UMC Utrecht

New designs for randomized controlled trials

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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?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2010 VOL. 362 NO. 1

Preventing Surgical-Site Infections in Nasal Carriers of *Staphylococcus aureus*

Lonneke G.M. Bode, M.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Heiman F.L. Wertheim, M.D., Ph.D.,

N Engl J Med 2010;362:9-17.

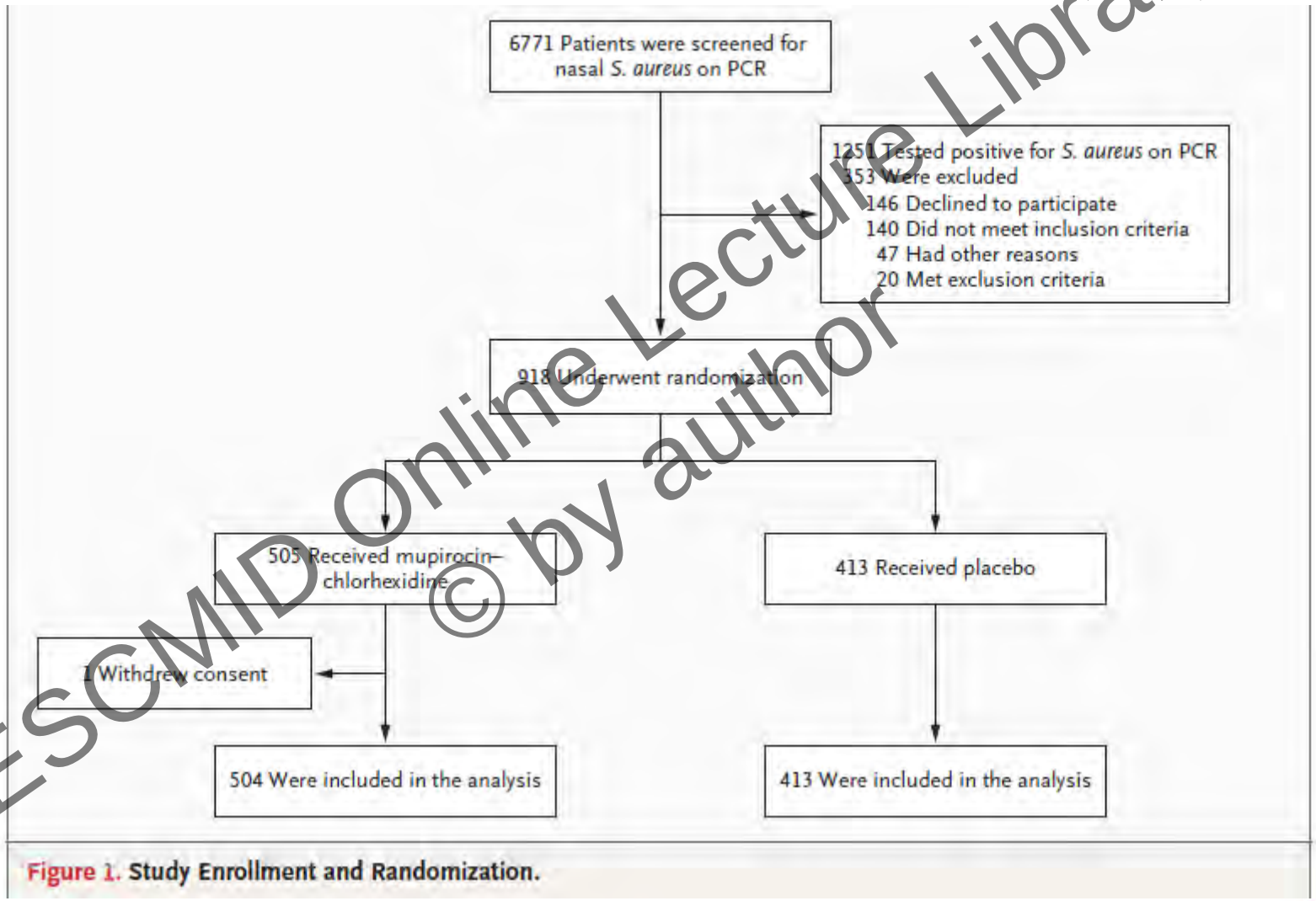


Figure 1. Study Enrollment and Randomization.

Table 1. Baseline Characteristics of the 917 Study Patients.

Characteristic	Mupirocin–Chlorhexidine (N=504)	Placebo (N=413)	P Value
Mean (±SD) age — yr	61.8±13.9	62.8±13.3	0.25
Male sex — no. (%)	331 (65.7)	251 (60.8)	0.13
Hospital service — no. (%)			
Surgery	441 (87.5)	367 (88.9)	0.53
Internal medicine	63 (12.5)	46 (11.1)	0.53
Admission durin no./total		3)	0.76
McCabe score at			
Median			
Interquartile			

