Statistical Considerations for Procalcitonin-Guided Evaluation and Management of Lower Respiratory Tract Infections and Sepsis

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Outline

- Evaluation of diagnostic tests
- Meta-analysis hypotheses and results
- Limitations of Meta-analysis
- Study design and analysis considerations
- Conclusion

Evaluation of Diagnostic Devices Fryback-Thornbury Model*

Level	Objective	Study Type**
1	Technical efficacy	Analytical performance
2	Diagnostic accuracy efficacy	Clinical performance
3	Diagnostic thinking efficacy	
4	Therapeutic efficacy	
5	Patient outcome efficacy	Clinical outcome
6	Society efficacy	

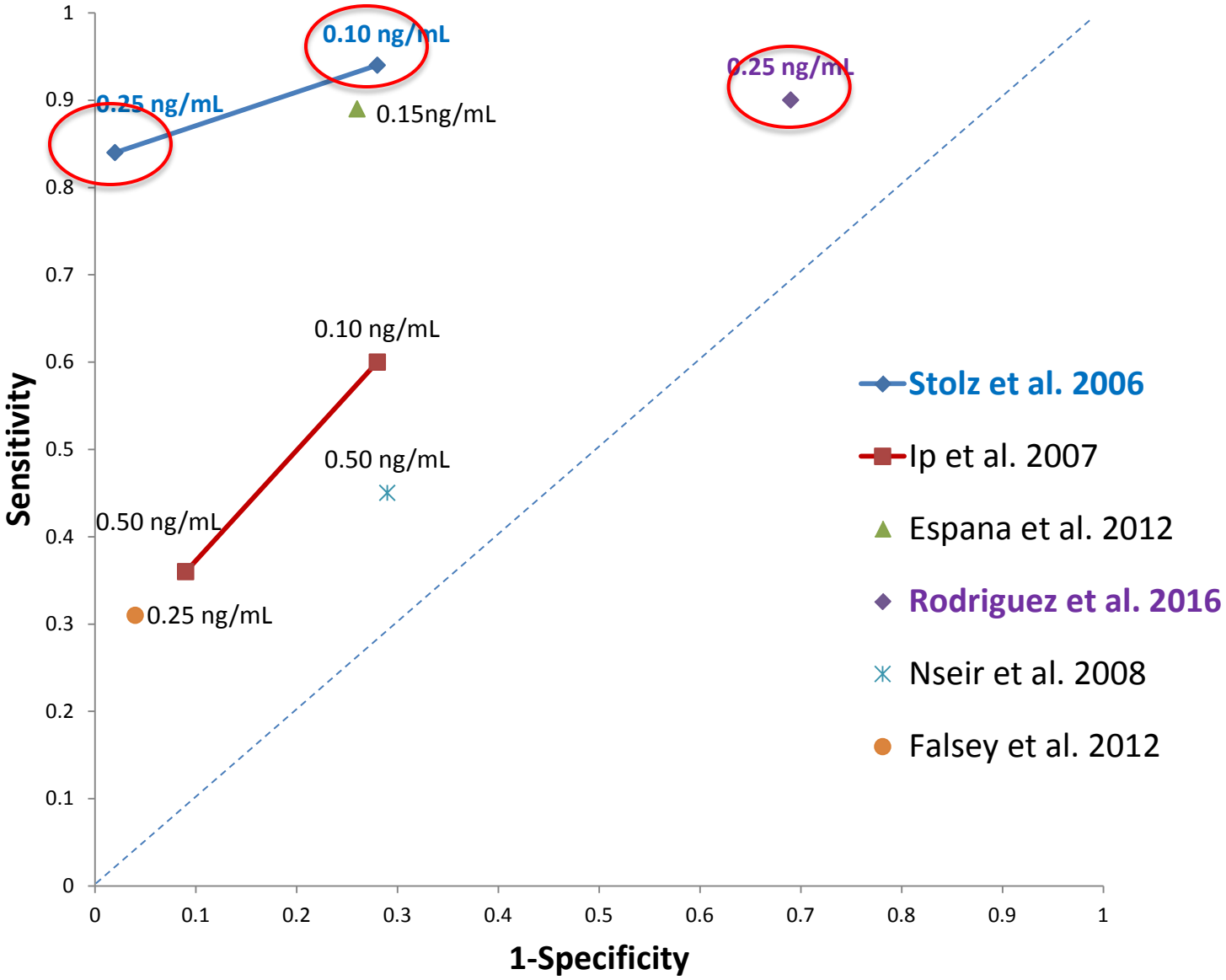
* Fryback DG and Thornbury JR. The Efficacy of Diagnostic Imaging. *Med Decis Making* 1991; 11(2): 88-94.

** FDA CDRH/CBER Guidance. *Design Considerations for Pivotal Clinical Investigations for Medical Devices*, 2013 (Sections 7.7, 8).

Evaluation of Diagnostic Performance of PCT

- Diagnostic accuracy of PCT for bacterial infection can be difficult to assess because of the biological and technological difficulties in identifying the truth.
- Sensitivity, specificity, positive predicted value (PPV) and negative predicted value (NPV) vary greatly in literature.

