A-PREP

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.

- Sheila Sprague
- Mohit Bhandari
- Gerard Slobogean

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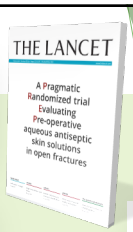
A-PREP trial is very unique

- 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
- Indiana University Health
- Vanderbilt University Medical Center
- University of Texas Health Center
- Hamilton Health Sciences
- Prisma Health Upstate
- San Antonio Military Medical Center
- Wright State University
- Banner University Medical Center, Tucson
- University of California San Francisco
- University of Florida
- The CORE Institute
- Vall d'Hebron University Hospital
- Parc Tualí Hospital Universitari

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Committee Members

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PJ Devereaux
Nathan O'Hara
Jeff Friedrich
Debra Marvel
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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 / gyne surgery

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Pre-Op Antiseptic Skin Solutions

There are no skin antisepsis 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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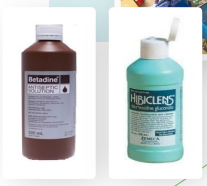
Purpose

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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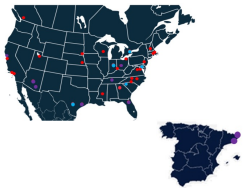
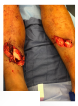
Population

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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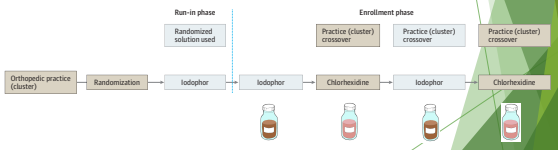
Randomization

Multiple period, cluster randomized, crossover trial



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Protocol

01. Last solution used prior to skin incision

02. Use the allocated solution for all surgeries

03. Analysis based on solution used at fracture fixation surgery

Intervention Fidelity

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)

- Superficial within 30 days, Deep within 90 days of definitive fixation

Unplanned reoperation with 1 year

- Infection, wound healing, fracture healing

A-TREP

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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
52% ASA I/II	35% Smoker

93% One Fracture	6% Two Fractures
1% Three Fractures	13 ISS

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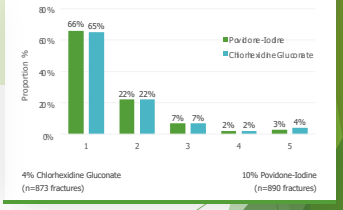
Injuries

25% Upper extremity

75% Lower extremity or pelvis



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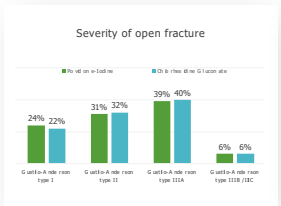
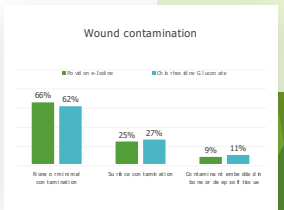
Severity





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Surgical Site Infection

	10% Povidone-Iodine (n=828) number (%)	4% Chlorhexidine Gluconate (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 Gluconate (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 Gluconate (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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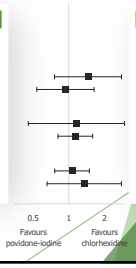
Results

Subgroup	Povidone-Iodine	Chlorhexidine	Odds Ratio (95% CI
Surgical Site Infection			
Severity of the Open fracture			**Interaction p-value=0.337**
Gustilo-Anderson type I or II	19/431	15/424	1.47 (0.72, 2.98)
Gustilo-Anderson type III	40/356	43/360	0.97 (0.59, 1.59)
Location of the Open fracture			**Interaction p-value=0.946**
Upper extremity	6/204	5/184	1.15 (0.35, 3.85)
Lower extremity	53/583	53/600	1.10 (0.72, 1.68)
Wound Contamination			**Interaction p-value=0.523**
None, minimal, or surface contamination	47/717	44/695	1.04 (0.67, 1.63)
Embedded wound contamination	12/70	14/89	1.44 (0.59, 3.52)



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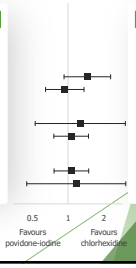
Results