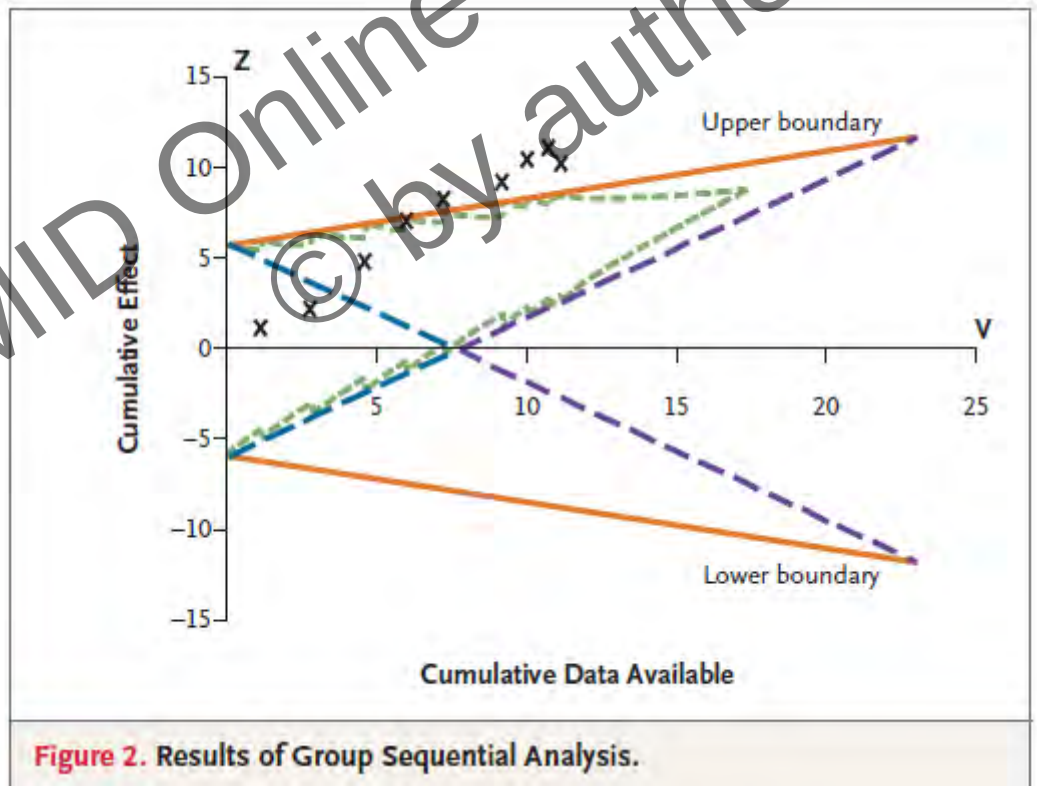


Figure 2. Results of Group Sequential Analysis.

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

Variable	Mupirocin–Chlorhexidine (N=504)	Placebo (N=413)	Relative Risk (95% CI)*
	no. (%)		
S. aureus infection	17 (3.4)	32 (7.7)	0.42 (0.23–0.75)
Source of infection†			
Endogenous	12 (2.4)	25 (6.1)	0.39 (0.20–0.77)
Exogenous	4 (0.8)	6 (1.5)	0.55 (0.16–1.92)
Unknown	1 (0.2)	1 (0.2)	
Localization of infection			
Deep surgical site‡	4 (0.9)	16 (4.4)	0.21 (0.07–0.62)
Superficial surgical site‡	7 (1.6)	13 (3.5)	0.45 (0.18–1.11)
Lower respiratory tract	2 (0.4)	2 (0.5)	0.82 (0.12–5.78)
Urinary tract	1 (0.2)	0	
Bacteremia	1 (0.2)	1 (0.2)	
Soft tissue	2 (0.4)	0	

* 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. Generalizibility
   - 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

	Mupirocin + CHX	Placebo	RR (95% CI)
Non-surgical patients (n=109)			
S. aureus HAI			
Cardiothoracic surgery (n=391)			
S. aureus HAI			
Orthopedics (n=172)			
S. aureus HAI			
Vascular surgery (n=95)			
S. aureus HAI			
Gastrointestinal surgery (n=43)			
S. aureus HAI			
General surgery (107)			
S. aureus HAI			

Subgroups

	Mupirocin + CHX	Placebo	RR (95% CI)
Non-surgical patients (n=109)	63	46	
S. aureus HAI	1 (1.6%)	1 (2.2%)	0.73 (0.04-11.92)
Cardiothoracic surgery (n=391)	220	171	
S. aureus HAI	3 (1.4%)	15 (8.8%)	0.15 (0.04-0.51)
Orthopedics (n=172)	85	87	
S. aureus HAI	1 (1.2%)	4 (4.6%)	0.25 (0.03-2.26)
Vascular surgery (n=95)	53	42	
S. aureus HAI	7 (13.2%)	6 (14.3%)	0.91 (0.28-2.96)
Gastrointestinal surgery (n=43)	22	21	
S. aureus HAI	2 (9.1%)	3 (14.3%)	0.60 (0.09-4.01)
General surgery (107)	61	46	
S. aureus HAI	3 (4.9%)	3 (6.5%)	0.74 (0.14-3.85)

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
  - Fluorquinolone 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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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 I.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Wim G. 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*

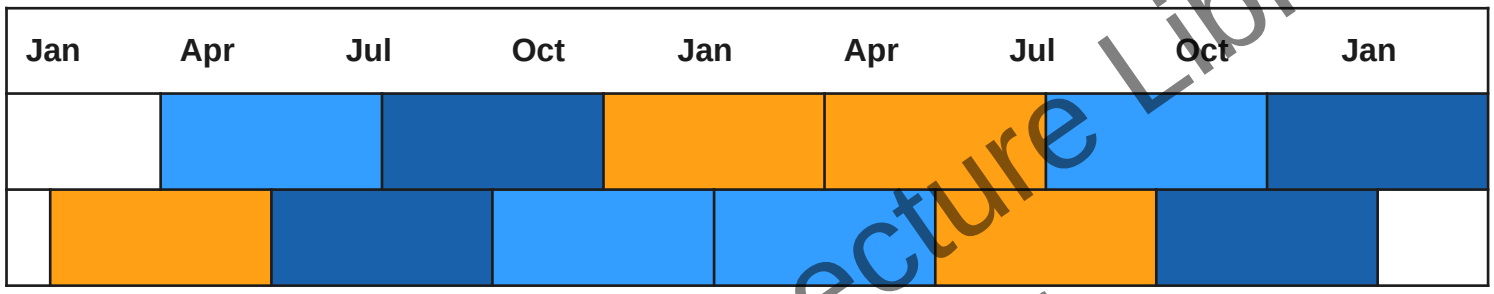
Study design

- 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

BL	BLM	FQL
• Amoxicillin • Amoxiclav • 2nd & 3rd gen. cephalosporins	BL (including penicillin) + • Erytromycin • Claritromycin • Azitromycin	• Levofloxacin • Moxifloxacin

