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):

LRTI AB initiation	**Strongly discouraged**	**Discouraged**	**Encouraged**	**Strongly encouraged**
	<0.10	**0.10-0.25**	**0.26-0.50**	**>0.50**

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)

Author, year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Branche, 2015	+	-	-	+	+	+
Briel, 2008	+	+	+	?	+	+
Burkhardt, 2010	+	+	+	+	+	+
Christ-Crain, 2004	+	?	-	?	+	+
Christ-Crain, 2006	?	+	-	-	-	+
Corti, 2016	+	+	-	-	+	+
Kristoffersen, 2009	+	+	-	-	+	+
Long, 2011	?	-	-	+	+	+
Schuetz, 2009	+	+	+	?	+	+
Stolz, 2007	?	?	+	+	+	+
Verduri, 2015	+	+	-	-	+	?

Low risk  unclear  high risk 

Generalizability using Non-US Studies

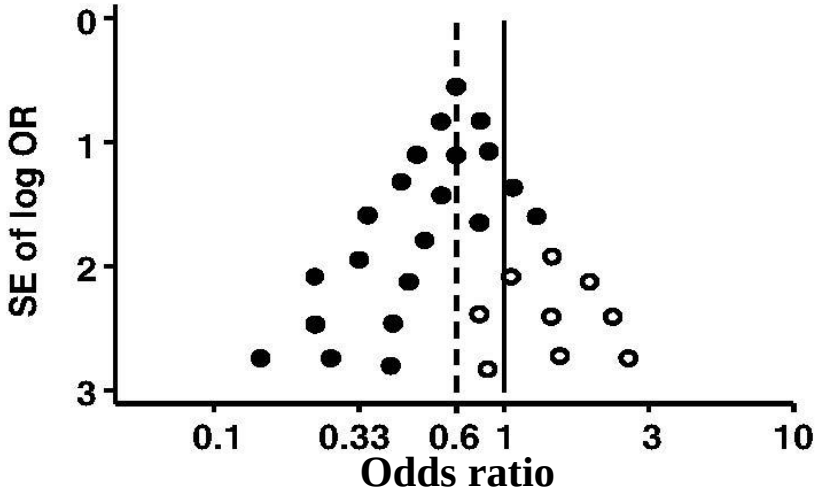
Meta-Analysis	Disease type	Selected RCT Studies	Sample size		US sites
			PCT	Cntrl	
Study-Level	LRTI	11 RCTs	2040	2050	1 (year 2015) PCT: n=151 Cntrl: n=149
	Sepsis	10 RCTs	1735	1754	
Patient-Level	LRTI	13 RCTs	1536	1606	
	Sepsis	5 RCTs	287	311	1 in Stolz 2009

Selection Bias

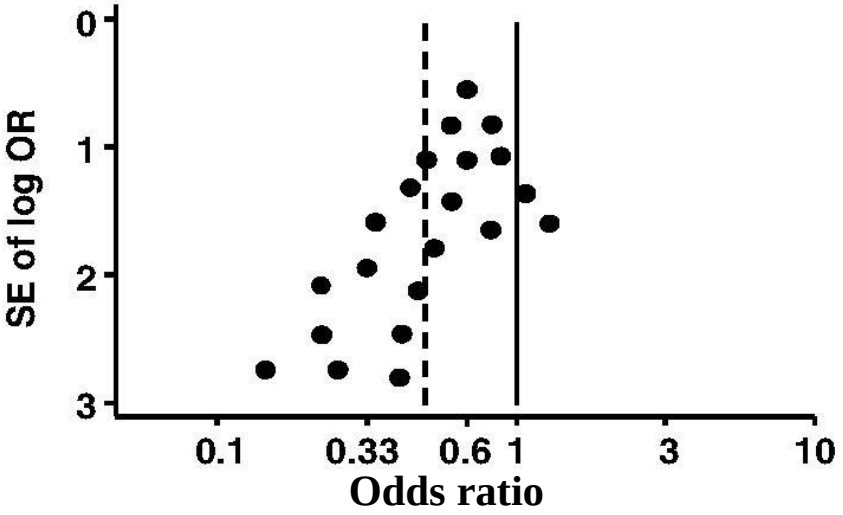
- Publication bias: studies with insignificant results or poor outcomes are typically not published.
- Approaches to minimize the selection bias
  - Two reviewers perform the literature search and data extraction independently.
  - Redact the study outcomes from abstract, text, etc.
  - Mask author names, affiliations, journal name, etc.
  - Pre-define the inclusion and exclusion criteria
    - E.g. Randomized control trial

Funnel Plot

- 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
- Statistical test (Egger et al. 1997; Harbord 2005; Begg & Mazumdar, 1994).

