Statistical Considerations in Using Meta-analysis for Regulatory Decision Making for Medical Devices

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Device Validation

- Different stages of medical product development
  - Exploratory stage (development)
  - Pivotal stage (validation)
  - Post-market stage

- Device validation
  - Pivotal clinical studies
    - Prospective study: subjects prospectively enrolled
    - Retrospective study: subject samples retrospectively obtained with a prospective plan
  - Systematic review with meta-analysis
    - Quantitatively combine and integrate comparable studies and trials through a systematical review.
Objective Performance Criteria (OPC) and Performance Goals (PG)

- Design Considerations for Pivotal Clinical Investigations for Medical Devices
  - An OPC needs to be carefully constructed from a prior meta-analytic review of all relevant sources, and a subject-level meta-analysis is preferred.

- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
  - From a sufficiently relevant and reliable observational data source, a PG can be constructed using appropriate statistical methods, such as a subject-level meta-analysis.
Benefits and Challenges of using Meta-analysis

- **Benefits in using Meta-analysis**
  - Better precision of pooled estimate of the effect than from a single study
  - Allow an examination of the existence and the causes of heterogeneity

- **Challenges in using Meta-analysis**
  - Quality assessment
  - Selection bias, publication bias
  - Heterogeneity across studies
  - Aggregation bias (summary level data vs. individual patient data)
VIDAS BRAHMS Procalcitonin (PCT) Assay

- To help clinicians better predict a patient’s risk of mortality or becoming sicker due to sepsis.
- To use PCT as a biomarker to help making antibiotic management decisions (initiation/cessation) in patients with lower respiratory tract infections and sepsis.
- Panel on 11/10/2016; Cleared in Feb, 2017
- Systematic literature reviews and meta-analyses of published randomized control trials were conducted.

510k summary https://www.accessdata.fda.gov/cdrh_docs/reviews/K162827.pdf
Panel meeting material
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm515517.htm
VIDAS BRAHMS Procalcitonin (PCT) Assay

- Algorithm (Device):

<table>
<thead>
<tr>
<th>LRTI AB initiation</th>
<th>Strongly discouraged</th>
<th>Discouraged</th>
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<tbody>
<tr>
<td>&lt;0.10</td>
<td>0.10-0.25</td>
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</table>

LRTI AB cessation: PCT ≤ 0.25 ng/mL or decrease > 80%
Sepsis AB cessation: PCT ≤ 0.5 ng/mL or decrease > 80%

- 2 groups: PCT-guided therapy vs. standard therapy
- Endpoints: AB initiation, AB duration, mortality, complications, length of hospital stay
- Hypothesis: Lower AB use in PCT guidance group + no significant increase in safety endpoints
Assessment of Study Quality

- Conduct quality assessment before any quantitative analysis.
- The quality assessment of the literature review is crucial to meta-analysis because the validity and reliability of meta-analyses depend on the quality of data extracted from the studies.
  - Cochrane Risk of Bias Assessment tool (Higgins and Green, 2011)
  - Downs and Black instrument (Downs and Black, 1998)
  - Chalmers quality scale, etc.
Assessment of Study Quality

- Treatment assignment mechanism (RCT, non-RCT or single arm)
- Masking (blinding of treatment assignment to physicians, patients, and evaluators of outcome)
- Prospective data or retrospective data
- Pre-specified protocol and sample size
- Cross-over, drop-out, missing data
- Generalizability of study results to current US medical practice, etc.

→ Quality score: selection, interpretation, weighting factors in the effect estimation.
## Bias Assessment for LRTI (PCT test)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
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</thead>
<tbody>
<tr>
<td>Branche, 2015</td>
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<td>Christ-Crain, 2004</td>
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<td>Schuetz, 2009</td>
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<tr>
<td>Verduri, 2015</td>
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<td>?</td>
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</tbody>
</table>

**Legend:**
- **Low risk** (green)
- **unclear** (yellow)
- **high risk** (red)

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# Generalizability using Non-US Studies

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Disease type</th>
<th>Selected RCT Studies</th>
<th>Sample size</th>
<th>US sites</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>PCT</td>
<td>Cntrl</td>
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<td>Study-Level</td>
<td>LRTI</td>
<td>11 RCTs</td>
<td>2040</td>
<td>2050</td>
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<td>Sepsis</td>
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<td>1735</td>
<td>1754</td>
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<tr>
<td>Patient-Level</td>
<td>LRTI</td>
<td>13 RCTs</td>
<td>1536</td>
<td>1606</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>5 RCTs</td>
<td>287</td>
<td>311</td>
</tr>
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</table>
Selection Bias

- Publication bias: studies with insignificant results or poor outcomes are typically not published.

