Challenges in data collection for HABP/VABP trials:
Investigator’s Perspective

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Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
  - Expected complications/abnormalities
  - Rapid monitoring of therapeutic interventions
  - Excess of testing
16 episodes of hypokalemia, 7 episodes of hyperchloremia
Sepsis with DKA

Bedside Glucose

New VAP
Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
- Esoteric testing – external EKG analysis
  - Short term, no-cost lease agreement
  - Biomedical clearance
  - Collection of additional concomitant meds
  - Investigator review and sign-offs
Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

A Cardiovascular Death

Entire 10 days: Hazard ratio, 1.86 (95% CI, 1.27–2.73)  
\( P = 0.002 \)

Days 1–5:  
Hazard ratio, 2.88  
(95% CI, 1.79–4.63)  
\( P < 0.001 \)

Days 6–10:  
Hazard ratio, 0.88  
(95% CI, 0.43–1.80)  
\( P = 0.72 \)
Azithromycin and the Risk of Cardiovascular Death

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A Cardiovascular Death

Entire 10 days: Hazard ratio, 1.86 (95% CI, 1.27–2.69); P=0.002

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Azithromycin (N=1,102,419)</th>
<th>Penicillin V (N=7,364,292)</th>
<th>Rate Ratio (95% CI)*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>no./1000 patient-yr</td>
<td>no. of events</td>
<td>no./1000 patient-yr</td>
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<td>Primary analysis</td>
<td>17</td>
<td>1.1</td>
<td>146</td>
<td>1.5</td>
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<td>Subgroup analysis</td>
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<tr>
<td>Sex</td>
<td></td>
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<td>Male</td>
<td>9</td>
<td>1.7</td>
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<td>Female</td>
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<tr>
<td>Age</td>
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<tr>
<td>18–44 yr</td>
<td>3</td>
<td>0.3</td>
<td>17</td>
<td>0.3</td>
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<tr>
<td>45–64 yr</td>
<td>14</td>
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<td>129</td>
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<tr>
<td>History of cardiovascular disease‡</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>10</td>
<td>9.7</td>
<td>62</td>
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<tr>
<td>No</td>
<td>7</td>
<td>0.5</td>
<td>84</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Challenges in data collection for HABP/VABP trials

- Excessive amount of irrelevant data collection
- ICU is unique environment
- Esoteric testing – external EKG analysis

- Excessive regulatory documentation
  - Lot number, expiration date, signature of pharmacy preparer and saved vials/infusion bags for FDA-approved drugs taken from hospital stock
  - Training in general and drug-specific GCP for all RNs who may potentially infuse study drug

- Inadequate HIPPA standards
Clinical Response in Carbapenem VAP Trial

Kollef, Crit Care, 2012

Doripenem overall clinical cure rate difference was -11.2%, 95% CI of difference -26.3 to 3.8%
Pseudomonas Pneumonia Cases

\[ p = 0.04 \]
Mortality: 0% imipenem vs. 35.3% doripenem
95% CI of difference: 12.6\% to 58.0\%

N = 274 Overall
Dori = 115
Imi = 112
Poor GCP = 41

Pseudomonas
N = 27
Dori = 17
Imi = 10

Kollef, Crit Care, 2012
Results

- **Excess time = excess cost**
- **Fatigue = loss of sites/patients**
  - Investigator/ Research coordinator fatigue
  - Monitor fatigue = lose the forest for the trees
- **Audit risk**
- **No clear patient benefit**
  - ? unexpected side effects detected by extensive data collection in Phase III trials
  - Most unusual side effects detected by post marketing surveillance
Humanity has but three great enemies: Fever, famine, and war.
Of these, by far the greatest,
By far the most terrible, is fever.

Sir William Osler