Subgroup	Povidone-Iodine	Chlorhexidine	Odds Ratio (95% CI
Unplanned Reoperation			
Severity of the Open fracture			**Interaction p-value=0.086**
Gustilo-Anderson type I or II	44/401	32/402	1.51 (0.93, 2.46)
Gustilo-Anderson type III	74/333	83/336	0.89 (0.60, 1.30)
Location of the Open fracture			**Interaction p-value=0.510**
Upper extremity	19/184	14/174	1.36 (0.65, 2.83)
Lower extremity	99/550	101/564	1.04 (0.72, 1.49)
Wound Contamination			**Interaction p-value=0.699**
None, minimal, or surface contamination	98/668	90/654	1.06 (0.77, 1.46)
Embedded wound contamination	20/66	25/84	1.24 (0.60, 2.57)



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

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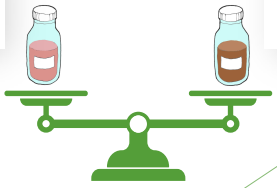
Discussion

- Contaminated open fractures:
  16% SSI
  30% reoperation rate
- Type III fractures:
  12% SSI
  24% reoperation rate



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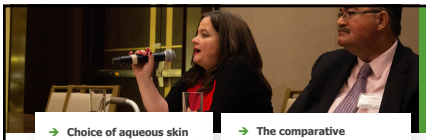

Conclusion

- **Choice of aqueous skin antisepsis 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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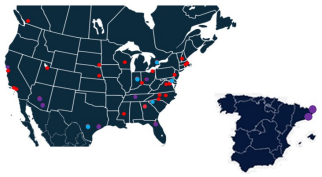

https://www.prepittrial.com/sites

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

Sheila Sprague, PhD
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 J, Staniszewska S, Mockford C, et al. A Systematic Review of the Impact of Patient and Public Involvement on Service Users, Researchers and Communities. Patient. 2014;7:387–95.

2. Robinson A. Patient and public involvement: In theory and in practice. Journal of Lymphoedema and Chatsey. 2014;138:318–25.

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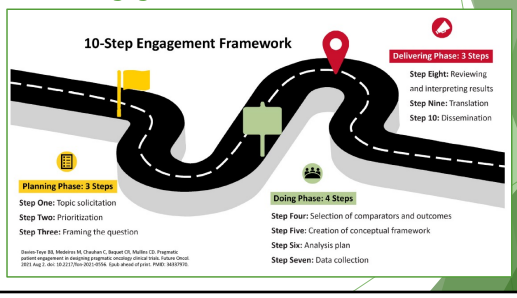
Patient Engagement in PREP-IT



Devin-Teye BB, Medeiros M, Chauhan C, Baquet CR, Mullins CD. Pragmatic patient engagement in designing pragmatic oncology clinical trials. Future Oncol. 2021 Aug 2. doi: 10.2217/fon-2021-0556. Epub ahead of print. PMID: 34347935.

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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. 2019. Available at:

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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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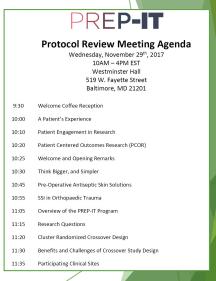
Initial Planning Meetings

- 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
10AM – 4PM EST
Westminster Hall
519 W. Fayette Street
Baltimore, MD 21201

9:30	Welcome Coffee Reception
10:00	A Patient's Experience
10:10	Patient Engagement in Research
10:20	Patient Centered Outcomes Research (PCOR)
10:25	Welcome and Opening Remarks
10:30	Think Bigger, and Simpler
10:45	Pre-Operative Antiseptic Skin Solutions
10:55	SSI in Orthopaedic Trauma
11:05	Overview of the PREP-IT Program
11:15	Research Questions
11:20	Cluster Randomized Crossover Design
11:30	Benefits and Challenges of Crossover Study Design
11:35	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.)


JAMA NETWORK Open.

