



**Health**  
Hunter New England  
Local Health District



# The NewSKIN study

## The Newcastle Skin Preparation Study

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# Thanks



- HNE Health Executive: Michael Di Rienzo, Patricia Davidson  
Debbie Bradley, Michael Hensley, Jane Gray
- HMRI and CReDITSS: John Attia, Christopher Oldmeadow,  
Matthew Clapham
- Newcastle Private Hospital: Michael Mitchell
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- Ulrich Liedvogel

# Thanks



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  - Theatre staff JHH, RNC, NPH
  - Surgeons
  - Participants
- 
- Gill Harris, Monica O'Neill, Lyndal Asquith, Michael Morphett, Emma Downey, Sally-Anne Johnston, Georgia Marr, Jacob Hampton, Lisa Lloyd



- Rosemary Carroll and Natalie Lott



# Current significance of SSI

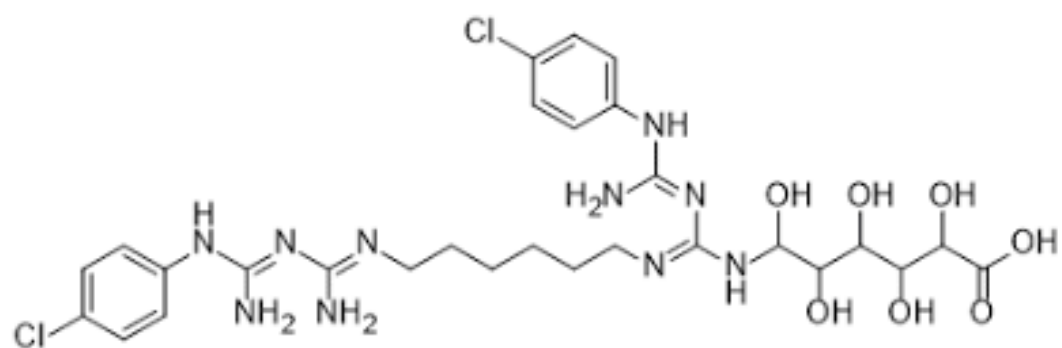
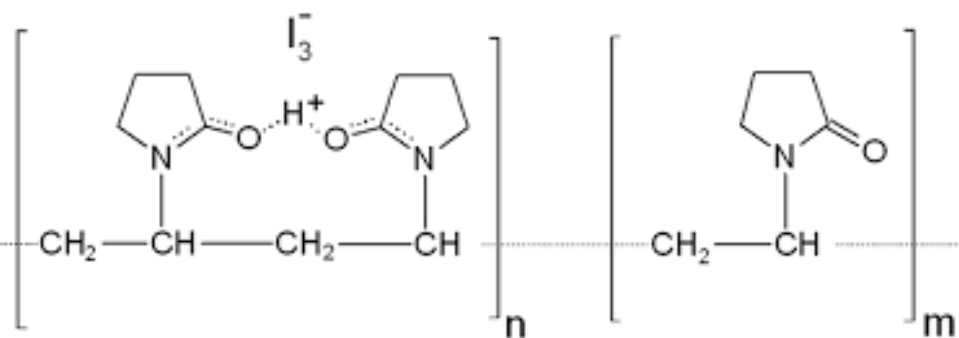


# Background



- Joseph Lister
- 1827-1912
- Scottish surgeon
- 1853: Edinburgh, assistant to Syme
- 1861: Glasgow Royal Infirmary, mortality from amputations 45-50%
- 1865: Carbolic acid
- Mortality reduced to 15%









- PVP-I
- 1955 USA (Industrial Toxicology Laboratories)
- Broad spectrum microbicide that destroys microbial protein and DNA
- No resistance



- Chlorhexidine
- 1954 UK (Imperial Chemical Industries)
- Broad spectrum that disrupts cell wall and membrane





- Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis
  - N=849, PRCT
  - Clean-contaminated surgery
  - 409 chlorhexidine-alcohol (CA) v 440 povidone-iodine (PI)
  - SSI: 9.5% CA v 16.1% PI, RR 0.59, 95% CI 0.41 to 0.85; p=0.004
  - 8/12 authors received grants from Cardinal Health, 1/12 authors was an employee of Cardinal Health



- 2002: FDA approve one step ChloraPrep® for use by Medi-Flex hospital products
- March 2008: Cardinal Health agrees to acquire ChloraPrep® for US \$490 million
- Trial recruitment ran from April 2004 to May 2008