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

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

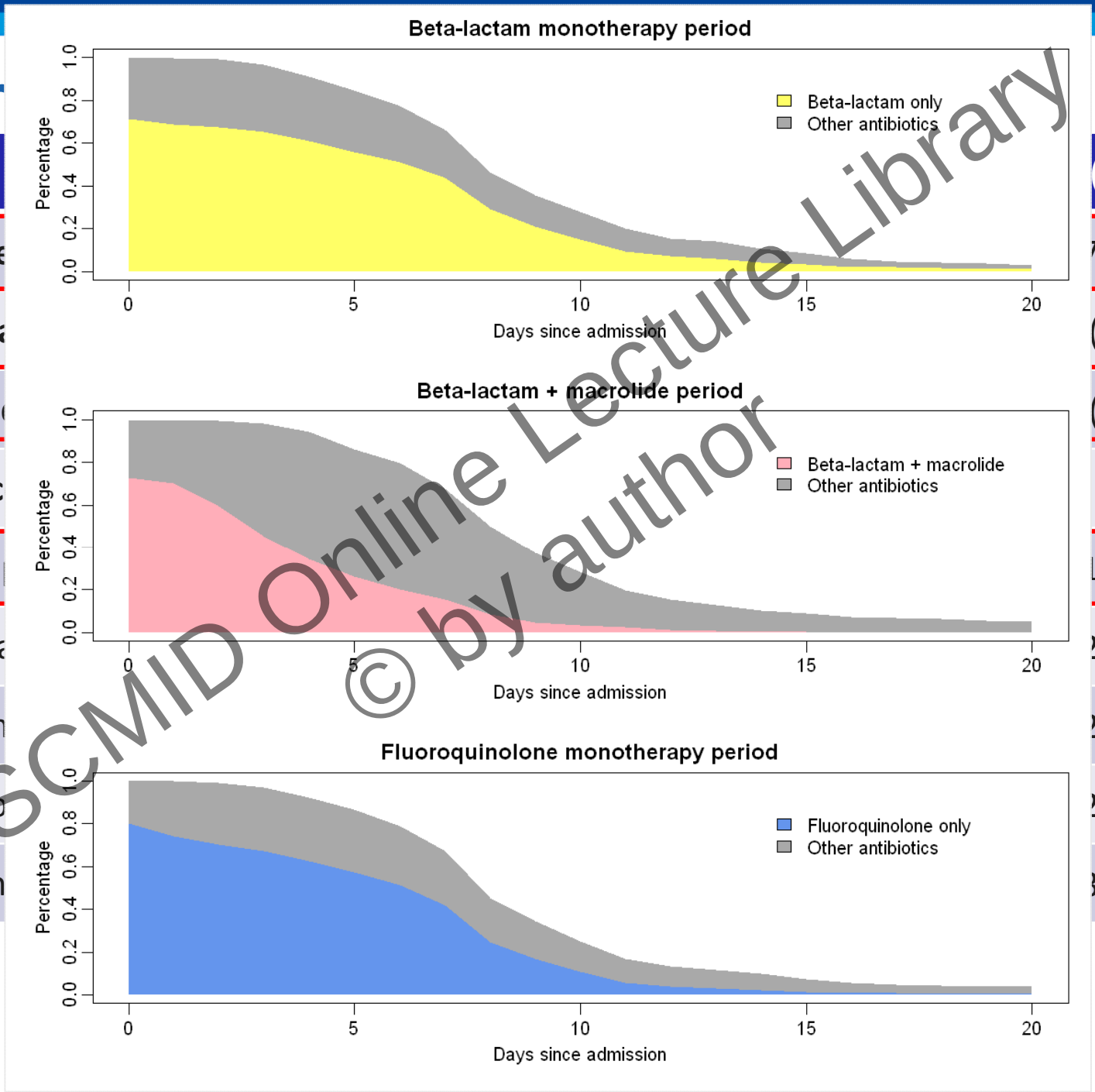
Legend: * Mean (SD) ^ Median (IQR)