Heterogeneity in Diagnostic Accuracy Estimates, LRTI



Evaluation of Diagnostic Devices

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- Meta-analysis
- Therapeutic efficacy: Patient management based on diagnostic test result
- Patient outcome efficacy: Clinical outcome improvement

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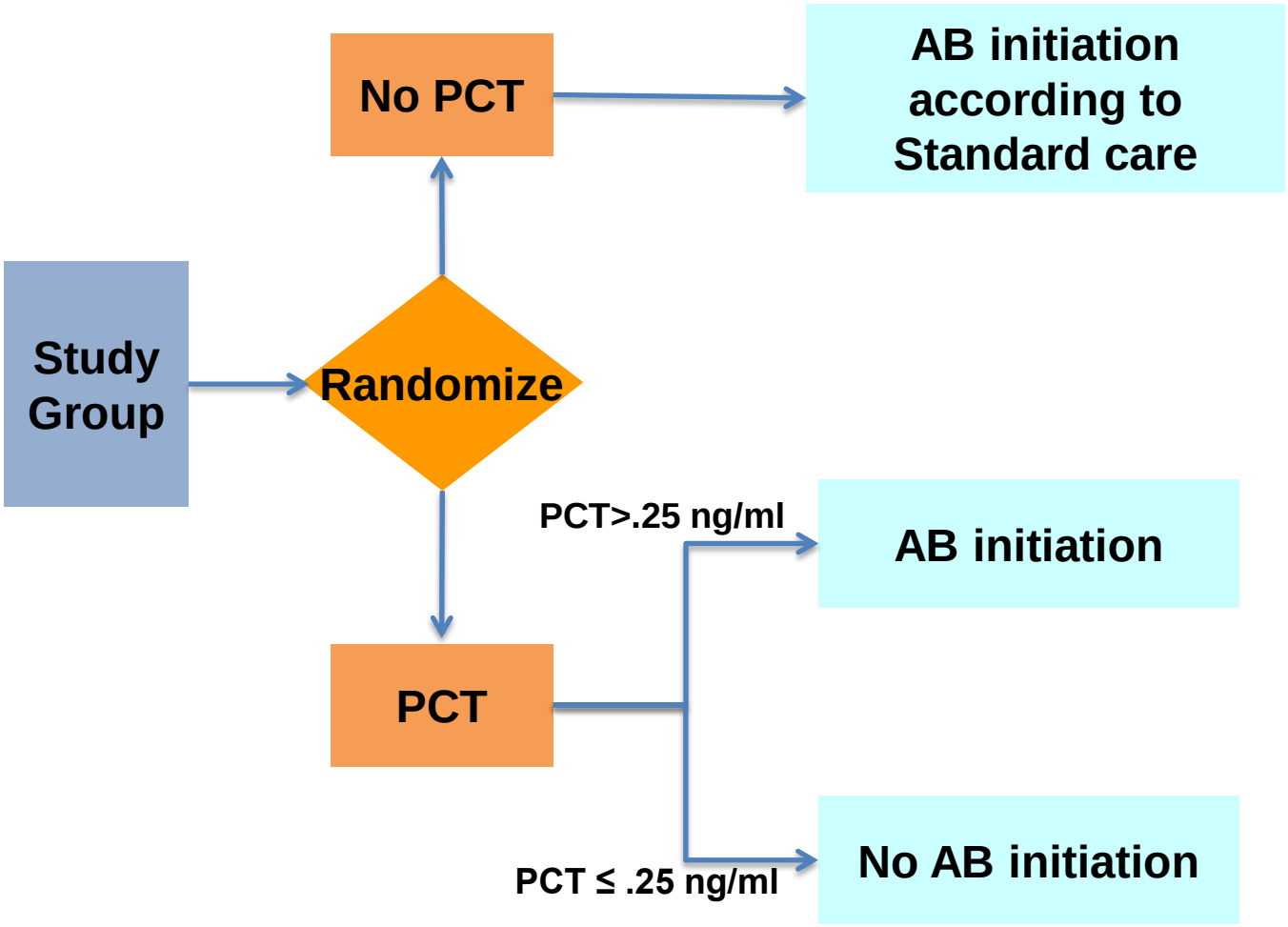
Clinical Outcome Study

- Meta-analysis, compare PCT guidance vs. standard care
- Effectiveness (Therapeutic efficacy, Level 4)
  - Antibiotic (AB) initiation (LRTI)
  - AB duration, exposure
- Safety (Patient outcome efficacy, level 5)
  - All cause mortality at 30 days
  - Complications at 30 days
  - Length of hospital, ICU stay
- Hypothesis
  - Lower AB use in PCT guidance group
  - No success criteria (e.g., non-inferiority) for safety

Meta-analyses

Meta-Analysis	Publication Timeframe	Disease type	Selected RCT Studies	Sample size	
				PCT	Cntrl
Study-Level	January 2004 – May 2016	LRTI	11 RCTs	2040	2050
		Sepsis	10 RCTs	1735	1754
Patient-Level	January 2004 – May 2011 (Based on Schuetz 2012)	LRTI	13 RCTs	1536	1606
		Sepsis	5 RCTs	287	311

Study Design of RCTs in Literature
Marker Strategy Design



Effectiveness endpoints: Significant reduction in AB use

LRTI	PCT group	Control	OR or Diff	p val
Study level	2040	2050		
Initiation, n (%)	pooled from 10 trials		0.26 (0.13, 0.52)	<0.001
Duration median days	pooled from 3 trials		-1.3 (-2.9, 0.4)	0.14
Exposure median days	pooled from 5 trials		-2.8 (-4.6, -1.0)	0.003
Patient level	1536	1606		
Initiation, n (%)	1096(71.4%)	1420(88.4%)	0.27 (0.22, 0.33)	<0.001
Duration median days	7(4,10)	10(7,12)	-2.9 (-3.3, -2.5)	<0.001
Exposure median days	5(0,8)	9(6,12)	-3.6 (-4.0, -3.2)	<0.001

