



# Fusing RCTs with EHR 'Big Data'

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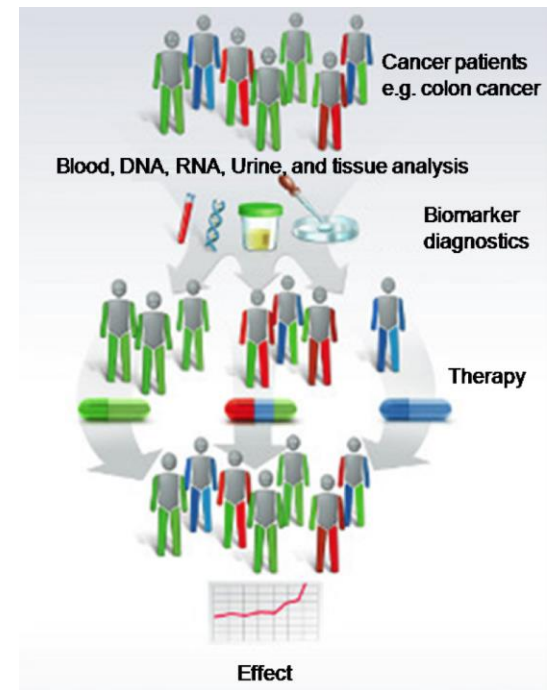
University of Pittsburgh Schools of the Health Sciences

# The post-approval world ...

- A data-poor, opinion-rich environment ...
- At approval, RCT evidence for a medical product
  - Too **broad**
    - Average, not 'personalized', efficacy estimates
  - Too **narrow**
    - Trial population not representative of general practice
  - Little **comparative** effectiveness
- **Nonetheless, ...**
  - Many want access
  - Others want more information
  - But, no one wants to be a guinea pig

# Enter the era of 'Big Data'

- **Integration of 'deep' personalized data**
  - Causal inferences on optimal care
  - **Broad** – 'real-world' practice
  - **Narrow** – 'personal' estimates
  - **Comparative** – considers all options
    - Vanderbilt-IBM 'BioVU' initiative
- **'Live' presentation of information at time of clinical decision-making**
  - 'Just-in-time' cohort study in EHR
  - No guinea pigs
    - Longhurst et al. Health Affairs 2013



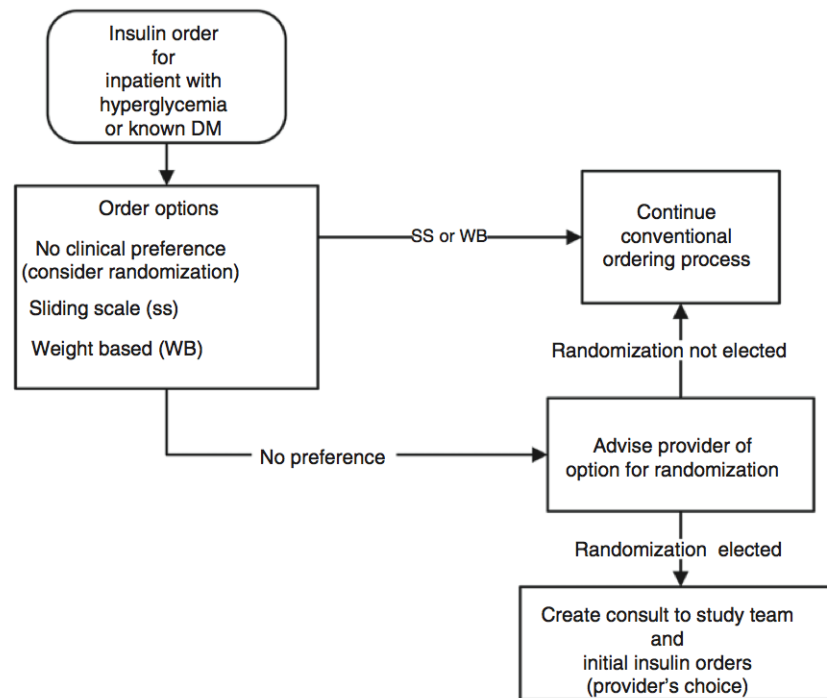
# Evidence Generator Report Card

Feature	'Big Data' Analytics
Leverage the EHR	✓
Low incremental costs	✓
Real-world 'effectiveness'	✓
Cost-effective	✓
'Personalized' medicine	✓
Offer 'live' tailored options	✓
Robust causal inference	✗