Pathogens in X-ray proven CAP

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

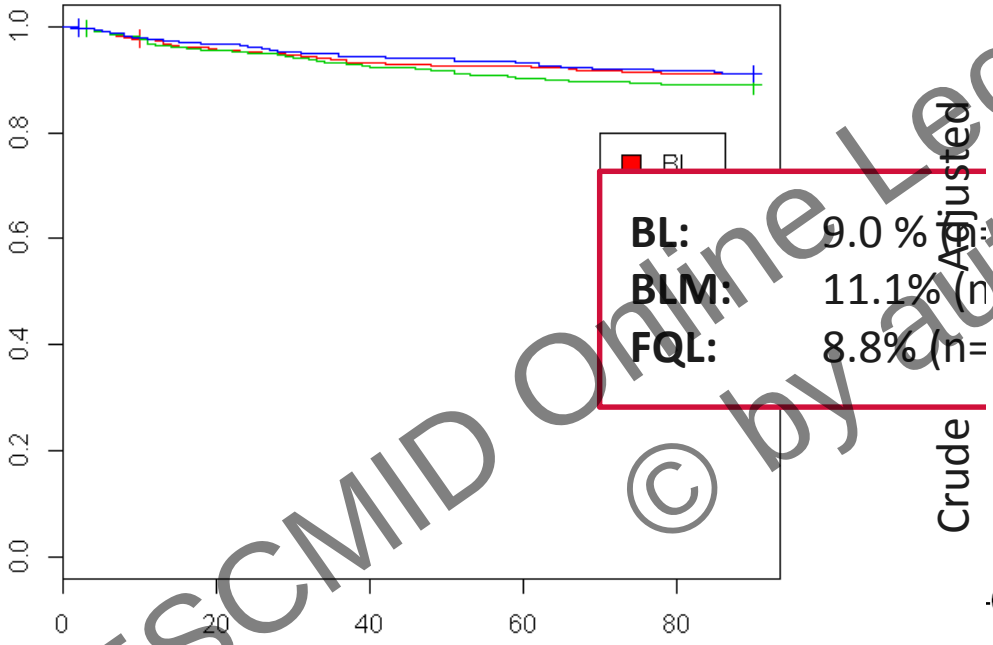
Pr

	(n=888)
Non-adhe	.3%)
Protocol a	(92.7%)
Treate	(80.2%)
Protoc	
Susp	.2%)
Rela	.6%)
Con	.8%)
Kno	.6%)
Oth	.5%)

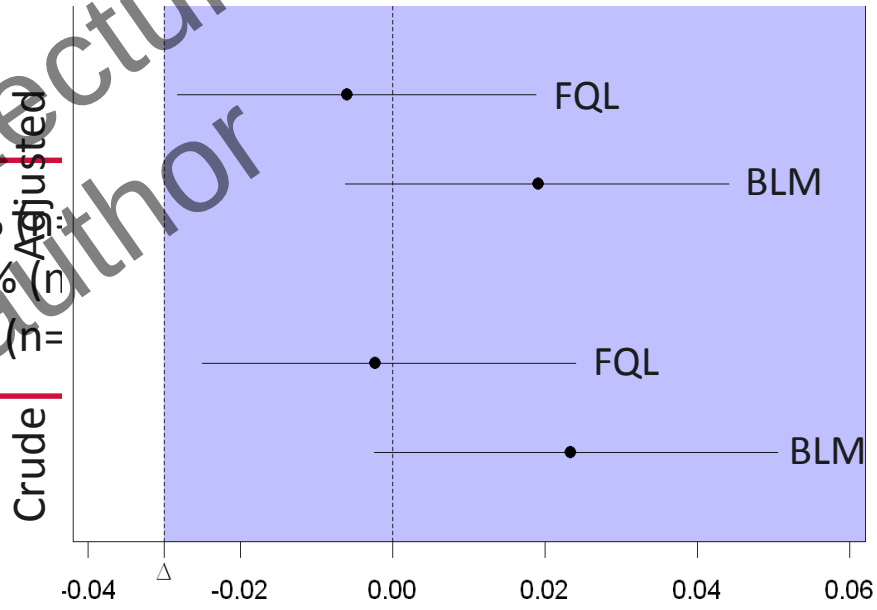


Primary outcome: day 90 mortality
Intention-to-treat analysis (ITT)

Survival curve



Risk difference



Primary outcome: risk difference day 90 mortality

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

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? ✗

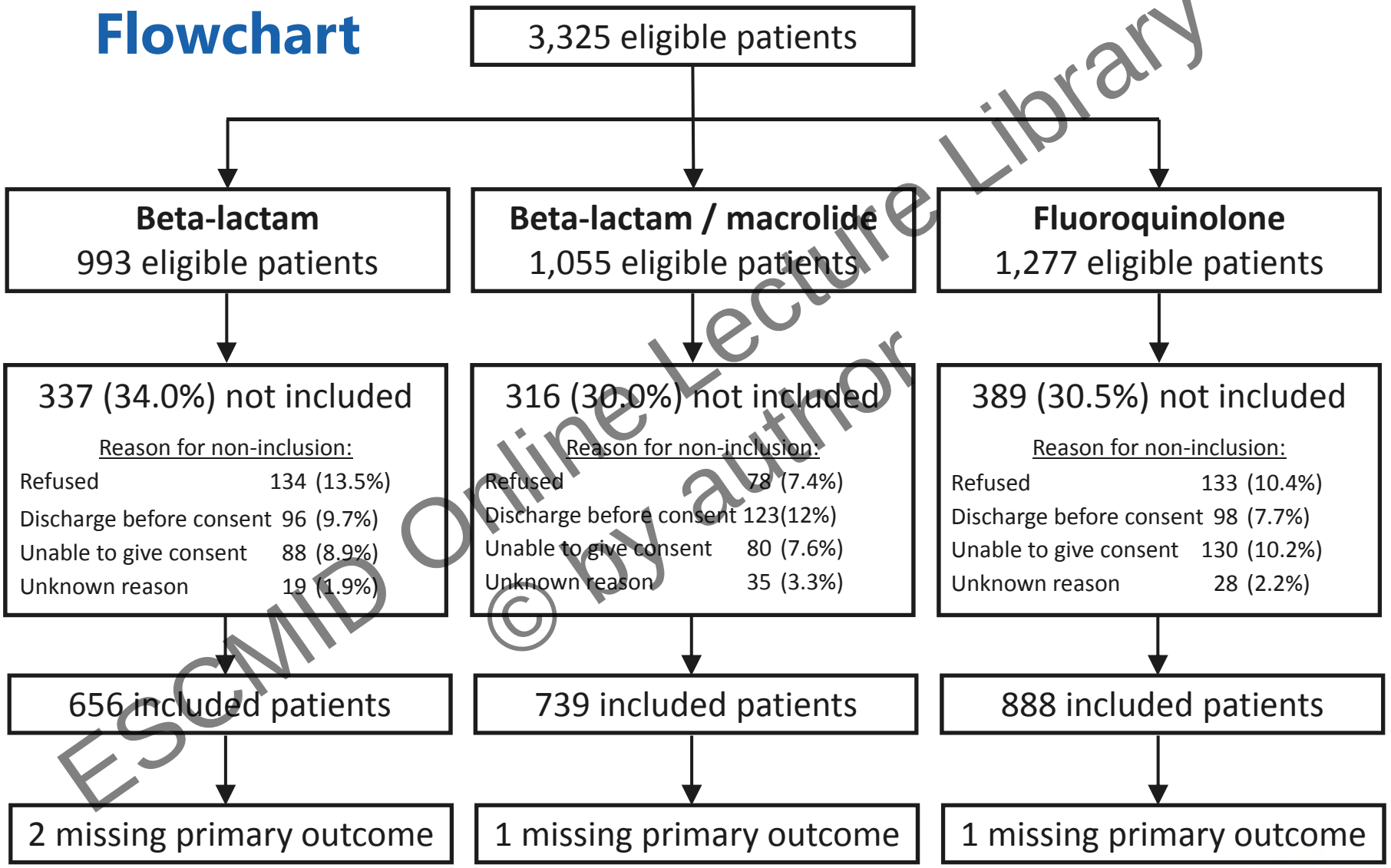
2. Precision of the results
   - Is the effect relevant and precise? ✗