Sepsis	PCT group	Control	OR or Diff	p val
Study level	1375	1754		
Duration median days	pooled from 8 trials		-1.5 (-2.3, -0.7)	<0.001
Patient level	287	311		
Exposure median days	8(5,15)	12(8,18)	-3.2 (-4.3, 2.1)	<0.001

Safety Endpoints: No Significance Observed

LRTI	PCT group	Control	OR or Diff	p val
Study level	2040	2050		
Mortality, n (%)	pooled from 9 trials		0.94 (0.69, 1.28)	0.68
LOH days	pooled from 7 trials		-0.2 (-0.6, 0.3)	0.51
Patient level	1536	1606		
Mortality, n (%)	103(6.7%)	119(7.4%)	0.95 (0.77, 1.16)	0.62
LOH median days	7(0,12)	6(0,13)	-0.2 (-0.9, -0.5)	0.61

Sepsis	PCT group	Control	OR or Diff	p val
Study level	1375	1754		
Mortality, n (%)	pooled from 10 trials		0.90 (0.79, 1.03)	0.11
ICU median days	pooled from 10 trials		-0.8 (-2.5, 0.8)	0.33
Patient level	287	311		
Mortality, n (%)	57(19.9%)	74(23.8%)	0.87 (0.64, 1.18)	0.36
LOH median days	21(11,37)	23(13,38)	-1.4 (-4.4, 1.7)	0.39
ICU median days	12(6, 23)	12(6,22)	1.1 (-1.2, 3.4)	0.37

Subgroup Analyses (Patient-Level)

- Type of LRTI
  - CAP
  - Bronchitis
  - AECOPD
- Setting for LRTI
  - Inpatients
  - Outpatients
- Initial PCT value
  - <0.10, 0.10-0.25, 0.26-0.5, >0.5 for LRTI
  - <0.5, >=0.5, NA for sepsis

Overall Impression

- Meta-analysis was conducted appropriately according to Cochrane Handbook.
- The process of literature search and publication selection appears appropriate.
- The hypotheses and analyses were pre-specified and the statistical analysis plan was followed.
- Bias of meta-analysis was examined through
  - quality assessment of studies
  - examination of publication bias with funnel plots
- Study heterogeneity incorporated into analysis with random effects for studies.

Interpretation of Results

- Effectiveness
  - PCT algorithm is designed to reduce antibiotic initiation, duration, and exposure.
  - Antibiotic use will be reduced if PCT recommendation is followed for some patients.
  - Statistical significance of reduction is not at issue.
  - Magnitude of reduction is important in the evaluation of device clinical significance.
- Safety
  - Patients for whom PCT algorithm recommends same antibiotic use as control arm dilute differences between arms in endpoints (e.g., mortality, length of stay), making the two arms appear more similar.
- Meta-analysis is subject to potential sources of bias.
- Study heterogeneity complicates interpretation.

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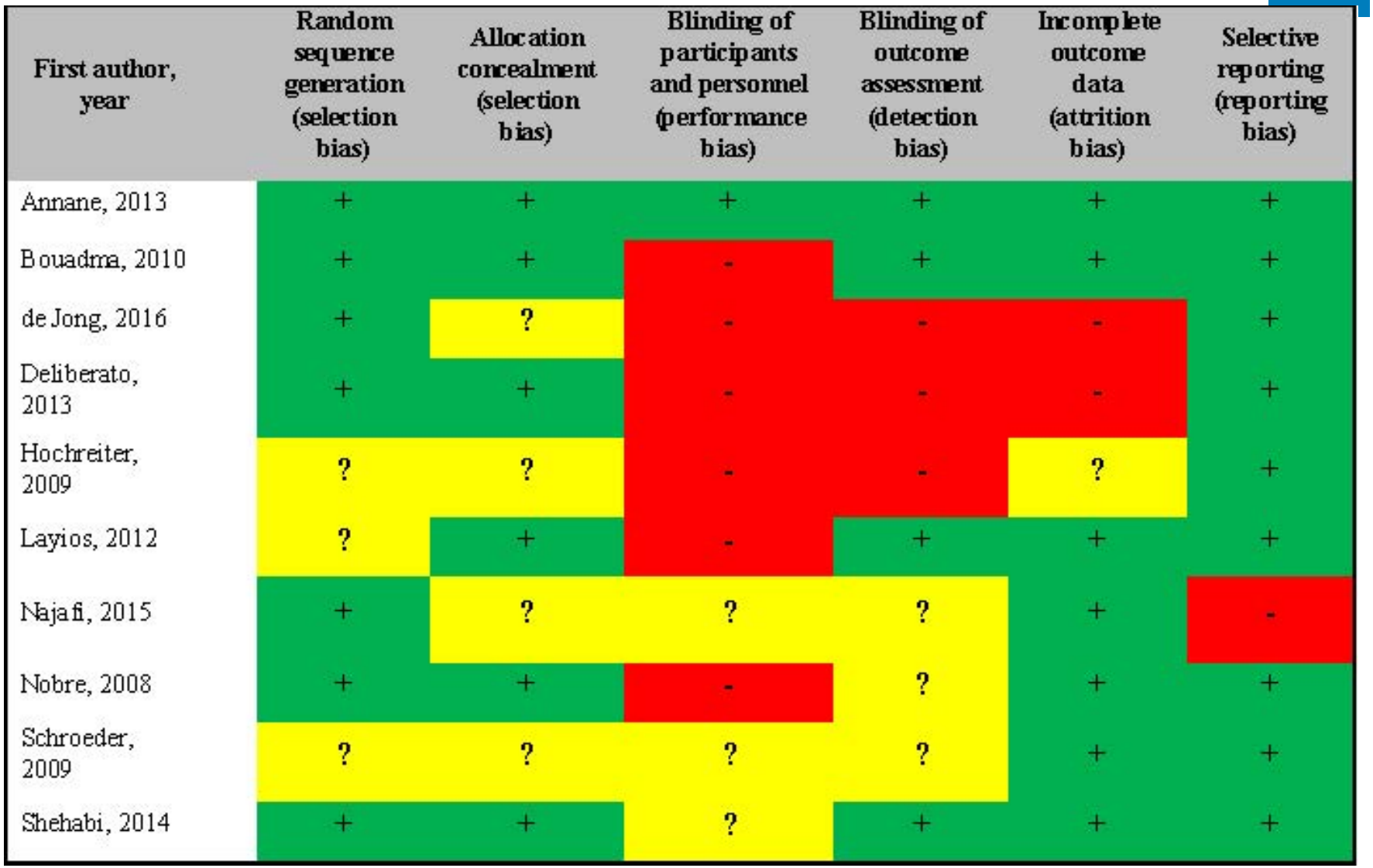
Bias Assessment, LRTI