**For causal inference, randomize!**

# Point-of-care (POC) Clinical Trials

- A clinical moment in the EHR ‘alerts’ the clinical trial machinery



Fiore et al. Clinical Trials 2011

- Targeting the large ‘pragmatic’ trial arena
  - 2 thiazide diuretics in >13k high BP Veterans (NCT02185417)
  - 2 aspirin doses in 20k CVD patients (ADAPTABLE) (PCORI)

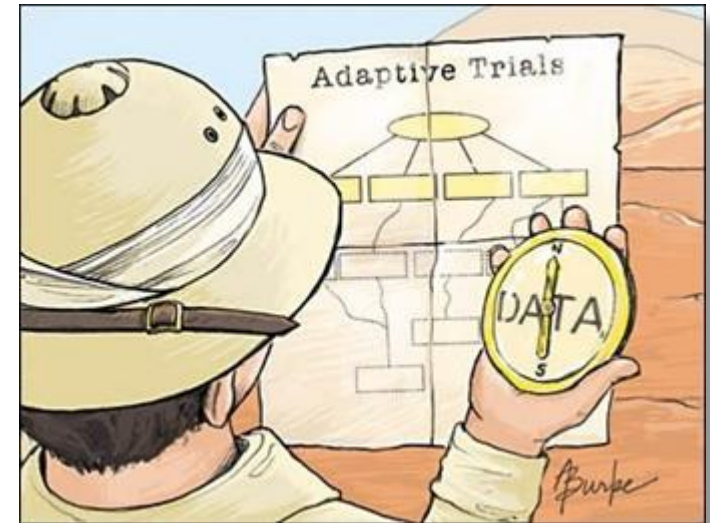
# Evidence Generator Report Card

Feature	'Big Data' Analytics	POC Trials
Leverage the EHR	✓	✓
Low incremental costs	✓	✓
Real-world 'effectiveness'	✓	✓
Consider multiple therapies	✓	X / ✓
'Personalized' estimates	✓	X
Offer 'live' tailored options	✓	X
Robust causal inference	X	✓

# Platform Trials

- **Adaptive trials**

- Focus on disease, not a particular Rx
- Multiple interventions (arms)
- 'Perpetual' enrollment
- Tailor choices over time
  - Response-adaptive randomization (RAR)
  - Biomarker-based 'enrichment' strategies