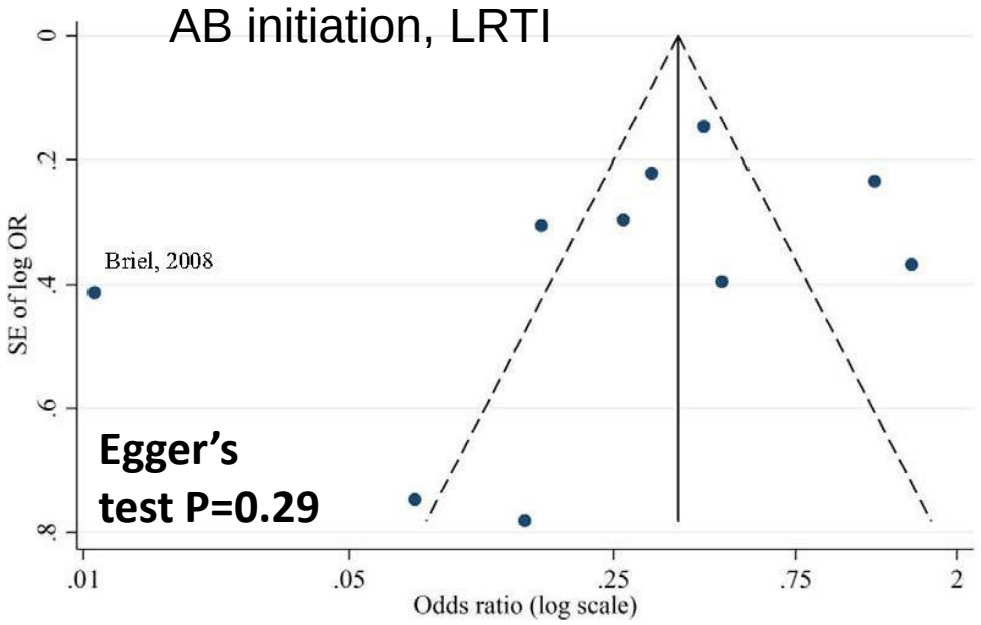


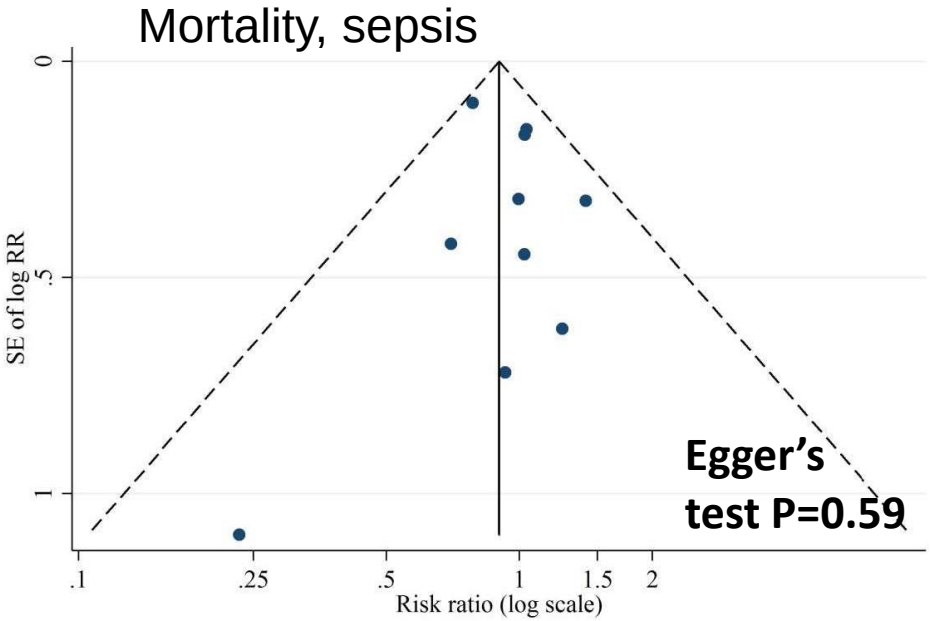
Absence of publication bias

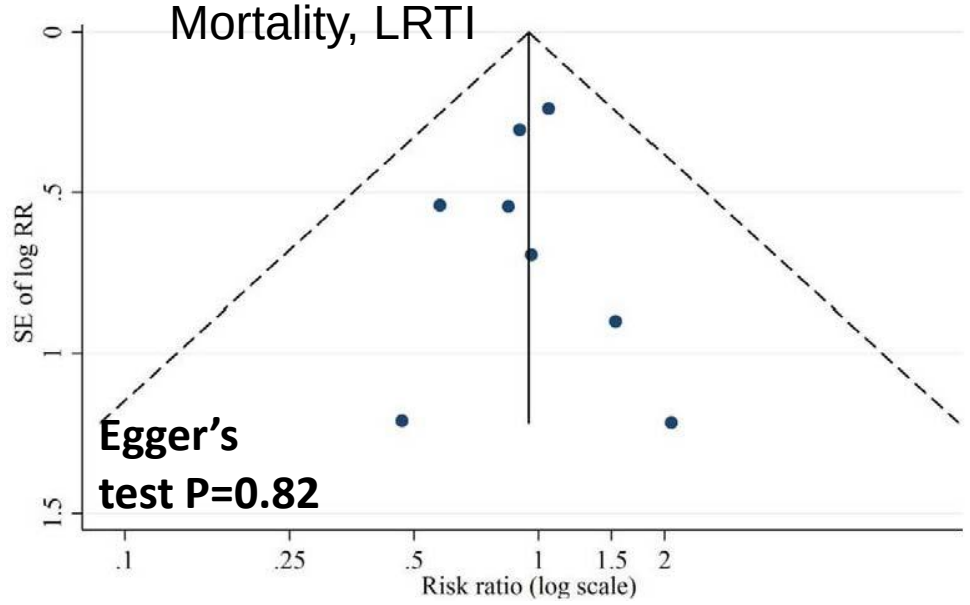


Presence of publication bias

Funnel Plots (PCT test)