- Approaches to minimize the selection bias
  - Two reviewers perform the literature search and data extraction independently.
  - Redact the study outcomes from abstract, text, etc.
  - Mask author names, affiliations, journal name, etc.
  - Pre-define the inclusion and exclusion criteria
    - E.g. Randomized control trial
A descriptive approach for evaluating if selection bias is present (Sterne and Harbord, 2004).

- X-axis: treatment effect
- Y-axis: precision of effect size estimate
Funnel Plots (PCT test)

AB initiation, LRTI

Mortality, LRTI

Mortality, sepsis

- Studies with significant findings tend to be published.
- Visual inspection indicates some degree of asymmetry.
- Difficult to interpret due to small number of studies.
Heterogeneity Across Studies

- Heterogeneity is inevitable in a meta-analysis (Higgins 2003).

- Clinical heterogeneity
  - Study populations (enrollment criteria), endpoints, length of follow-up, treatment arm, control arm, available data, device used in studies, etc.

- Statistical heterogeneity
  - exists when the true effects being evaluated differ between studies.

- Cochran’s $\chi^2$ or Q (Higgins and Thompson 2002; 2003)
Forest Plot of OR: Antibiotic Initiation, LRTI

$I^2 = 93.1\%$ AB initiation, LRTI

Figure 7: Antibiotic initiation (fixed effects model)
Different Devices for PCT Measurement

- **LRTI (study level)**
  - 2 out of 11 studies used **VIDAS BRAHMS PCT**
  - 9 out of 11 studies used BRAHMS PCT sensitive Kryptor

- **Sepsis (study level)**
  - 1 out of 10 studies used **VIDAS BRAHMS PCT**
  - 2 out of 10 studies used VIDAS BRAHMS PCT as one of multiple assays
  - 5 out of 10 studies used BRAHMS PCT sensitive Kryptor
  - 2 out of 10 studies used BRAHMS PCT LIA
Different Cutoffs in Guidance Algorithms

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Different Follow-up Times and Rates

- Follow-up time is different across studies: ranges from 5 days, 1 month to 6 months.

- Follow-up rate varied across studies:
  - LRTI: range was 83% to 99% with 1 study unreported
  - Sepsis: range was 67% to 99% with 4 studies unreported
Summary Level analysis (Aggregation Bias)

- Meta-regression using summary level data (aggregate data) can be subject to aggregation bias (ecological fallacy, Berlin et al., 2002).

- The phenomenon that a relationship across studies does not reflect the relationships within studies (Harbord & Higgins, 2008; Higgins, Thompson, Deeks, & Altman, 2002)
Aggregation Bias
Patient Level Analysis

- Individual patient-level data (IPD)
  - Whether patient characteristics are related to treatment/outcome
  - Controlling for the covariate effects (confounding risk factors, baseline characteristics)
- IPD is considered as a gold standard approach
- But NOT a solution
Verification of Meta-analysis

- Compare IPD analysis to the summary-level analysis if possible (Fortin et al, 1995; Olkin and Sampson, 1998)

- Predict the results for the Nth study from a meta-analysis of the first N – 1 studies (Simon, 1999; Pennello and Thompson, *J Biopharmaceutical Statistics*, 2008)
Summary

- An opportunity to combine and integrate comparable studies of the device identified through systematic review.
- Many challenges to be overcome for a meta-analysis result to be interpretable and generalizable.
Acknowledgement

Dr. Gene Pennello, FDA/CDRH
References


References (cont.)


References (cont.)


- FDA guidance: Design Considerations for Pivotal Clinical Investigations for Medical Devices. [https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm](https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm)