New designs for randomized controlled trials

Marc Bonten
University Medical Center Utrecht/RIVM

@MarcBonten
https://reflectionspc.com
Conflicts of interest

Grants (received by hospital)
- Pfizer
- Johnson & Johnson
- Arsanis
- ImmuneExpress
- RevDiagnostics

Speaker fee
- Pfizer
Contents

• An example of an excellent trial that – nevertheless – doesn’t answer all questions

• An example of a trial that answers some questions

• An example of a 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. Kluymans, M.D., Ph.D., Heiman F.L. Wertheim, M.D., Ph.D.,

Figure 1: Study Enrollment and Randomization.

- 6771 Patients were screened for nasal S. aureus on PCR
- 1281 Tested positive for 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
  - Withdraw consent
    - 504 Were included in the analysis
- 413 Received placebo
  - 413 Were included in the analysis
### Table 1. Baseline Characteristics of the 917 Study Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mupirocin-Chlorhexidine (N=504)</th>
<th>Placebo (N=413)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD) age — yr</td>
<td>61.8±13.9</td>
<td>62.8±13.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>331 (65.7)</td>
<td>251 (60.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hospital service — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>441 (87.5)</td>
<td>367 (88.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>63 (12.5)</td>
<td>46 (11.1)</td>
<td>0.53</td>
</tr>
<tr>
<td>Admission during index hospital</td>
<td>3</td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>McCabe score at admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2. Results of Group Sequential Analysis.**
**Table 2. Relative Risk of Hospital-Acquired *Staphylococcus aureus* Infection and Characteristics of Infections (Intention-to-Treat Analysis).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mupirocin–Chlorhexidine (N = 504)</th>
<th>Placebo (N = 413)</th>
<th>Relative Risk (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td><strong>Localization of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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.
How to evaluate a clinical trial

1. Validity of the results
   - Is the design appropriate?
   - Is bias prevented?
   - Is the statistical analysis correct?

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

3. Generalizability
   - Does it apply to my patients?
   - Does it apply to your patients?
Questions

• Who was in the trial?

• What patients should now receive mupirocin/CHX?

• Was the study design ethical?
## Subgroups

<table>
<thead>
<tr>
<th>Subgroup</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic surgery (n=391)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedics (n=172)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal surgery (n=43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery (107)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. aureus</em> HAI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Subgroups

<table>
<thead>
<tr>
<th>Subgroup</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></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>1 (1.6%)</td>
<td>1 (2.2%)</td>
<td>0.73 (0.04-11.92)</td>
</tr>
<tr>
<td>Cardiothoracic surgery (n=391)</td>
<td>220</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>3 (1.4%)</td>
<td>15 (8.8%)</td>
<td>0.15 (0.04-0.51)</td>
</tr>
<tr>
<td>Orthopedics (n=172)</td>
<td>85</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>1 (1.2%)</td>
<td>4 (4.6%)</td>
<td>0.25 (0.03-2.26)</td>
</tr>
<tr>
<td>Vascular surgery (n=95)</td>
<td>53</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>7 (13.2%)</td>
<td>6 (14.3%)</td>
<td>0.91 (0.28-2.96)</td>
</tr>
<tr>
<td>Gastrointestinal surgery (n=43)</td>
<td>22</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>2 (9.1%)</td>
<td>3 (14.3%)</td>
<td>0.60 (0.09-4.01)</td>
</tr>
<tr>
<td>General surgery (107)</td>
<td>61</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>S. aureus HAI</td>
<td>3 (4.9%)</td>
<td>3 (6.5%)</td>
<td>0.74 (0.14-3.85)</td>
</tr>
</tbody>
</table>
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 are considered equally effective, at least according to Dutch guidelines.
  – Beta-lactam monotherapy
  – Beta-lactam + macrolide combination therapy
  – Fluoroquinolone monotherapy

• Blinding is possible, but difficult.
How would you design a RCT comparing beta-lactam monotherapy to fluoroquinolones

- Who should be eligible?
- When to randomize?
- What endpoint?
Challenges in study design

• How to avoid the effects of pre-randomization antibiotics in the ER?

• How to maximize patient enrolment?