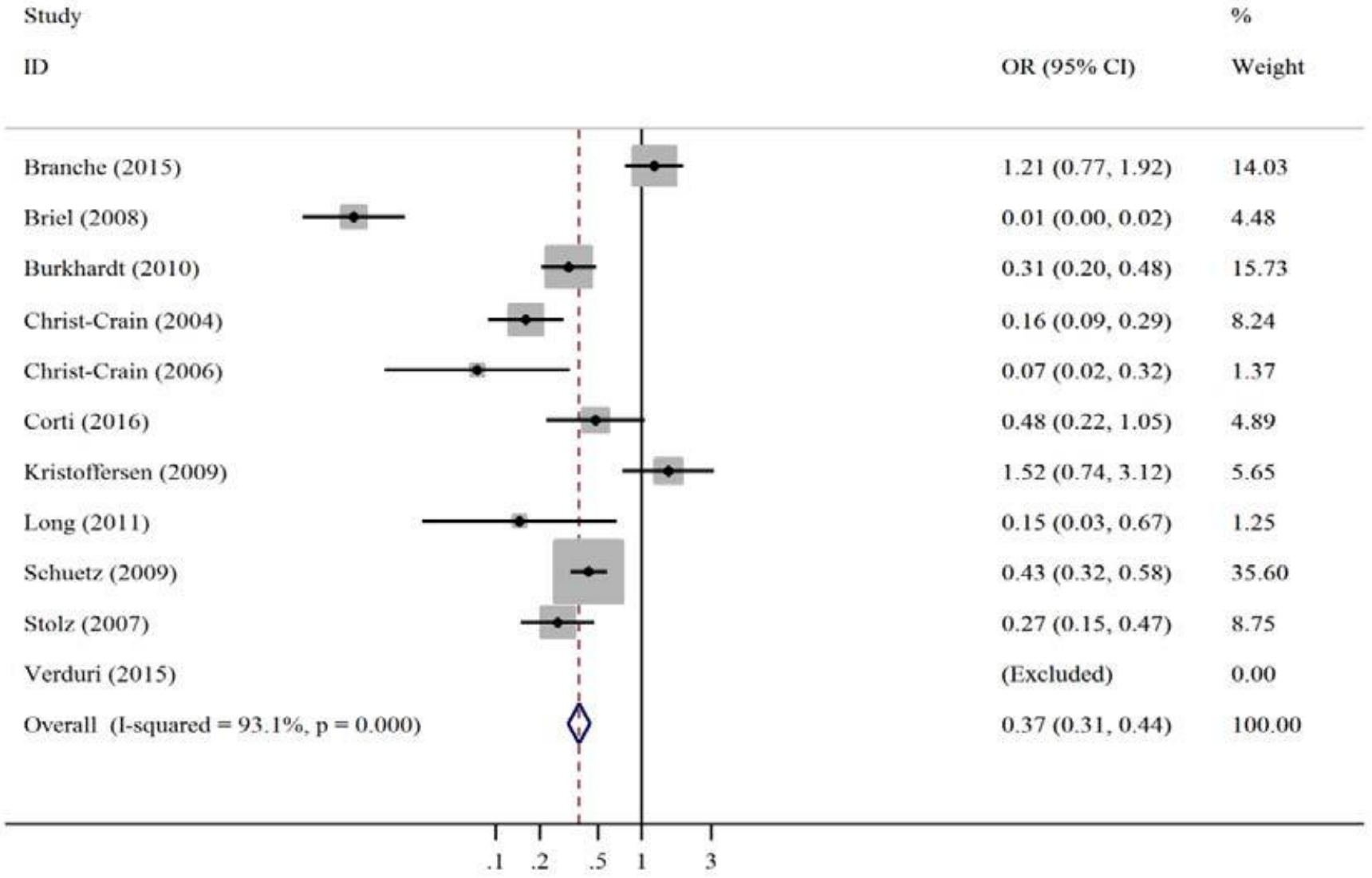


- Studies with significant findings tend to be published.
- Visual inspection indicates some degree of asymmetry.
- Difficult to interpret due to small number of studies.

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 χ^2 or Q (Higgins and Thompson 2002; 2003)

Forest Plot of OR: Antibiotic Initiation, LRTI