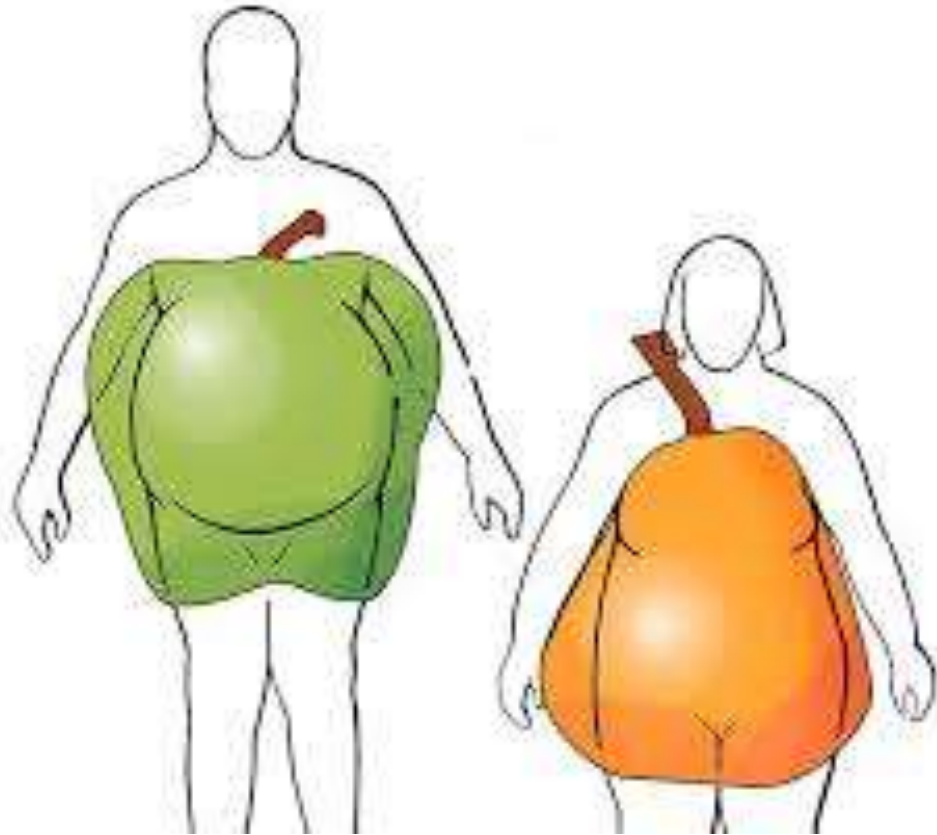


- Case of 25: \$450 (Betadine:\$12.49)

# Which compound is the good stuff?



- Chlorhexidine-alcohol v Povidone-Iodine





- Cochrane review: “Investment in at least **one large trial** (in terms of participants) is warranted in order to add definitive and hopefully conclusive data to the current evidence base. Ideally any future trial would evaluate the **iodine-containing and chlorhexidine-containing solutions** relevant to current practice as well as the type of solution used (**alcohol vs. aqueous**).”

Dumville JC, McFarlane E, Edwards P, Lipp A, Holmes A, Liu Z. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD003949. DOI: 10.1002/14651858.CD003949.pub4

# Study aims



- Primary aim:

To assess the **non-inferiority** of povidone-iodine and alcohol (less expense) compared to chlorhexidine and alcohol (current recognised standard).

- Secondary aim:

To compare the **superiority** of povidone-iodine and alcohol (known flammability risk and expense) to aqueous povidone-iodine.

# Outcome measures



- Primary outcome:
  - Surgical Site Infection (SSI) as per CDC criteria
- Secondary outcomes:
  - Readmissions within 30 days
  - Complications as per Clavien-Dindo classification
  - Length of Stay (LOS) in days during index admission
  - Allergic and adverse reactions



- John Hunter and Newcastle Private Hospitals, Newcastle, Australia
- Three armed randomized clinical trial
  - Arm A: 2% or 0.5% Chlorhexidine and 70% Alcohol
  - Arm B: 10% Povidone-Iodine and 70% Alcohol
  - Arm C: 10% Aqueous Povidone-Iodine
- 41 Surgeons across 10 specialties
- Web based randomization
- Redcap
- Blinded assessment as per CDC criteria
- Intention to Treat principles
- Follow up: 30 days, 90 days for implants



# Accrual target



- Power n=2970 (15% SSI: 80% power, 95% significance, 4% non-inferiority margin, 5% difference:15% v 20% for alcohol comparison)
- 1:1:1
- Stratification to
  - Clean
  - Clean-contaminated
  - Contaminated
  - Dirty
- **N=3300**

