Innovative clinical trial designs

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https://reflectionspc.com
Conflicts of interest

Grants or consulting fees (received by hospital)
- ImmuneExpress
- Janssen Vaccines
- Vedanta Biosciences

Speaker fee
None
An excellent trial that – nevertheless – doesn’t answer all questions

Two innovative trials that answered some questions (and from which I learned a lot)

The trial that will answer all questions
How to evaluate a clinical trial

1. Validity of the results
   – Is the design appropriate?
     • Starts with a proper research question
   – Is bias prevented?
   – Is the statistical analysis correct?

2. Precision of the results
   – Is the effect relevant and precise?

3. Generalizibility
   – Does it apply to my patients?
Preventing Surgical-Site Infections in Nasal Carriers of Staphylococcus aureus

Lonneke G.M. Bode, M.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Heiman F.L. Wertheim, M.D., Ph.D.,

6771 Patients were screened for nasal \textit{S. aureus} on PCR

1251 Tested positive for \textit{S. aureus} on PCR
353 Were excluded
146 Declined to participate
140 Did not meet inclusion criteria
47 Had other reasons
20 Met exclusion criteria

918 Underwent randomization

505 Received mupirocin–chlorhexidine

504 Were included in the analysis
1 Withdrew consent

413 Received placebo

413 Were included in the analysis

\textbf{Figure 1. Study Enrollment and Randomization.}
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mupirocin–Chlorhexidine (N = 504)</th>
<th>Placibo (N = 413)</th>
<th>Relative Risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. aureus infection</strong></td>
<td>17 (3.4)</td>
<td>32 (7.7)</td>
<td>0.42 (0.23–0.75)</td>
</tr>
<tr>
<td><strong>Source of infection†</strong></td>
<td></td>
<td></td>
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<tr>
<td>Endogenous</td>
<td>12 (2.4)</td>
<td>25 (6.1)</td>
<td>0.39 (0.20–0.77)</td>
</tr>
<tr>
<td>Exogenous</td>
<td>4 (0.8)</td>
<td>6 (1.5)</td>
<td>0.55 (0.16–1.92)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
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<tr>
<td><strong>Localization of infection</strong></td>
<td></td>
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<tr>
<td>Deep surgical site‡</td>
<td>4 (0.9)</td>
<td>16 (4.4)</td>
<td>0.21 (0.07–0.62)</td>
</tr>
<tr>
<td>Superficial surgical site‡</td>
<td>7 (1.6)</td>
<td>13 (3.5)</td>
<td>0.45 (0.18–1.11)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>2 (0.4)</td>
<td>2 (0.5)</td>
<td>0.82 (0.12–5.78)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>2 (0.4)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Relative risks are for S. aureus infection in the mupirocin–chlorhexidine group.
† The source of the S. aureus infections was determined by comparing nasal strains with strains isolated from the infection site by pulsed-field gel electrophoresis.
‡ Data are for surgical patients only: 441 in the mupirocin–chlorhexidine group and 367 in the placebo group.
## Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mupirocin + CHX</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Non-surgical patients (n=109)</td>
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<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic surgery (n=391)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
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<tr>
<td>Orthopedics (n=172)</td>
<td></td>
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<td></td>
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<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular surgery (n=95)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
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<tr>
<td>Gastrointestinal surgery (n=43)</td>
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<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
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<tr>
<td>General surgery (107)</td>
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<td></td>
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</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
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</tbody>
</table>
## Was the study design ethical?

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Mupirocin + CHX</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-surgical patients (n=109)</td>
<td>63</td>
<td>46</td>
<td>0.73 (0.04-11.92)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>1 (1.6%)</td>
<td>1 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic surgery (n=391)</td>
<td>220</td>
<td>171</td>
<td>0.15 (0.04-0.51)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>3 (1.4%)</td>
<td>15 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Orthopedics (n=172)</td>
<td>85</td>
<td>87</td>
<td>0.25 (0.03-2.26)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>1 (1.2%)</td>
<td>4 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>Vascular surgery (n=95)</td>
<td>53</td>
<td>42</td>
<td>0.91 (0.28-2.96)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>7 (13.2%)</td>
<td>6 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal surgery (n=43)</td>
<td>22</td>
<td>21</td>
<td>0.60 (0.09-4.01)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>2 (9.1%)</td>
<td>3 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>General surgery (107)</td>
<td>61</td>
<td>46</td>
<td>0.74 (0.14-3.85)</td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>3 (4.9%)</td>
<td>3 (6.5%)</td>
<td></td>
</tr>
</tbody>
</table>
The philosophy of Selective Digestive Decontamination*

- Prevention of carriage (in intestinal and respiratory tract) with those Gram-negative bacteria most frequently causing ICU-acquired infections (especially VAP) is beneficial.