• How to avoid bias in endpoint detection?

• How to avoid the possibility of worse clinical outcome (while realizing more “appropriate” antibiotic use)?
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 realizing more “appropriate” antibiotic use)?
  – Use a non-inferiority design
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 J.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluymans, M.D., Ph.D., Wim C. Boersma, M.D., Ph.D., Clara J. Compaijen, 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*
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) +</td>
<td>• Levofloxacin</td>
</tr>
<tr>
<td>• Amoxiclav</td>
<td></td>
<td>• Moxifloxacin</td>
</tr>
<tr>
<td>• 2nd &amp; 3rd gen. cephalosporins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment strategy comparison

- 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

- Deviation for medical reason allowed

- Patient inclusion irrespective of antibiotic treatment
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>BL (n=656)</th>
<th>BLM (n=739)</th>
<th>FQL (n=888)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> *</td>
<td>67.5 (15.5)</td>
<td>67.8 (15.7)</td>
<td>67.2 (15.9)</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>381 (58.1%)</td>
<td>431 (58.3%)</td>
<td>505 (56.9%)</td>
</tr>
<tr>
<td><strong>Hospitalised last year</strong></td>
<td>271 (41.5%)</td>
<td>298 (41.3%)</td>
<td>351 (39.8%)</td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>153 (23.3%)</td>
<td>154 (20.8%)</td>
<td>172 (19.4%)</td>
</tr>
<tr>
<td><strong>COPD or Asthma</strong></td>
<td>260 (39.6%)</td>
<td>281 (38.0%)</td>
<td>377 (42.5%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>118 (18.0%)</td>
<td>101 (13.7%)</td>
<td>161 (18.1%)</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>106 (16.2%)</td>
<td>124 (16.8%)</td>
<td>151 (17.0%)</td>
</tr>
<tr>
<td><strong>Immunosuppressive therapy</strong></td>
<td>59 (9.0%)</td>
<td>57 (7.7%)</td>
<td>93 (10.5%)</td>
</tr>
<tr>
<td><strong>PSI score</strong> *</td>
<td>84.6 (29.0)</td>
<td>84.8 (27.8)</td>
<td>85.4 (28.5)</td>
</tr>
<tr>
<td><strong>CURB-65 score ^</strong></td>
<td>1 (1;2)</td>
<td>1 (1;2)</td>
<td>1 (1;2)</td>
</tr>
<tr>
<td><strong>Radiologically confirmed CAP</strong></td>
<td>506 (77.1%)</td>
<td>566 (76.6%)</td>
<td>665 (74.9%)</td>
</tr>
</tbody>
</table>

Legend:  * Mean (SD)  ^ Median (IQR)
## Pathogens in X-ray proven CAP

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>BL proven</th>
<th>BL possible</th>
<th>BLM proven</th>
<th>BLM possible</th>
<th>FQL proven</th>
<th>FQL possible</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>60 (11.9%)</td>
<td>16 (3.2%)</td>
<td>77 (13.6%)</td>
<td>15 (2.7%)</td>
<td>94 (14.1%)</td>
<td>20 (3.0%)</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>1 (0.2%)</td>
<td>37 (7.3%)</td>
<td>3 (0.5%)</td>
<td>45 (8.0%)</td>
<td>2 (0.3%)</td>
<td>40 (6.0%)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>-</td>
<td>6 (1.2%)</td>
<td>11 (1.9%)</td>
<td>-</td>
<td>7 (1.1%)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2 (0.4%)</td>
<td>15 (3.0%)</td>
<td>2 (0.4%)</td>
<td>17 (3.0%)</td>
<td>4 (0.6%)</td>
<td>15 (2.3%)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>1 (0.2%)</td>
<td>15 (3.0%)</td>
<td>5 (0.9%)</td>
<td>17 (3.0%)</td>
<td>3 (0.5%)</td>
<td>7 (1.1%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>-</td>
<td>4 (0.8%)</td>
<td>1 (0.2%)</td>
<td>5 (0.9%)</td>
<td>-</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>-</td>
<td>11 (2.2%)</td>
<td>-</td>
<td>16 (2.8%)</td>
<td>-</td>
<td>8 (1.2%)</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>6 (1.2%)</td>
<td>-</td>
<td>7 (1.2%)</td>
<td>-</td>
<td>2 (0.3%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>-</td>
<td>7 (1.4%)</td>
<td>-</td>
<td>2 (0.4%)</td>
<td>-</td>
<td>12 (1.8%)</td>
</tr>
<tr>
<td>Other pathogens</td>
<td>4 (0.8%)</td>
<td>46 (9.1%)</td>
<td>4 (0.7%)</td>
<td>61 (10.8%)</td>
<td>11 (1.7%)</td>
<td>48 (7.2%)</td>
</tr>
<tr>
<td>No Pathogen</td>
<td>323 (63.8%)</td>
<td>342 (60.4%)</td>
<td>436 (65.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Protocol adherence (n=888) 