Effectiveness of Iodophor vs Chlorhexidine Solutions for Surgical Site Infections and Unplanned Reoperations for Patients Who Underwent Fracture Repair
The PREP-IT Master Protocol

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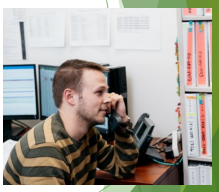
Informed Consent Form Development

- 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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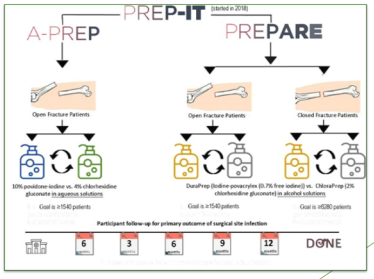
Development of a Trial Visual



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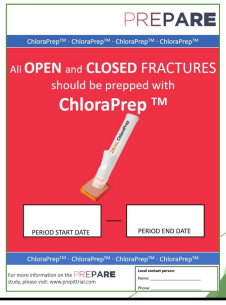
Development of a Clinical Site Posters



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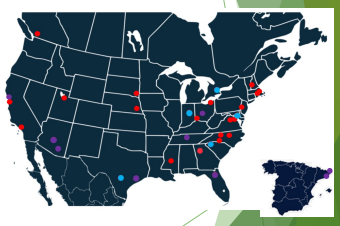
Clinical Site Initiation Visits

- 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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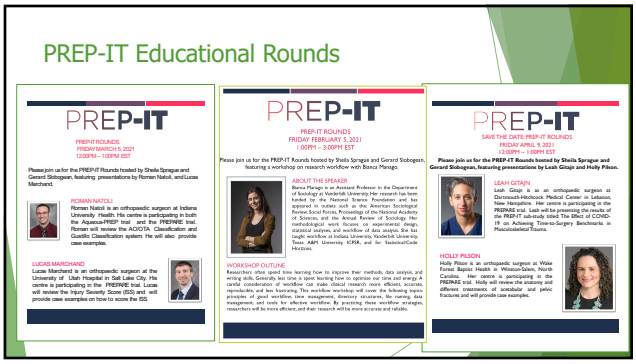
PREP-IT Educational Rounds



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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

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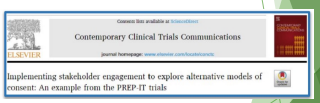
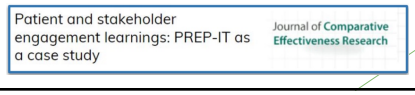
Engagement Manuscripts and Sub-Studies

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





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Engagement Manuscripts and Sub-Studies

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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


THE LANCET

ARTICLES | VOLUME 400, ISSUE 10360, P1334-1344, OCTOBER 15, 2022

Aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP): a multiple-period, cluster-randomised, crossover trial

PREP-IT Investigators † • Show footnotes

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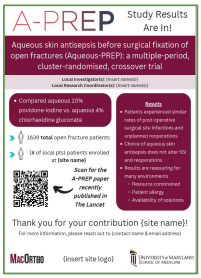
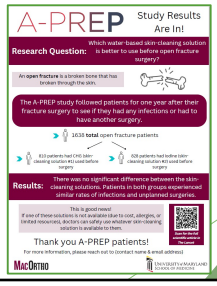
Knowledge Dissemination of Primary Results


A-PREP Study Results Are In!

Aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP): a multiple-period, cluster-randomised, crossover trial

Thank you for your contribution (site name)!


A-PREP Study Results Are In!

Research Question: Which water-based skin-cleaning solution is better to use before open fracture surgery?

Results: There was no significant difference between the skin-cleaning solutions. Patients in both groups experienced similar rates of infections and unplanned surgeries.

Thank you A-PREP patients!

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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 FiO_2
- 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 FiO_2
- 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 cointerventions
- Statistical analyses
  - Chronologic time within the trial lifespan as a fixed effect variable
  - Sensitivity analyses:
    - Key cointerventions added as covariates
    - Key cointerventions 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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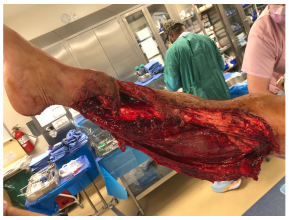
"Alcohol pre-wash" Example

- Rationale why it was included
  - 63% used it
  - No alcohol antisepsis 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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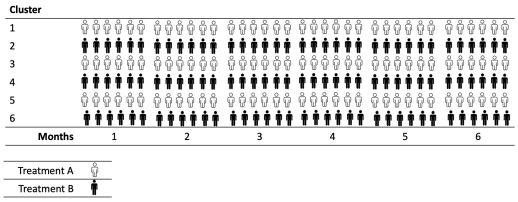
Cluster Randomized Trial Design