3. Generalizibility
   - Does it apply to my patients? ✗
   - Does t apply to your patients? ?

Questions

- Who was in the trial?
- What patients should now receive beta-lactam monotherapy?
- Were the ethical regulations ethical?

Flowchart



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 Elsaesser, MD, Daniel Drozdov, MD, Birsen Arici, MD, Sandrine Andrea Urwyler, MD, Julie Refardt, 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?

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

JAMA Published online March 23, 2015

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

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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

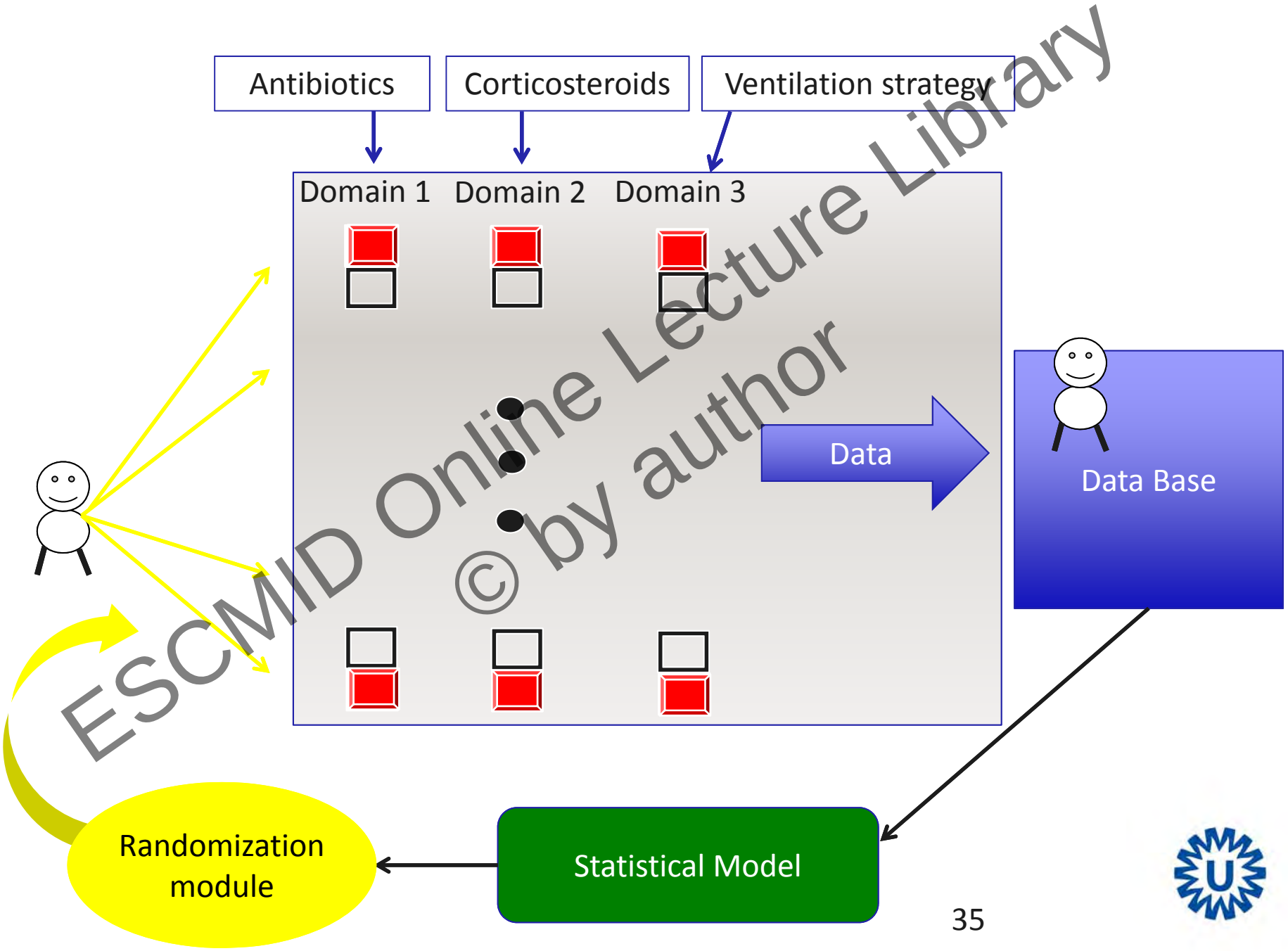
- Randomized:
  - Using Response-adaptive randomization (RAR)
- Embedded:
  - Nested in daily clinical care (point-of-care randomization)
- Multifactorial:
  - Testing multiple interventions alone and in combination
- Adaptive
  - Option to adapt trial based on prespecified rules
- Platform
  - Focus 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.