Non-adherence: 46 (7.0%) 
Protocol adherence: 610 (93.0%) 
Treated per protocol: 468 (71.3%) 

Protocol adherent deviations: 
- Suspected pathogen: 56 (8.5%) 
- Relating to pre-hospital antibiotics: 27 (4.1%) 
- Contraindication: 21 (3.2%) 
- Known colonization: 17 (2.6%) 
- Other reasons: 22 (3.4%) 

Beta-lactam monotherapy period 

Beta-lactam + macrolide period 

Fluoroquinolone monotherapy period
Primary outcome: day 90 mortality
Intention-to-treat analysis (ITT)

Survival curve

Risk difference

BL:
9.0% (n=59)

BLM:
11.1% (n=82)

FQL:
8.8% (n=78)

Adjusted Crude Risk difference Favors Beta-lactam

Favors Other Strategy

Days since admission

Crude
## Primary outcome: risk difference day 90 mortality

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BLM</th>
<th>FOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT crude</td>
<td>2279</td>
<td>2.3% (-0.2%;5.0%)</td>
<td>-0.2% (-2.5%;2.4%)</td>
</tr>
<tr>
<td>ITT adjusted</td>
<td>2279</td>
<td>1.9% (-0.6%;4.4%)</td>
<td>-0.6% (-2.8%;1.9%)</td>
</tr>
<tr>
<td>AA crude</td>
<td>1717</td>
<td>1.3% (-1.2%;4.8%)</td>
<td>-1.7% (-4.1%;1.1%)</td>
</tr>
<tr>
<td>AA adjusted</td>
<td>1717</td>
<td>2.1% (-0.5%;5.0%)</td>
<td>-1.4% (-2.7%;2.2%)</td>
</tr>
<tr>
<td><strong>Radiologically proven CAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT crude</td>
<td>1733</td>
<td>2.9% (0.0%;6.1%)</td>
<td>-0.1% (-2.9%;2.8%)</td>
</tr>
<tr>
<td>ITT adjusted</td>
<td>1733</td>
<td>2.5% (-0.6%;5.2%)</td>
<td>-0.7% (-3.4%;1.8%)</td>
</tr>
<tr>
<td>AA crude</td>
<td>1309</td>
<td>1.8% (-1.6%;5.7%)</td>
<td>-2.2% (-5.4%;0.9%)</td>
</tr>
<tr>
<td>AA adjusted</td>
<td>1309</td>
<td>3.0% (-0.3%;6.2%)</td>
<td>-0.5% (-3.5%;2.4%)</td>
</tr>
</tbody>
</table>

ITT intention-to-treat, AA antibiotic adherent
How to evaluate a clinical trial

1. Validity of the results
   - Is the design appropriate?  
   - 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?  
   - Does it apply to your patients?
Questions

• Who was in the trial?

• What patients should now receive beta-lactam monotherapy?