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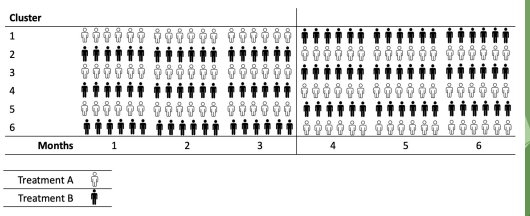
Cluster-Crossover Trial Design



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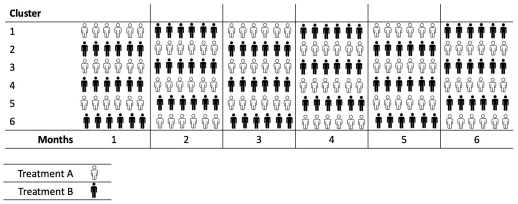
Multiple-Period, Cluster Crossover Trial Design



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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 Forbes[5]

IEA

Methods

A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator

Karla Hemming, Jessica Kasza, Richard Hooper, Andrew Forbes and Monica Taljaard

Statistics in Medicine

Research Article

Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome

Katy E. Morgan, Andrew B. Forbes, Ruth H. Keogh, Vipul Jairath and Brennan C. Kahan

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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 compatability 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

$$Prior\ Evidence \times Observed\ Data = Posterior\ Probability$$

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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)

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Comparative Effectiveness

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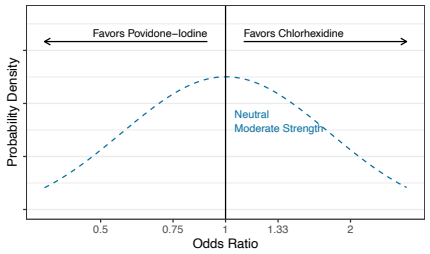
Incorporating Prior Knowledge



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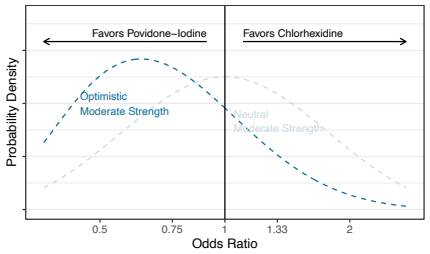
Incorporating Prior Knowledge



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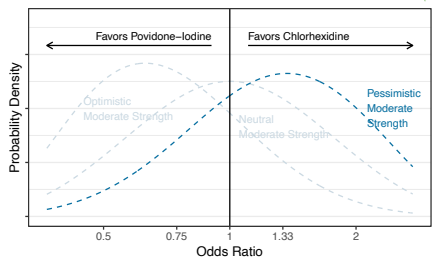
Incorporating Prior Knowledge



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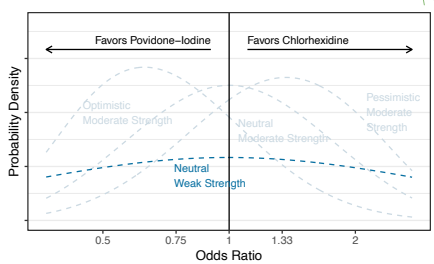
Incorporating Prior Knowledge



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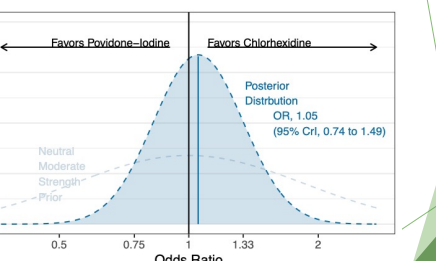
Prior Knowledge + New Evidence



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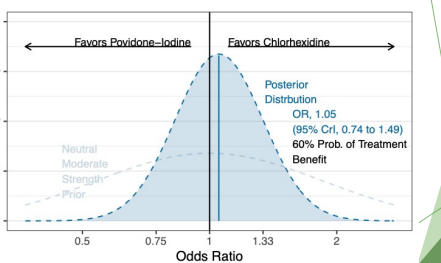
Informing Decision



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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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