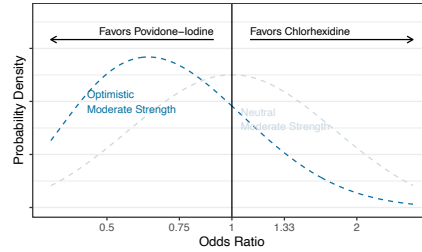
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Incorporating Prior Knowledge



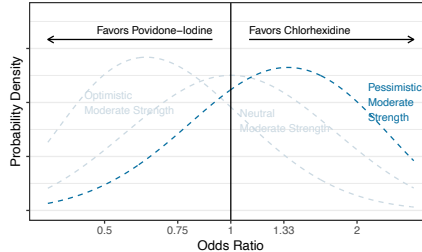
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Incorporating Prior Knowledge



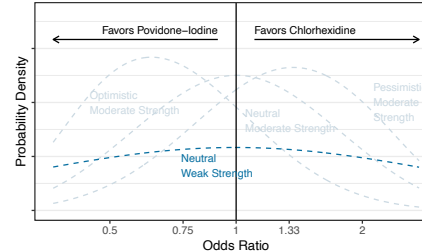
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Incorporating Prior Knowledge



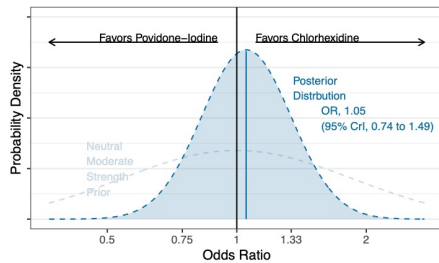
87

Incorporating Prior Knowledge



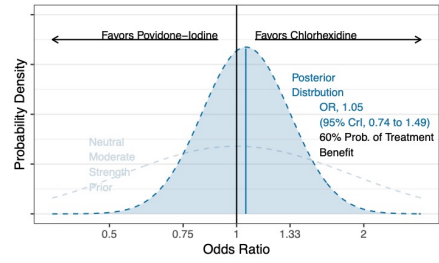
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Prior Knowledge + New Evidence



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Informing Decision



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Sensitivity of Posterior Probability to Priors

Prior	Odds Ratio (95% CrI)	Prob. of Povidone-Iodine Benefit
Neutral, Moderate Strength	1.05 (0.74 to 1.49)	40%
Optimistic, Moderate Strength	0.98 (0.68 to 1.41)	54%
Pessimistic, Moderate Strength	1.10 (0.76 to 1.58)	30%
Neutral, Weak Strength	1.06 (0.71 to 1.57)	39%

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Summary

- ▶ When comparing existing interventions
 - ▶ Some prior evidence often exists (i.e., priors)
 - ▶ A "significant" result from the frequentist perspective might not always be needed to inform clinical practice.
- ▶ Bayesian analyses allow:
 - ▶ Quantification of subjective priors with the aim of an objective understanding.
 - ▶ Ascertain the probability of treatment benefits at various minimally clinically important thresholds.

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