# Funding, ethics and protocol



- 2015 John Hunter Charitable Trust Grant: \$20,000
- HNEHREC 13/12/11/3.02
- ACTRN12615000021572

# WHO guidelines on prevention of SSI



- ‘Clorhexidine-alcohol rather than aqueous povidone-iodine or povidone-iodine with alcohol for surgical skin preparation.’
  - “strong recommendation” with “low to moderate” quality of evidence

Allegranzi B, Bischoff P, DeJonge S et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence based global perspective. *Lancet Infect Dis* 2016; **16**; 276-287



**Timeframe of recruitment:  
1/7/2015 – 1/12/2018**

Assessed for eligibility (n=3879)

- ◆ Refused (n=267)
- ◆ Consented (n=3612)
- ◆ Excluded (n=311)
  - Patient factors (n=28)
  - System factors (n=179)

Randomized (n= 3301)

**Allocation**

- Allocated to intervention (n=1102)
- ◆ Received allocated intervention (n=1034)
  - ◆ Did not receive allocated intervention (n= 39), clinical decision or error
  - ◆ Withdrawn (25) OT cancelled, consent withdrawn, no incision made

- Allocated to intervention (n=1103)
- ◆ Received allocated intervention (n=1055)
  - ◆ Did not receive allocated intervention (n=57) wrong prep used clinical decision or error
  - ◆ Withdrawn (n=29) OT cancelled, consent withdrawn, no incision made

- Allocated to intervention (n=1096)
- ◆ Received allocated intervention (n=984)
  - ◆ Did not receive allocated intervention (n=78) wrong prep used clinical decision or error
  - ◆ Withdrawn (n=34) OT cancelled, consent withdrawn, no incision made

**No allergic or adverse reactions**

**Follow-Up**

- For follow-up (n=1077)
- ◆ Lost to follow-up (n=35) uncontactable at follow-up.
  - ◆ Died prior to D30 (n=2)

- For follow-up (n=1074)
- ◆ Lost to follow-up (n=22) uncontactable at follow-up.
  - ◆ Died prior to D30 (n=1)

- For follow-up (n=1062)
- ◆ Lost to follow-up (n=26) uncontactable at follow-up
  - ◆ Died prior to D30 (n=1)

# Demographics by treatment arm



Characteristic	Class/Statistic	Arm A (n=1076)	Arm B (n=1075)	Arm C (n=1062)	Total (n=3213)
Sex	Male	494 (46%)	480 (45%)	476 (45%)	1450 (45%)
	Female	581 (54%)	595 (55%)	586 (55%)	1762 (55%)
	Missing	1	0	0	1
Age	Mean (SD)	56 (17)	57 (17)	57 (17)	57 (17)
	Median (min,max)	58 (18,94)	60 (18,96)	60 (18,93)	59 (18,96)
Admission mode	Elective	1050 (98%)	1060 (99%)	1043 (98%)	3153 (98%)
	Transfer	19 (1.8%)	13 (1.2%)	18 (1.7%)	50 (1.6%)
	Emergency	3 (0.3%)	1 (0.1%)	1 (0.1%)	5 (0.2%)

# Demographics by treatment arm



Stratum	Arm A (n=1076)	Arm B (n=1075)	Arm C (n=1062)	Total (n=3213)
Clean	505 (47%)	502 (47%)	499 (47%)	1506 (47%)
Clean-contaminated	543 (50%)	543 (51%)	535 (50%)	1621 (50%)
Contaminated and dirty	28 (2.6%)	30 (2.8%)	28 (2.8%)	86 (2.7%)



# Demographics by treatment arm



Characteristic	Class	Arm A (n=1076)	Arm B (n=1075)	Arm C (n=1062)	Total (n=3213)
Smoking status	Daily	177 (16%)	179 (17%)	162 (15%)	518 (16%)
	Weekly	2 (0.2%)	2 (0.2%)	3 (0.3%)	7 (0.2%)
	Irregular	12 (1.1%)	5 (0.5%)	6 (0.6%)	23 (0.7%)
	Ex-smoker	381 (35%)	361 (34%)	373 (35%)	1115 (35%)
	Never	504 (47%)	527 (49%)	518 (49%)	1549 (48%)
Diabetic status	Yes	162 (15%)	161 (15%)	187 (18%)	510 (16%)
Immunosuppressive agents	Yes	78 (7.3%)	98 (9.1%)	99 (9.3%)	275 (8.6%)
Recent radiotherapy	Yes	22 (2.0%)	30 (2.8%)	21 (2.0%)	73 (2.3%)
BMI	Mean (SD)	31 (7)	30 (7)	31 (8)	31 (7)