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

Bias Assessment, Sepsis



First 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)
Annane, 2013	+	+	+	+	+	+
Bouadma, 2010	+	+	-	+	+	+
de Jong, 2016	+	?	-	-	-	+
Deliberato, 2013	+	+	-	-	-	+
Hochreiter, 2009	?	?	-	-	?	+
Layios, 2012	?	+	-	+	+	+
Najafi, 2015	+	?	?	?	+	-
Nobre, 2008	+	+	-	?	+	+
Schroeder, 2009	?	?	?	?	+	+
Shehabi, 2014	+	+	?	+	+	+

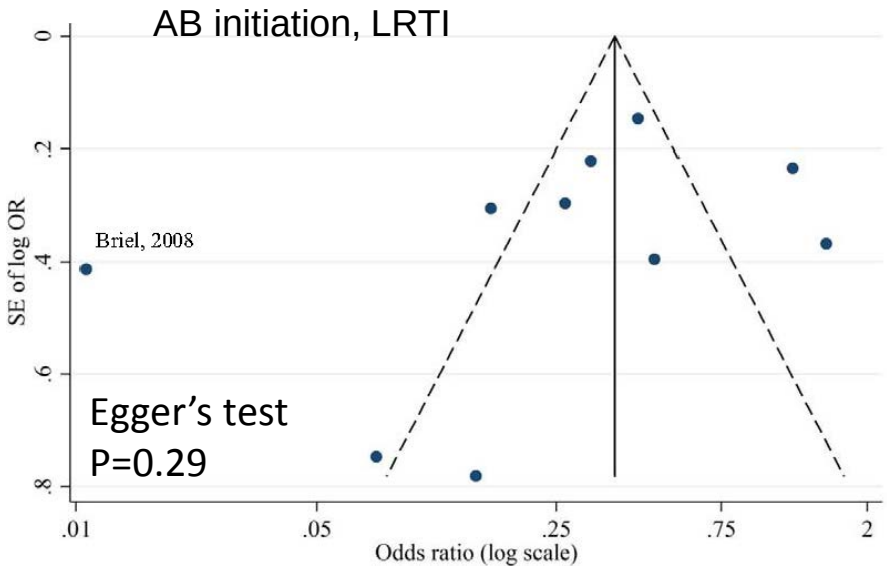
Low risk unclear high risk

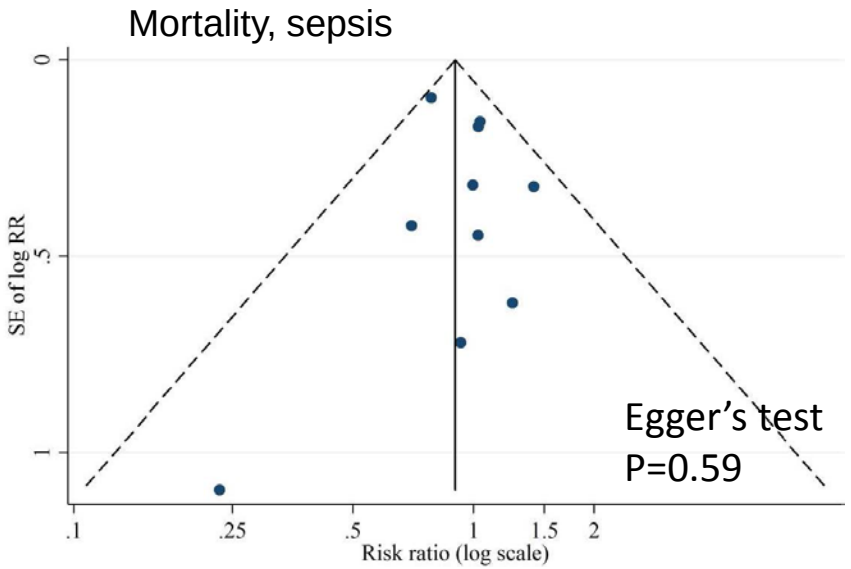
Blinding (Performance Bias)