- This also holds for *S. aureus* and yeasts

- The anaerobic flora is beneficial (as these bacteria provide colonization resistance).

- Prophylactic treatment of community-acquired respiratory tract infections in all patients during the first days of admission/intubation is beneficial.

* Not necessarily my opinion
Selective Digestive Decontamination

- Oropharyngeal application 4 dd 0.5 gr. paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B (SOD).

- Intragastric application 4 dd 10 ml of suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B (suppositoria in case of stoma).

- Cefotaxim 4 dd 1 gr. i.v. during first 4 days of treatment.

- Surveillance cultures of throat, sputum and rectum on admission and twice weekly.

- Use of colonization resistance impairing antibiotics was discouraged.
Selective Oropharyngeal Decontamination

- Oropharyngeal application 4 dd 0.5 gr. paste containing 2% polymyxin E, 2% tobramycin and 2% amphotericin B (SOD)
- ...
- ...
- Surveillance cultures of throat, sputum on admission and twice weekly.
- ...
Considerations for study design

- Blinding is not feasible
  - Open comparison of SDD and SOD to Standard Care
  - Unambiguous primary endpoints: ICU-mortality and hospital-mortality

- Treatment (and non-treatment) of individual patients may influence outcome in other patients (contamination)
  - Intervention per ward and not per individual patient
  - Also better reflects real-life setting

- Large heterogeneity between ICUs (case-mix, practices)
  - Cross-over of interventions to control for residual ward-specific confounding

- Interventions may have sequential effects (incl. carry-over effects)
  - Randomisation of intervention sequence per ICU
  - Wash-out wash-in between interventions
Study design

- Cluster-randomized controlled multi-centre cross-over trial (ICUs in 13 hospitals)
  - 2 non-teaching; 7 teaching; 4 university
- Study periods: SDD, SOD and standard care
- Six months per study period
- 1 month wash in/wash out before and between study periods
- Order of study periods randomized per study centre
Order of interventions in 13 ICUs
Patients

• Inclusion criteria:
  – Expected stay in ICU >72 hours
  – and/or expected duration of ventilation >48 hours

• Evaluation for eligibility must be performed in all study periods:
  – SDD/SOD -> ordering medication and cultures
  – Standard care -> no further action

Potential for selection bias!
## Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>SDD (N = 2045)</th>
<th>SOD (N = 1904)</th>
<th>Standard Care (N = 1990)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yr ‡</strong></td>
<td>62.4 ± 15.9</td>
<td>61.4 ± 16.3</td>
<td>61.4 ± 16.2</td>
</tr>
<tr>
<td><strong>Male sex – no. of patients (%)</strong></td>
<td>1244 (61.2%)</td>
<td>1213 (63.7%)</td>
<td>1220 (61.3%)</td>
</tr>
<tr>
<td><strong>Mean APACHE II score</strong> *</td>
<td>19.6 ± 7.8</td>
<td>19.5 ± 8.2</td>
<td>18.6 ± 7.9 #</td>
</tr>
<tr>
<td><strong>Mechanical ventilation (%)</strong></td>
<td>1890 (92.9%)</td>
<td>1793 (94.2%)</td>
<td>1753 (88.1%) #</td>
</tr>
<tr>
<td><strong>Admission type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>923 (45.4%)</td>
<td>866 (45.5%)</td>
<td>973 (48.9%) #</td>
</tr>
<tr>
<td>Medical</td>
<td>1111 (54.6%)</td>
<td>1038 (54.5%)</td>
<td>1016 (51.1%) #</td>
</tr>
<tr>
<td><strong>Specialism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>605 (29.7%)</td>
<td>551 (28.9%)</td>
<td>609 (30.6%)</td>
</tr>
<tr>
<td>Cardiothoracic surgery</td>
<td>353 (17.4%)</td>
<td>284 (14.9%)</td>
<td>321 (16.1%)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>105 (5.2%)</td>
<td>140 (7.4%)</td>
<td>145 (7.3%)</td>
</tr>
<tr>
<td>Neurology</td>
<td>124 (6.1%)</td>
<td>144 (7.6%)</td>
<td>128 (6.4%)</td>
</tr>
<tr>
<td>Medical</td>
<td>382 (18.8%)</td>
<td>371 (19.5%)</td>
<td>393 (19.8%)</td>
</tr>
</tbody>
</table>
How to adjust for these potential confounders