CI: confidence interval; OR: odds ratio

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

Algorithm (Device):

LRTI AB initiation	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
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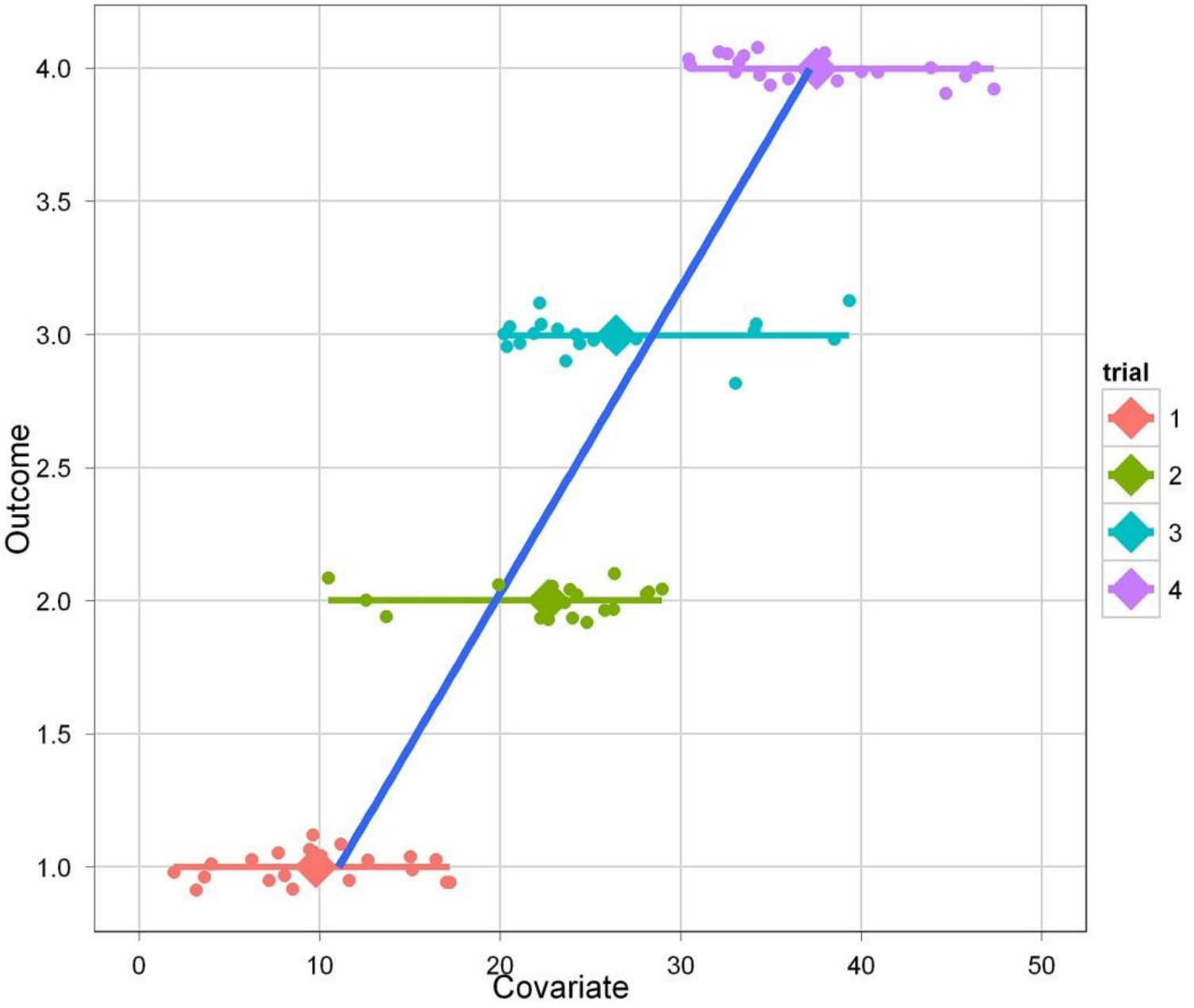
Different Follow-up Times and Rates