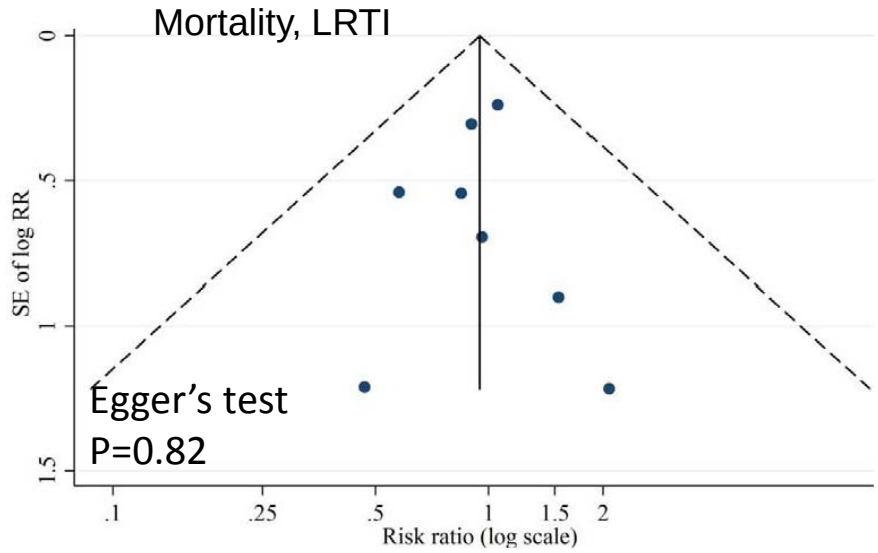
- Lack of blinding of participants and personnel is common across included studies.
- Physicians may consciously or unconsciously manage patients differently in the PCT group than the standard care group.

  →Hawthorne effect

Funnel Plots (Publication Bias)







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

Missing Data (Attrition Bias)

- 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
- In patient-level analysis for safety events (lost to follow-up rate < 10%), patients lost to follow-up were assumed not to have experienced the event.
- There may be other reasons for missing data.

Heterogeneity

- Statistical heterogeneity is inevitable in a meta-analysis (Higgins 2003).
- Measurement of heterogeneity:

$$I^2 = (\frac{Q - df}{Q})^2 \in (0, 100\%)$$

where Q is the chi-squared statistic and df is its degree of freedom.

- Considerable heterogeneity:
  - I^2 =93.1% AB initiation, LRTI
  - I^2 =94.9% AB duration, LRTI
  - I^2 =81.3% AB duration, sepsis
  - I^2 =80.1% ICU stay, sepsis

Different PCT Devices in the Selected Studies

- 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
- LRTI (patient level)
  - 2 out of 13 studies used BRAHMS PCT LIA
  - 10 out of 13 studies used BRAHMS PCT sensitive Kryptor
  - 1 did not report
- Sepsis (patient level)
  - 2 out of 5 studies used BRAHMS PCT LIA
  - 3 out of 5 studies used BRAHMS PCT sensitive Kryptor

Some Discordance Between VIDAS and KRYPTOR

		KRYPTOR					
		≤ 0.10 ng/mL	>0.1 and ≤0.25 ng/mL	> 0.25 and < 0.50 ng/mL	≥ 0.5 and < 2.00 ng/mL	≥ 2.00 ng/mL	TOTAL
VIDAS	≤ 0.10 ng/mL	99	15	0	0	0	114
	> 0.1 and ≤ 0.25 ng/mL	12	19	3	0	0	34
	> 0.25 and < 0.50 ng/mL	0	2	8	0	0	10
	≥ 0.5 and < 2.00 ng/mL	0	0	2	19	0	21
	≥ 2.00 ng/mL	0	0	0	5	19	24
	TOTAL	111	36	13	24	19	203

	Positive Agreement (%)	CI 95%	Negative Agreement (%)	CI 95%
0.10 ng/mL	83.7	74.5 - 90.6	89.2	81.9 - 94.3
0.25 ng/mL	94.6	85.1 - 98.9	98.6	95.2 - 99.8
0.50 ng/mL	100.0	91.8 - 100.0	98.8	95.6 - 99.8
2.00 ng/mL	100.0	82.4 - 100.0	97.3	93.8 - 99.1

Different Algorithm/Thresholds, LRTI AB Initiation

Study	Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged
Bouadma (2010) (P)	< 0.25	0.25 - 0.49	0.5 - 0.99	≥ 1
Branche (2015) (S)	≤ 0.1	0.11 - 0.25	≥0.25 - 0.49	≥ 0.5
Briel (2008) (S)(P)	< 0.1	0.10 - 0.25	> 0.25	-
Burkhardt (2010) (S)(P)	-	< 0.25	≥ 0.25	-
Christ-Crain (2004) (S)(P)	≤ 0.1	0.11 - ≤0.25	0.25 - 0.49	≥ 0.5
Christ-Crain (2006) (S)(P)	< 0.1	0.1 - 0.25	0.25 - 0.5	> 0.5
Corti (2016) (S)	≤ 0.15	0.16 - 0.25	> 0.25	-
Hochreiter (2009) (P)	-	-	-	-
Kristoffersen (2009) (S)(P)	-	< 0.25	0.25 - 0.5	> 0.5
Long (2009) (P)	-	< 0.25	≥ 0.25	-
Long (2011) (S)(P)	< 0.1	0.1 - 0.25	> 0.25	-
Nobre (2007) (P)	-	-	-	-
Schroeder (2009) (P)	-	-	-	-
Schuetz (2009) (S)(P)	< 0.1	0.1 - 0.25	0.26 - 0.5	> 0.5
Stolz (2007) (S)(P)	< 0.1	0.1 - 0.25	> 0.25	-
Verduri (2015) (S)	-	-	-	-
Applicant proposal	**< 0.10**	**0.10 - 0.25**	**0.26 - 0.50**	**> 0.50**