- Cox regression?
  - "informative censoring" is a major violation (pts discharged alive from ICU were censored)
  - Cluster-effects not included in analysis
- Logistic regression?
  - Neglects differences in duration of follow-up
  - Cluster-effects not included in analysis
- Random effects logistic regression model?
  - Neglects differences in duration of follow-up
  - Adjustment for cluster-effects

- Thus was decided (after trial completion) for Random effects logistic regression
  - To equalize follow-up duration for all patients
  - Primary endpoint: survival/death at day 28
  - Derive status at day 28 from 2300 patients (discharged alive before day 28)
Clinical endpoints: adjusted analysis

<table>
<thead>
<tr>
<th></th>
<th>Adjusted outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Care</td>
</tr>
<tr>
<td></td>
<td>N=1990 OR</td>
</tr>
<tr>
<td>Mortality at day 28</td>
<td>1</td>
</tr>
<tr>
<td>ICU Mortality</td>
<td>1</td>
</tr>
<tr>
<td>Hospital Mortality</td>
<td>1</td>
</tr>
<tr>
<td>Duration of intubation</td>
<td>1</td>
</tr>
<tr>
<td>Duration of ICU-stay</td>
<td>1</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>1</td>
</tr>
</tbody>
</table>

Random effects logistic regression model with adjustment for age, gender, APACHE II score, ventilation, surgical/non-surgical and study center.
Decontamination of the Digestive Tract and Oropharynx in ICU Patients

The philosophy of treating Community-Acquired Pneumonia

- Antibiotic treatment should start as soon as possible, and is mostly empirical.

- The spectrum of antibiotic coverage increases with disease severity. For patients hospitalized (but not in ICU), three strategies were considered equally effective, according to Dutch guidelines:
  - Beta-lactam monotherapy
  - Beta-lactam + macrolide combination therapy
  - Fluoroquinolone monotherapy

- Empirical treatment is mostly based on clinical suspicion (and started before all criteria have been determined)
Challenges in study design

• How to avoid the effects of pre-randomization antibiotics in the ER?
  – Immediate treatment with study antibiotic (before informed consent has been obtained)

• How to maximize patient enrolment?
  – Enroll all patients with the presumed diagnosis of CAP (and in which antibiotics are started)

• How to avoid bias in endpoint detection?
  – Use mortality at a fixed day

• How to avoid the possibility of worse clinical outcome (while using more “appropriate” antibiotic use)?
  – Use a non-inferiority design
Study design

- Multicentre trial comparing empiric strategies for CAP patients admitted to non-ICU ward

- Antibiotic strategies
  - Beta-lactam monotherapy (BL)
  - Beta-lactam + macrolide (BLM)
  - Fluoroquinolone monotherapy (FQL)

- Outcome measures
  - Primary:
    - Non-inferiority of Beta-lactam strategy on day 90 mortality
  - Secondary:
    - Length of iv treatment
    - Length of stay
    - Complications
## Antibiotics allowed in strategy arms

<table>
<thead>
<tr>
<th>BL</th>
<th>BLM</th>
<th>FQL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>BL (including penicillin) + Erytromycin</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Amoxiclav</td>
<td>Claritromycin</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>2(^{nd}) &amp; 3(^{rd}) gen. cephalosporins</td>
<td>Azitromycin</td>
<td></td>
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</tbody>
</table>
### Treatment strategy comparison

<table>
<thead>
<tr>
<th>Jan</th>
<th>Apr</th>
<th>Jul</th>
<th>Oct</th>
<th>Jan</th>
<th>Apr</th>
<th>Jul</th>
<th>Oct</th>
<th>Jan</th>
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</table>

- Empiric strategy randomised for each centre
  - Rotating every 4 months
  - Cluster randomization with cross-over

- Applies to all CAP-patients admitted to non-ICU ward
  - Deferred informed consent

- Deviation for medical reason allowed

- Intention-to-treat analysis (irrespective of antibiotic treatment)
Primary outcome: day 90 mortality
Intention-to-treat analysis (ITT)

Survival curve

Risk difference

Favors Other Strategy

Favors Beta-lactam mono

BL: 9.0% (n=59)
BLM: 11.1% (n=82)
FQL: 8.8% (n=78)

Adjusted
Crude

Beta-lactam mono
Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Douwe F. Postma, M.D., Cornelis H. van Werkhoven, M.D., Leontine J. R. van Elden, M.D., Ph.D., Steven F. T. Thijsen, M.D., Ph.D., Andy I. M. Hoepelman, M.D., Ph.D., Jan A. J. W. Kluytmans, M.D., Ph.D., Wim G. Boersma, M.D., Ph.D., Clara J. Compaïjen, M.D., Eva van der Wall, M.D., Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and Marc J. M. Bonten, M.D., Ph.D., for the CAP-START Study Group*
Next question