- 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

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References

- Sterne, J.A.C. and Harbord, R.M (2004). Funnel plots in meta-analysis, *Stata J.*, Volume 4, Issue 2: 127-141.
- Begg, C. B. and Mazumdar, M. (1994). Operating Characteristics of a Rank Correlation Test for Publication Bias, *Biometrics*, 50, 1088-1101.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.
- Lambert, P.C., Sutton, A.J., Abrams, K.R. and Jones, D.R. (2002). A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *Journal of Clinical Epidemiology*, Volume 55, Issue 1: 86 – 94.
- Higgins JPT, Thompson SG (2004). Controlling the risk of spurious results from meta-regression. *Statistics in Medicine*, 23: 1663-1682.
- Pocock, Assman, Enos, Kasten. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems *Statist. Med*. 2002; 21:2917–2930 (DOI: 10.1002/sim.1296).

References (cont.)

- Senn SJ. Covariate imbalance and random allocation in clinical trials. *Statist. Med*. 1989; 8:467– 475.
- Permutt, T. (2007). A note on stratification in clinical trials. *Drug Information Journal* 41:719–722.
- Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI, Anti-lymphocyte antibody induction therapy study group. 2002. Individual patient-versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Statistics in Medicine 21: 371–387. DOI: 10.1002/sim.1023
- Permutt, T. (2007). A note on stratification in clinical trials. *Drug Information Journal* 41:719–722.
- Simon, R. (1999) Bayesian Design and Analysis of Active Control Clinical Trials. *Biometrics*, Vol. 55, No. 2 , pp. 484-487.
- Pennello, G. and Thompson, L. (2008) Experience with Reviewing Bayesian Medical Device Trials. *Journal of Biopharmaceutical Statistics*. 18:1, 81 – 115.

References (cont.)

- Senn SJ. Covariate imbalance and random allocation in clinical trials. *Statist. Med*. 1989; 8:467– 475.
- Permutt, T. (2007). A note on stratification in clinical trials. *Drug Information Journal* 41:719–722.
- Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI, Anti-lymphocyte antibody induction therapy study group. 2002. Individual patient-versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Statistics in Medicine 21: 371–387. DOI: 10.1002/sim.1023
- Permutt, T. (2007). A note on stratification in clinical trials. *Drug Information Journal* 41:719–722.
- FDA guidance: Design Considerations for Pivotal Clinical Investigations for Medical Devices. https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm
- FDA Draft guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm513027.pdf