Different Algorithm/Thresholds, LRTI AB Discontinuation

Study	Stop 1	Stop 2
Bouadma (2010) (P)	Refer to initiation cut-offs (≤ 0.49)	decrease by ≥ 80% of the initial PCT level
Branche (2015) (S)	Refer to initiation cut-offs (≤ 0.24)	-
Briel (2008) (S)(P)	≤ 0.25	-
Burkhardt (2010) (S)(P)	-	-
Christ-Crain (2004) (S)(P)	< 0.25	-
Christ-Crain (2006) (S)(P)	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 10 ng/mL, use decrease by > 90% of the initial PCT
Corti (2016) (S)	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 5 ng/mL, use decrease by > 80% of the peak PCT
Hochreiter (2009) (P)	< 1	≥ 65-75% change from initial PCT level AND current PCT level > 1 ng/mL
Kristoffersen (2009) (S)(P)	< 0.25	-
Long (2009) (P)	Refer to initiation cut-offs (< 0.25)	-
Long (2011) (S)(P)	Refer to initiation cut-offs (< 0.25)	-
Nobre (2007) (P)	< 0.25 ng/mL if initial PCT level ≥ 1, or <0.1 ng/mL if initial PCT level <1	> 90% change if initial PCT ≥ 1 ng/mL
Schroeder (2009) (P)	≤ 1	≥ 65-75% change from initial PCT level
Schuetz (2009) (S)(P)	Refer to initiation cut-offs (≤ 0.25)	If PCT(on admission) > 10 ng/mL, use decrease by ≥ 80% of the initial PCT
Stolz (2007) (S)(P)	-	-
Verduri (2015) (S)	< 0.1 ng/mL or < 0.25 ng/mL for patients without severe disease	-
Applicant proposal	**PCT level ≤ 0.25 ng/mL or decrease > 80%**	

Different algorithm/cutoffs for Sepsis AB Discontinuation

Study	Antibiotics stop (option 1)	Antibiotics stop (option 2)	Antibiotics stop (option 3)
Annane (2013) (S)	< 0.5	-	-
Bouadma (2010) (S)(P)	< 0.5	-	> 80% decrease from peak PCT level
De Jong (2016) (S)	≤ 0.5	-	≥ 80% decrease from peak PCT level
Deliberato (2013) (S)	< 0.5	-	> 90% decrease from peak PCT level
Hochreiter (2009) (S)(P)	< 1	-	≥ 65-75% decrease from initial PCT level if current PCT level >1
Laiyos (2012) (S)	< 0.5	-	-
Najafi (2015) (S)	≤ 0.5	-	-
Nobre (2007) (S)(P)	< 0.25 if initial PCT level ≥ 1	< 0.1 if initial PCT level < 1	> 90% decrease if initial PCT ≥ 1
Schroeder (2008) (S)(P)	≤ 1	-	≥ 65-75% decrease from initial PCT level
Shehabi (2014) (S)	< 0.10	0.10-0.25 if infection unlikely	> 90% decrease from baseline PCT level
Stolz (2009) (P)	≤ 0.5	-	≥ 80% decrease from initial PCT level
Applicant proposal	**PCT level ≤ 0.5 ng/mL or decrease > 80%**		

Thresholds for AB initiation, LRTI

PCT Result	<0.10 ng/mL	0.10-0.25 ng/mL	0.26-0.50 ng/mL	>0.50 ng/mL
Interpretation	Antibiotic therapy strongly discouraged. Indicates absence of bacterial infection.	Antibiotic therapy discouraged Bacterial infection unlikely.	Antibiotic therapy encouraged. Bacterial infection possible.	Antibiotic therapy strongly encouraged. Suggestive of presence of bacterial infection.

- In the PCT group, the initiation of antibiotic therapy was guided based on a single cutoff.

  initiate AB if PCT > 0.25

  do not initiate AB if PCT≤ 0.25

- The additional cutoffs were not evaluated.

Adherence

- Physicians can override the PCT recommendation.
- The subgroup in which physicians did not adhere to the PCT recommendation may dilute difference(s) of interest between PCT and control groups.
- Adherence rate to the PCT level recommendation in PCT group:
  - LRTI: Adherence rate reported in 8 out of 11 studies
  - Sepsis: Adherence rate reported in 4 out of 10 studies.
- Adherence rate varied across studies reporting it:
  - LRTI: Range was 59% to 91%.
  - Sepsis: Range was 47% to 93%.