Trial adaptations

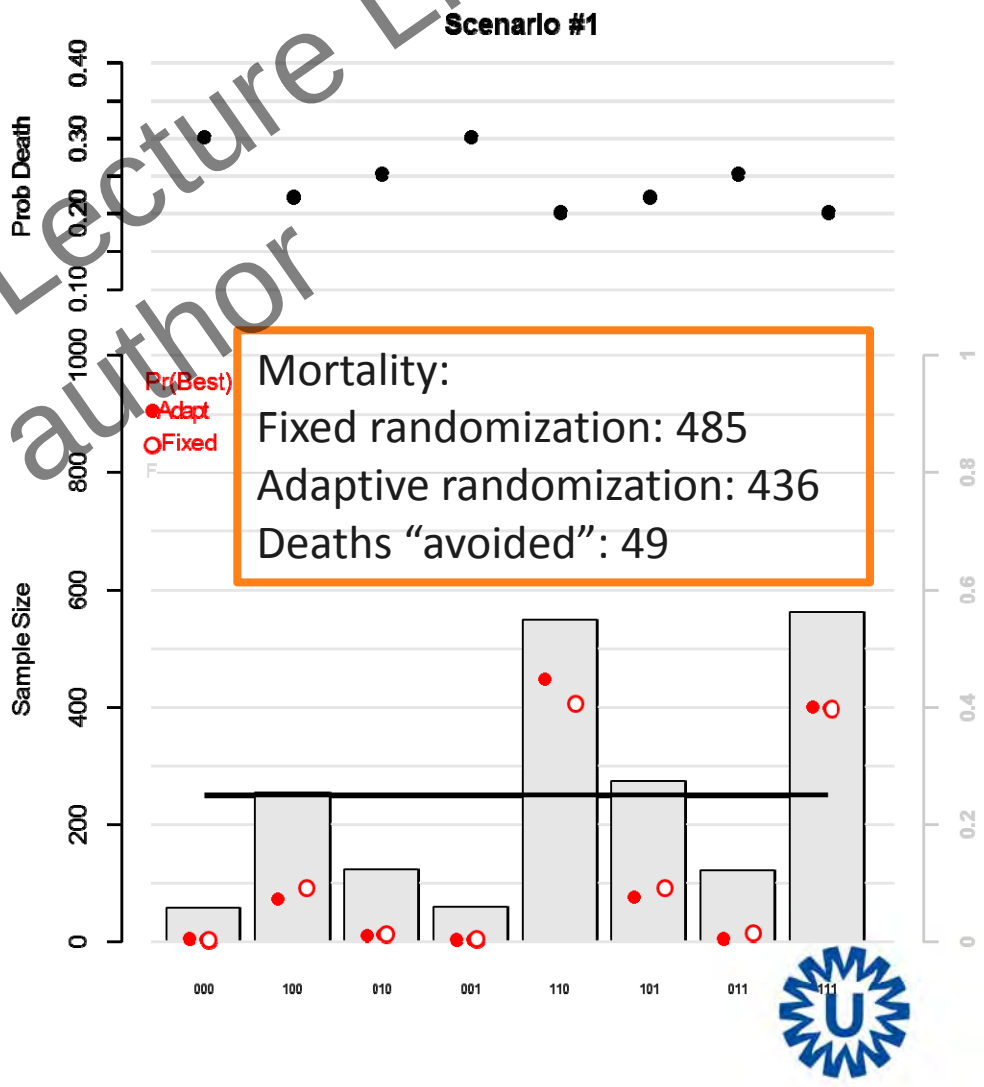
Many adaptations possible:

1. Randomization allocation
2. Target population
3. Number of treatments

1. Randomization allocation

Response-Adaptive Randomization (RAR)