# Results

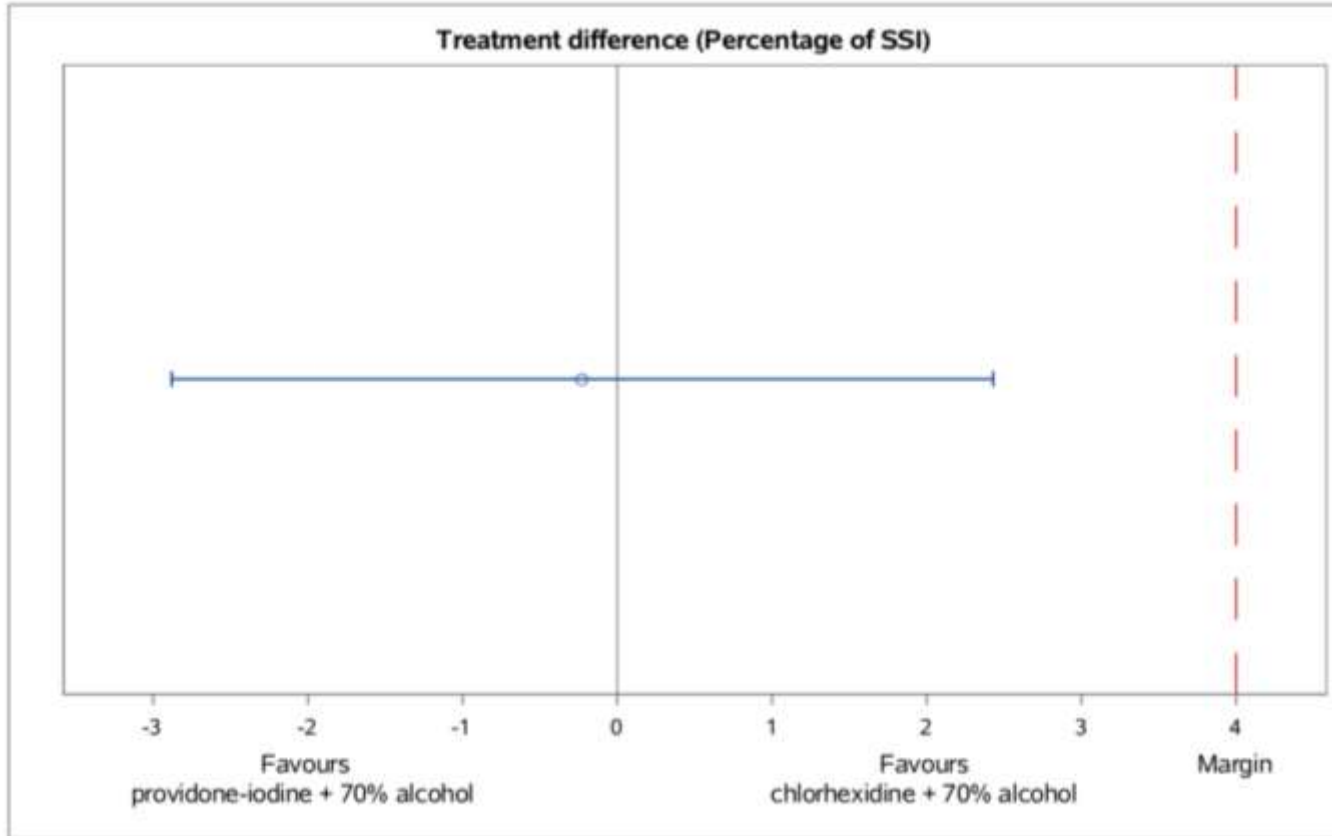


- Non-inferiority between povidone-iodine and chlorhexidine compounds

Outcome	Class	Arm B (PI +70% Alcohol) N=1075	Arm A (Chl + 70% Alcohol) N=1076	Arm B – Arm A Mean difference (95% CI)
SSI	Yes	117 (10.91%)	119 (11.14%)	-0.23% (-2.88 to 2.43)

Hypothesized margin was 4% and the upper CI for the difference is 2.43%: Povidone-iodine is non-inferior to chlorhexidine