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

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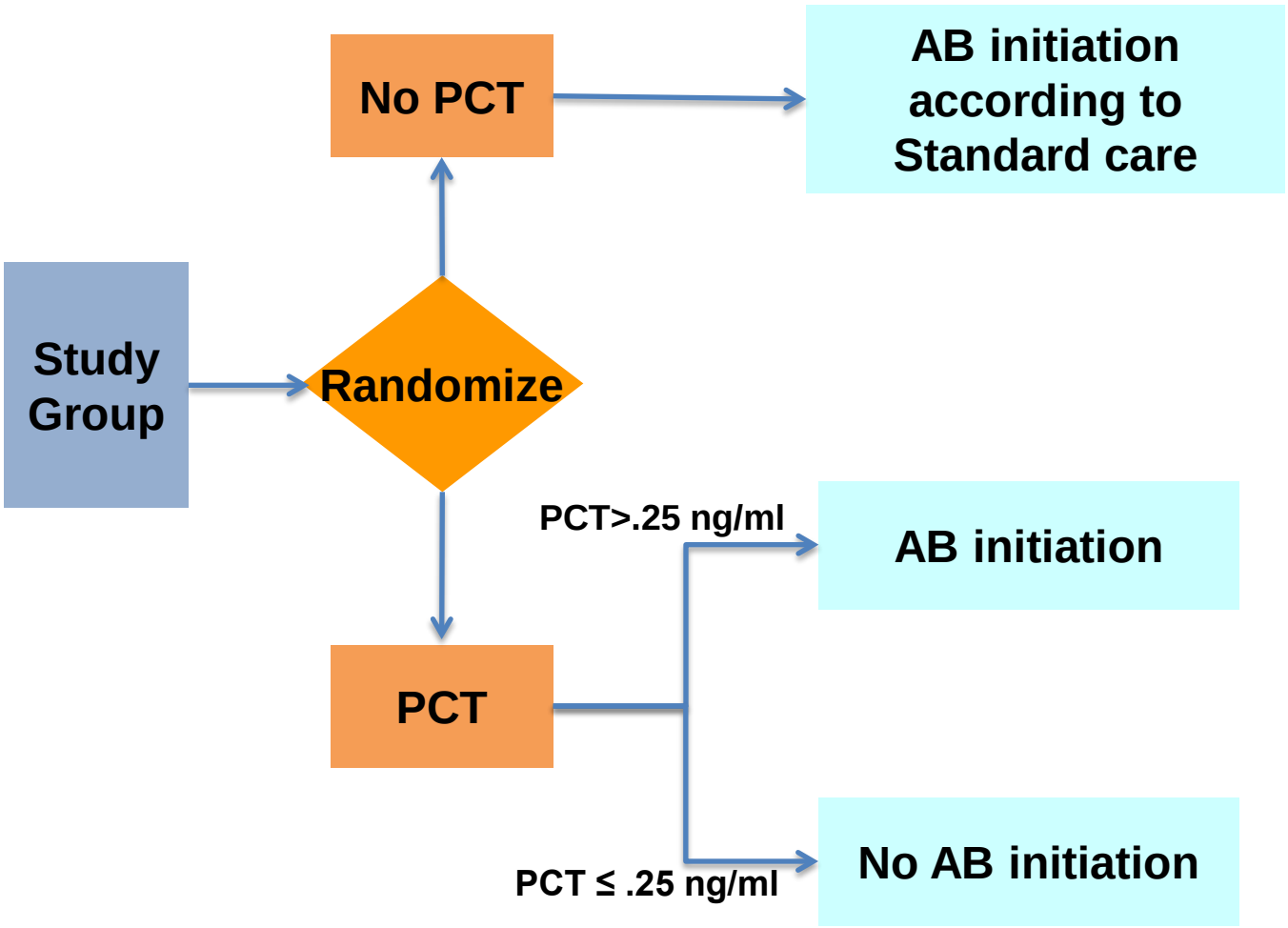
Marker Strategy Design (LRTI)



Marker Strategy Design

- Device effect size on (e.g., safety) endpoints may be under-estimated.
- Differences between PCT and control groups on endpoints are diluted by subgroups of patients for whom PCT algorithm recommends the same antibiotic use as given in the control group.
- Adherence effect on safety is unknown.

Key Subgroups for Adjunctive Tests

- Marker-strategy design compares PCT + SoC and SoC groups on whole population.
- Alternatively, the comparison can be restricted to those subgroups for whom PCT mattered (**changed** the treatment decision):

	SoC + PCT	
SoC	**no ABI**	**ABI**
no ABI	**No Change**	**Change**
ABI	**Change**	**No Change**

ABI = antibiotic initiation

Marker Strategy Design

- Differences in outcomes between PCT and control groups can depend on several factors:
  - treatment effect on outcome
  - diagnostic accuracy of PCT for bacterial infection.
  - adherence to PCT level recommendation
  - proportion of subjects for whom PCT and SoC indicate the same treatment decision.
  - any differential between the arms in management of subjects apart from influence of PCT level.
- Effect of diagnostic accuracy on group differences cannot be separated from these other factors.

Safety Endpoints: No Significance Observed

LRTI	PCT group	Control	OR or Diff	p val
Study level	2040	2050		
Mortality, n (%)	pooled from 9 trials		0.94 (0.69, 1.28)	0.68
LOH days	pooled from 7 trials		-0.2 (-0.6, 0.3)	0.51
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Study level	1375	1754		
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LOH median days	21(11,37)	23(13,38)	-1.4 (-4.4, 1.7)	0.39
ICU median days	12(6, 23)	12(6,22)	1.1 (-1.2, 3.4)	0.37

Patient Level Data, LRTI

PCTd0 stratum	PCT group	AB initiation (death)	
		no	yes
PCT<0.1	Control	120 (0, 0%)	334 (11, 3.3%)
	PCT	254 (1, 0.4%)	140 (1, 0.7%)
0.1<=PCT<=0.25	Control	52 (0, 0%)	361 (23, 6.37%)
	PCT	175 (3, 1.7%)	234 (15, 6.41%)
0.25<PCT<=0.5	Control	11 (0, 0%)	204 (22, 10.8%)
	PCT	5 (0, 0%)	212 (15, 7.1%)
PCT>0.5	Control	3 (0, 0%)	521 (63, 12.1%)
	PCT	6 (1, 16.7%)	510 (67, 13.1%)

Patients lost-to-follow-up are assumed to have not died.

Association between PCT Group and Death, Controlling for Baseline PCT

PCT d0 strata	PCT group	AB initiation (death, %)	
		no	yes
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PCT > 0.5	Control	3 (0, 0%)	521 (63, 12.1%)
	PCT	6 (1, 16.7%)	510 (67, 13.1%)
All rows	**Common OR**	1.81* [.28,11.5]	0.93 [.70,1.23]
CMH test	**p value**	0.172	0.598

*Based on a correction of 0.5 in zero cells.