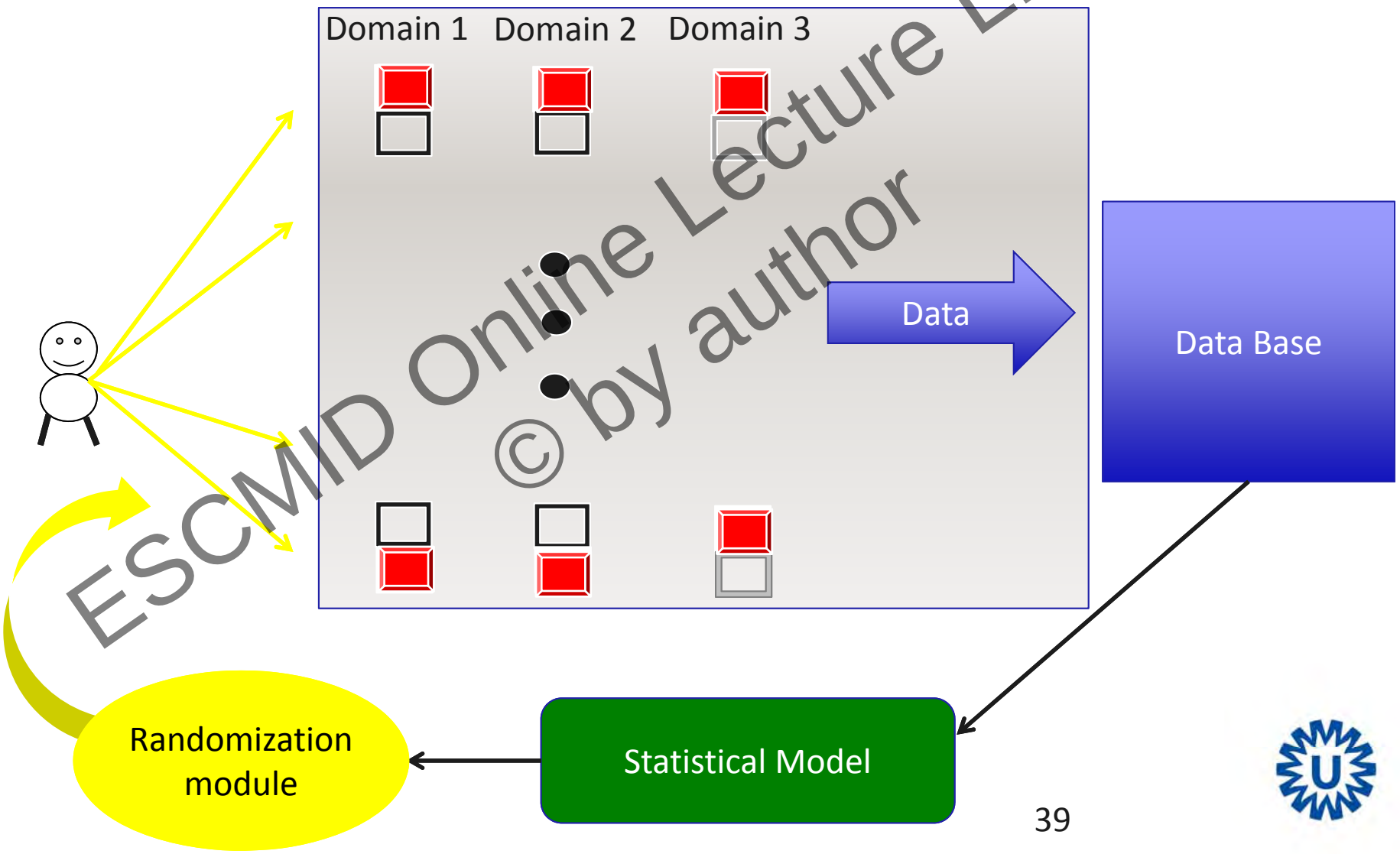
- Equal randomization first 400 pts
- Next 1600 RAR based on priors
- Postulated benefits:
  - More patients randomized to effective treatment(s)
  - Earlier identification of superior or inferior treatment option