• Dutch recommendation CAP patients hospitalized to non-ICU ward:
  – Benzylpenicillin or amoxicillin

• Guideline adherence in clinical practice was low
  – In CAP-START 22% in β-lactam monotherapy strategy received penicillin or amoxicillin

• How to determine whether a strategy can safely increase the use of Benzylpenicillin or amoxicillin?
The safety and effectiveness of an antibiotic stewardship intervention in hospitalized patients with community-acquired pneumonia: a stepped wedge cluster randomized trial

Inger van Heijl*1,2, Valentijn A. Schweitzer*2, Lufang Zhang2, Jan Jelrik Oosterheert3, Wendelien Dorigo-Zetsma4, Paul D. van der Linden1, C.H. Edwin Boel5, Cornelis H. van Werkhoven2, Marc J.M. Bonten2,5, on behalf of the CAP-PACT study group

*These authors contributed equally to the work

1 Department of Clinical Pharmacy, Tergooi hospital, Hilversum/Blaricum, the Netherlands
2 Julius Center for Health Sciences and Primary care, University Medical Centre Utrecht, the Netherlands
3 Department of Internal Medicine & Infectious Diseases, University Medical Centre Utrecht, The Netherlands
4 Department of Medical Microbiology, Tergooi hospital, Hilversum/Blaricum, the Netherlands
5 Department of Medical Microbiology, University Medical Centre Utrecht, the Netherlands
The “perfect” trial for comparisons of variations in routine care

• Is embedded in routine daily care practices

• Enables analysis of multiple interventions alone and in combination

• Continuously uses accumulating evidence

• Allows inclusion of new study arms

• Allows for adaptive randomization to optimize patient safety and trial efficiency
How?

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

JAMA Published online March 23, 2015

Platform trials are also being developed by PREPARE (Platform for European Preparedness Against Re-emerging Epidemics), a network funded by the European Commission, including the development of a randomized, response-adaptive, platform trial evaluating multiple treatments in the treatment of hospitalized patients with severe acute respiratory tract infection requiring intensive care. Interventions will be compared with standard care using a Bayesian approach, and the trial is intended to enroll 2000 to 4000 patients from more than 100 intensive care units across Europe.

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

Roger J. Lewis, MD, PhD
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.
Example: REMAP-CAP

• Adult patients with severe CAP admitted to ICU.

• What contributes to the patients’ outcome?
  – Antibiotic choice?
  – Corticosteroids?
  – Ventilation strategy?
  – Diagnostics of viral etiology of CAP?
  – Antiviral treatment?
  – Immune modulation by macrolides?

• Goal: To determine the effectiveness of different interventions in adult patients with severe CAP in improving survival (at day 60 after ICU admission).
REMAP design

• Randomized:
  – For each/multiple study domain
• Embedded:
  – Nested in daily clinical care (point-of-care randomization)
• Multifactorial:
  – Testing multiple interventions alone and in combination
• Adaptive
  – Possibility to adapt trial based using Response-adaptive randomization (RAR), based on prespecified rules
• Platform
  – Focus on disease instead of focus on treatment
Trial adaptations

Many adaptations possible:

1. Randomization allocation
2. Target population
3. Number of treatments
1. Randomization allocation

Response-Adaptive Randomization (RAR)

- Equal randomization first 400 pts
- Next 1600 RAR based on priors
- Postulated benefits:
  - More patients randomized to effective treatment(s)
  - Earlier identification of superior or inferior treatment option

Mortality:
- Fixed randomization: 485
- Adaptive randomization: 436
- Deaths “avoided”: 49
Conclusions

- The end is near for classical RCTs, for evaluating “best practices” -> pragmatic studies

- The “poor men’s” solution is cluster-RCTs

- The “rich men’s” solution is REMAP-like platform that can continue forever
  - Benefits from flexibility in design
    - Adding/dropping treatments
    - Subgroups
  - Potential to lower patient burden
    - RAR assigning more patients to the promising treatment(s)
    - Lowering of unfavourable outcomes
The integration of comparative effectiveness research into clinical practice retains the minimally intrusive effects of observational research while offering the strengths provided by the experimental method (including randomization).

It is unclear why point-of-care trials not intended for regulatory submission also need to comply with GCP. The fundamental question is why point-of-care trials are viewed as an activity that requires elaborate governance procedures rather than as quality improvement that is an intrinsic part of routine clinical care.