Association between PCT Group and Death, Controlling for baseline PCT

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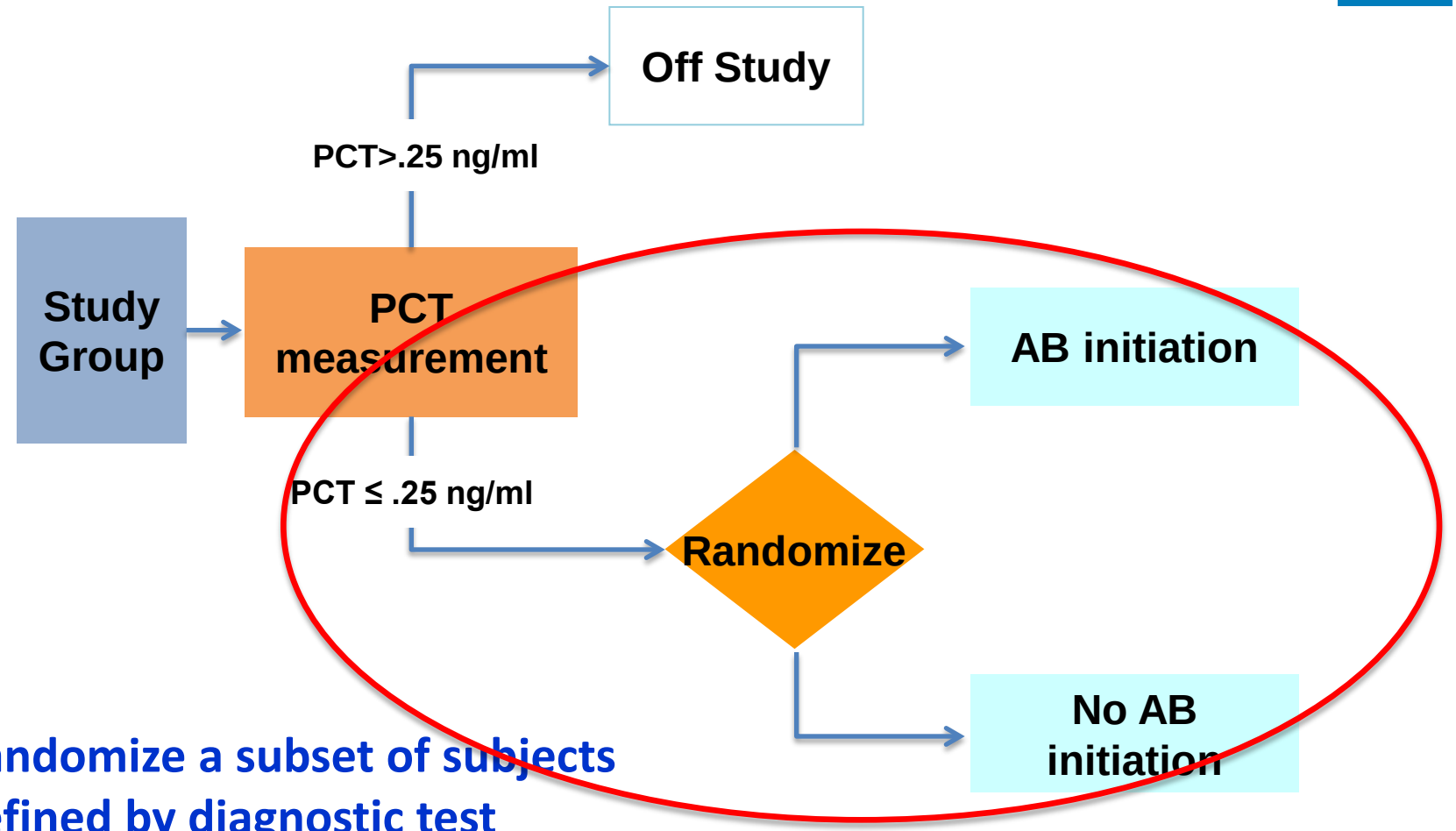
	PCT	5 (0)	212 (15, 7.1%)
PCT>0.5	Control	3 (0)	521 (63, 12.1%)
	PCT	6 (1)	510 (67, 13.1%)
First 2 rows	**Common OR**	1.77* [.20,15.70]	.79 [.42,1.46]
CMH test	**p value**	0.242	0.452

*Based on a correction of 0.5 in zero cells.

Enrichment Design



Randomize a subset of subjects defined by diagnostic test value (TRAP-LRTI on PCT ≤.1)

Simon, R. (2010) Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology, *Personalized Medicine*, 7(1), 33–47.

DOOR RADAR approach

- Composite endpoint: Construct outcome ranking based on the multiple endpoints.
- Desirability of Outcome Ranking (DOOR)
- Response adjusted for duration of antibiotic risk (RADAR)
- Compare arms using statistical test for rank data (Mann-Whitney test)

Evans, S. et al. (2015) Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR), *Clin Infect Dis*, 61(5): 800-6.

Conclusion

- The meta-analysis was conducted to demonstrate
  - effectiveness of using PCT to reduce antibiotic use compared with standard of care, and
  - to compare the safety of using PCT for the intended indications with standard of care.
- The meta-analysis demonstrated (not surprisingly) that antibiotic use is reduced when PCT is utilized for patient management under the proposed indications.
- No statistically significant differences in adverse outcomes were observed when PCT was utilized.

Conclusion

- The studies available in the literature have inherent limitations for evaluating safety and effectiveness.
- The studies selected for meta-analysis are heterogeneous in design and population studied.
- Precise data on diagnostic accuracy of the device would increase our understanding of its safety.
- The benefit of reducing antibiotic use could outweigh the risk of mistreating some patients based on PCT guided therapy if that subset were small enough.
- Unfortunately, the risk to patients of using PCT to guide their therapy is difficult to estimate precisely based on available data (and the BMx meta-analysis).