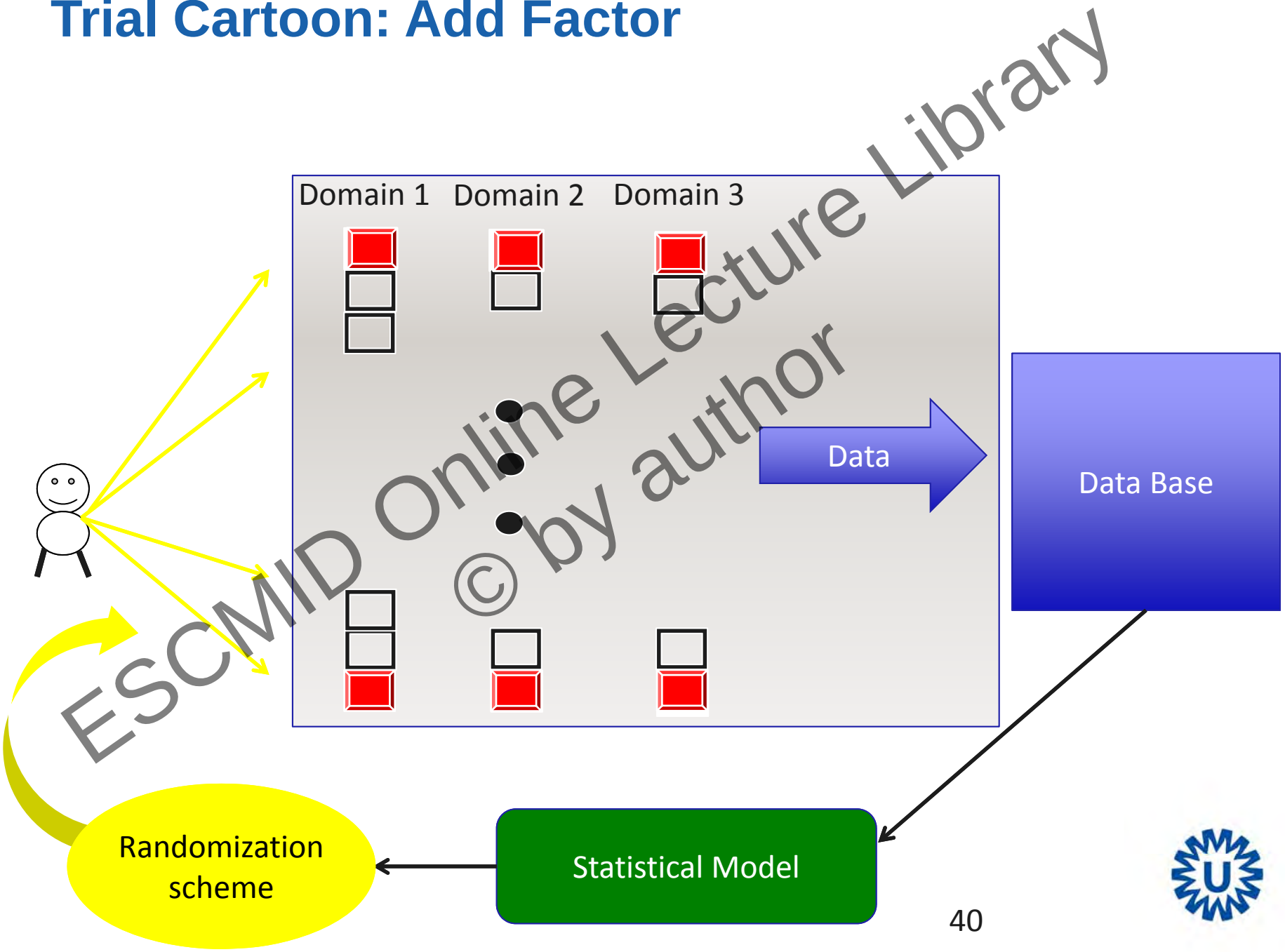
2. Number of treatments

- "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).

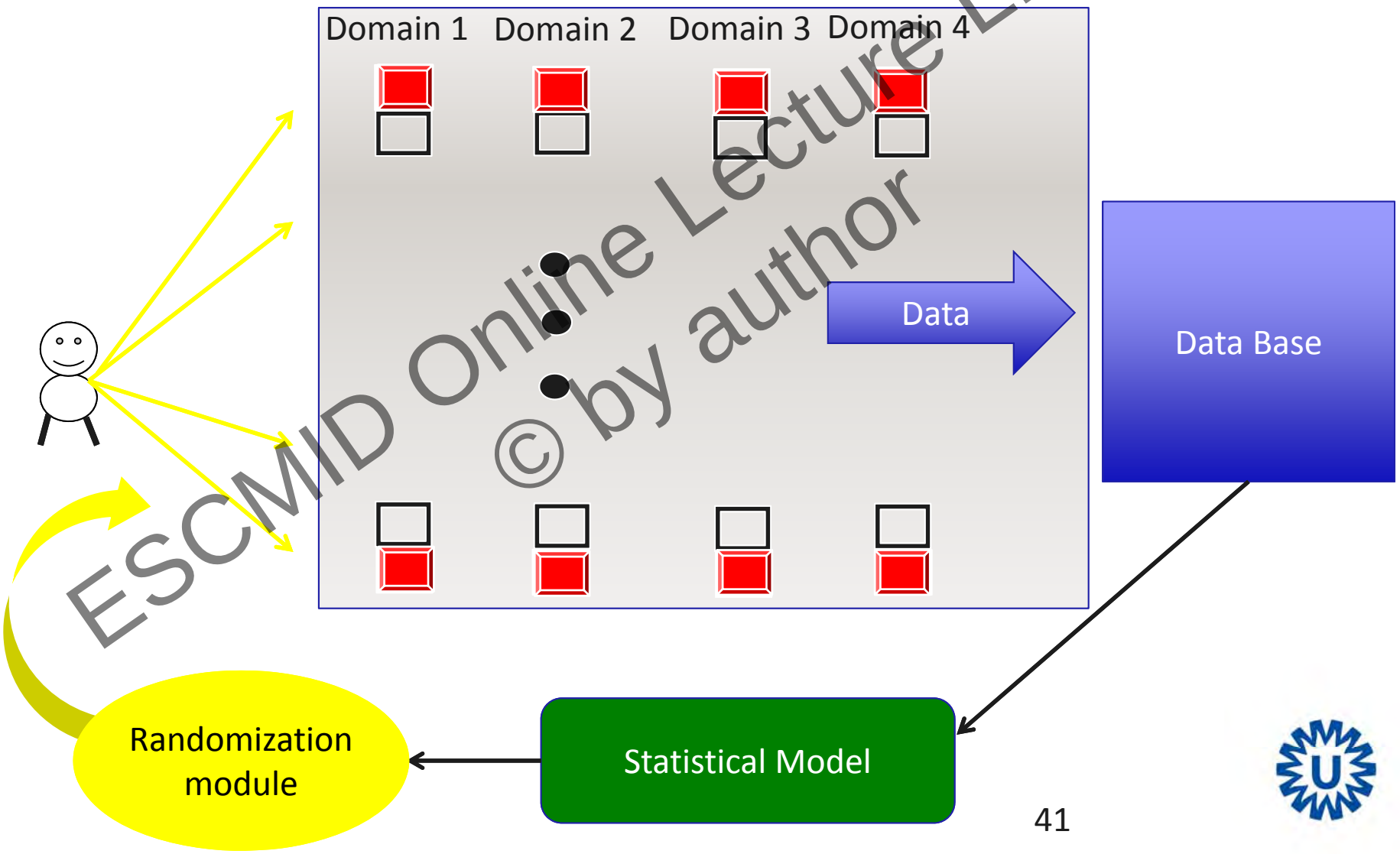
Trial Evolution: Drop Factor



Trial Cartoon: Add Factor



Trial Evolution: Add Domain



Practical issues

- Diffulculties 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 informent 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

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REVIEW ARTICLE

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).

Integrating Randomized Comparative

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.