• Were the ethical regulations ethical?
Flowchart

3,325 eligible patients

Beta-lactam
993 eligible patients

337 (34.0%) not included
Reason for non-inclusion:
- Refused 134 (13.5%)
- Discharge before consent 96 (9.7%)
- Unable to give consent 88 (8.9%)
- Unknown reason 19 (1.9%)

656 included patients
2 missing primary outcome

Beta-lactam / macrolide
1,055 eligible patients

316 (30.0%) not included
Reason for non-inclusion:
- Refused 78 (7.4%)
- Discharge before consent 123 (12%)
- Unable to give consent 80 (7.6%)
- Unknown reason 35 (3.3%)

739 included patients
1 missing primary outcome

Fluoroquinolone
1,277 eligible patients

389 (30.5%) not included
Reason for non-inclusion:
- Refused 133 (10.4%)
- Discharge before consent 98 (7.7%)
- Unable to give consent 130 (10.2%)
- Unknown reason 28 (2.2%)

888 included patients
1 missing primary outcome
Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Claudine Angela Blum, MD, Nicole Nigro, MD, Matthias Briel, MD, Philipp Schuetz, MD, Elke Ullmer, MD, Isabelle Suter-Widmer, MD, Bettina Winzeler, MD, Roland Bingisser, MD, Hanno Esaesser, MD, Daniel Drozda, MD, Birsen Arici, MD, Sandrine Andrea Unwyler, MD, Julie Refardi, MD, Philip Tarr, MD, Sebastian Wirz, MD, Robert Thomann, MD, Christine Baumgartner, MD, Hervé Duplain, MD, Dieter Burki, MD, Prof Werner Zimmerli, MD, Prof Nicolas Rodondi, MD, Prof Beat Mueller, MD, Prof Mirjam Christ-Crain, MD

Interpretation
Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability without an increase in complications. This finding is relevant from a patient perspective and an important determinant of hospital costs and efficiency.

Wouldn’t it be great to immediately include this intervention in your study, if you just started a study with another intervention in the same domain?
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.
Domain and challenges

- 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:
  – Using Response-adaptive randomization (RAR)
• Embedded:
  – Nested in daily clinical care (point-of-care randomization)
• Multifactorial:
  – Testing multiple interventions alone and in combination
• Adaptive
  – Option to adapt trial based on prespecified rules
• Platform
  – Focus on disease instead of focus on treatment
“Smarter” trial design

• During trial design, there is great uncertainty
  – Optimal dose, duration, target population, etc.
• Traditional design requires all parameters fixed up front
  – Increased risk of failed trial, unnecessary patient exposure to harm, etc.
• During trial, patients are enrolled and information accumulates
  – Reduces uncertainty.
• Adaptive trials take advantage of accumulating data
  – Allow modification of trial parameters.
**Trial adaptations**

- **Pre-planned**
  - Possible adaptations are anticipated and defined a priori.
- **Well-defined**
  - Explicit rules and algorithms for any change.
- **Limited to key parameters**
- **Statistically valid**
  - Requires pre-trial estimation of statistical inference.
- Generally, statistical inference estimated by Bayesian statistics.
Antibiotics  

Corticosteroids  

Ventilation strategy

Randomization module

Statistical Model

Data Base

Domain 1  Domain 2  Domain 3

Data
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
2. Number of treatments

- "drop-the-loser"/"pick-the-winner" design
  - To select best treatment option with least possible amount of patients;
  - Pre-specified rules to determine superiority/inferiority.

- Adding of new treatment(s) to comparison
  - Add factor: new (single) treatment option added to existing comparison.
  - Add domain: set of new treatments added to trial (usually in factorial design).
Trial Evolution: Drop Factor

Domain 1  Domain 2  Domain 3

Randomization module

Statistical Model

Data

Data Base
Trial Cartoon: Add Factor

Domain 1  Domain 2  Domain 3

Data Base

Randomization scheme

Statistical Model

Data Base
Trial Evolution: Add Domain

Randomization module  →  Statistical Model  →  Data  →  Data Base

Domain 1  Domain 2  Domain 3  Domain 4

- Domain 1
- Domain 2
- Domain 3
- Domain 4

Data Base

ESCMID Online Lecture Library © by author
Practical issues

- Difficulties of adaptive trial design:
  - Pre-planning of adaptations
  - Developing starting/stopping rules
  - Extensive trial simulations

- Conduct of actual trial **not** that different from traditional RCT
  - Screen and enroll eligible patients
  - Obtain informed consent
  - Deliver intervention(s)
  - Data collection
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.