# Results



# Results



- Non-inferiority between povidone-iodine and chlorhexidine compounds

	Outcome	Class/Statistic	Arm B (PI +70% Alcohol) N=1075	Arm A (Chl + 70% Alcohol) N=1076	Arm B – Arm A Mean difference (95% CI)
Secondary	30 day readmission	Yes	34 (3.16%)	28 (2.60%)	0.56% (-0.85 to 1.97)
	Complications	Yes	287 (26.72%)	293 (27.23%)	-0.51% (-4.26 to 3.24)
	Length of stay	Mean (SD)	4.4 (7.2)	4.2 (6.2)	0.18 (-0.38 to 0.75)

# Results



- Povidone-iodine with alcohol versus aqueous povidone-iodine

Outcome	Class	Arm B (PI and 70% Alcohol) N=1075	Arm C (Aqueous PI) N=1062	Odds ratio (95% CI)	P
SSI	Yes	117 (10.9%)	132 (12.5%)	0.85 (0.65 to 1.11)	0.2420

- The addition of alcohol did not result in a 5% improvement in SSI rate

# Results



- Povidone-iodine with alcohol versus aqueous povidone-iodine

	Outcome	Class/Statistic	Arm B (PI +70% Alcohol) N=1075	Arm C (Aqueous PI) N=1062	Odds ratio (95% CI)	P
Secondary	30 day readmission	Yes	34 (3.16%)	41 (3.86%)	0.81 (0.51 to 1.29)	0.3769
	Complications	Yes	287 (26.7%)	282 (26.6%)	1.01 (0.83 to 1.22)	0.9503
	Length of stay	Median (min, max)	3.0 (0, 120)	3.0 (0, 91)	0 (-0.02 to 0.02)	1.000

# Results



- Outcome for clean stratification

Outcome	Class	Arm A (ChI + 70% Alcohol) N=505	Arm B (PI +70% Alcohol) N=502	Arm C (Aqueous PI) N=499	Total N=1506	P
SSI	Yes	46 (9.22%)	36 (7.19%)	48 (9.74%)	130 (8.7%)	0.3198

# Results



- Outcome for clean-contaminated stratification

Outcome	Class	Arm A (Chl + 70% Alcohol) N=543	Arm B (PI +70% Alcohol) N=543	Arm C (Aqueous PI) N=535	Total N=1621	P
SSI	Yes	68 (12.55%)	74 (13.68%)	79 (14.79%)	221 (14%)	0.5621



# Chlorhexidine 0.5% v 2.0%



<i>Model</i>	<i>Outcome</i>	<i>N</i>	<i>0.5%</i>	<i>2%</i>	<i>Odds ratio</i>	<i>p</i>
adjusted	Post op SSI	1072	48 (13.1%)	71 (10.1%)	1.28 (0.86 to 1.90)	0.2209
adjusted	Complications	1076	91 (24.7%)	202 (28.6%)	0.73 (0.54 to 0.98)	0.0373

# Procedural outcomes: SSI rate



<b>Subset</b>	<b>Arm A (Chl + 70% Alcohol)</b>	<b>Arm B (PI + 70% Alcohol)</b>	<b>Arm C (Aqueous PI)</b>	<b>P-value</b>
Colorectal surgery N=482	<b>11 (15.71%)</b> 18 (25.35%)	44 (22.80%)	34 (22.97%)	0.5267
Hips N=80	0	1 (3.70%)	0	0.6500
Knees N=115	2 (5.56%)	5 (12.20%)	2 (5.26%)	0.5072
Herniae N=259	<b>7 (14.58%)</b> 7 (17.07%)	8 (8.99%)	13 (16.46%)	0.4158
Gynaecological N=273	<b>16 (21.92%)</b> 6 (24.00%)	11 (12.50%)	11 (12.79%)	0.2007
Cardiac N=31	2 (22.22%)	2 (28.57%)	5 (38.46%)	0.8741

# Conclusions



- Povidone-iodine preparation is non-inferior to chlorhexidine preparation in preventing SSI.
- The addition of alcohol to skin preparation does not decrease SSI by 5% or more.
- There is no difference between povidone-iodine and chlorhexidine compounds with respect to complication rates, readmission rates and length of stay.
- The addition of alcohol to skin preparation does not decrease complication rates, readmission rates or length of stay.
- All compounds appear safe when used correctly.

# Whats next?

- DVTPE
- \$250,000 annually JHH/RNC
- The utility of sequential calf compression devices in addition to chemical prophylaxis and anti-embolic stockings