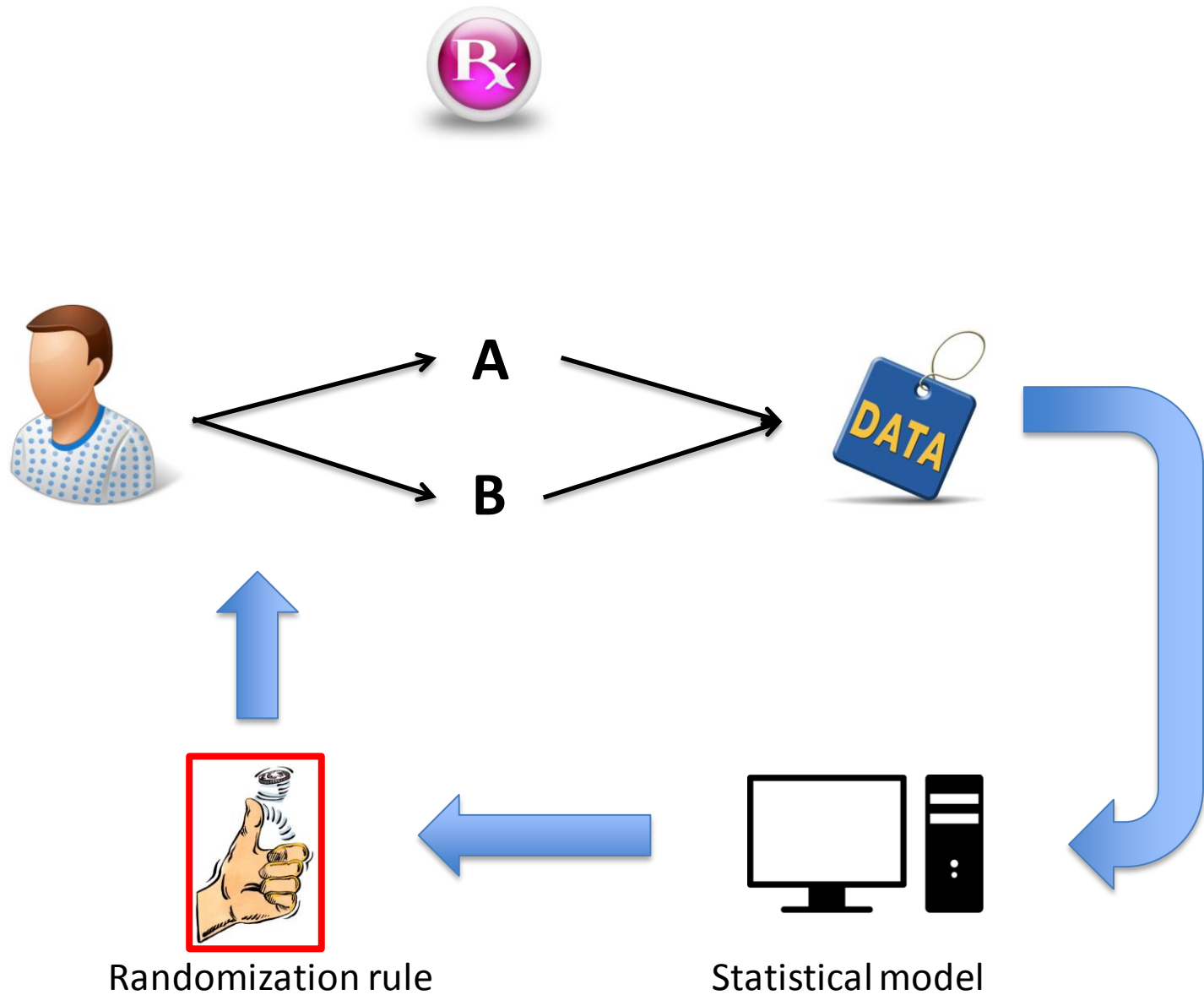
- **Focus on pre-approval space**

- Emphasis on efficiency with (very) small sample sizes
- Different therapies 'graduate' to next phase while trial continues

- **Examples**

- I-SPY-2 platform for rapid Phase 2 screening and discovery in Breast CA
- BATTLE for therapy-resistant NSCLC
  - Kim et al. Cancer Discovery 2011

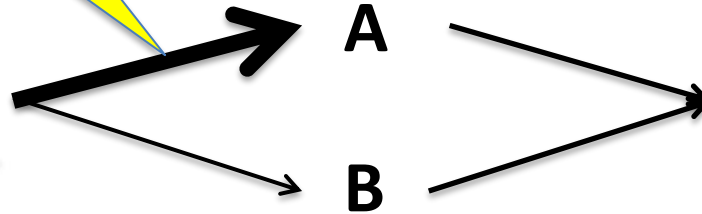
# Response-adaptive randomization



# Response-adaptive randomization



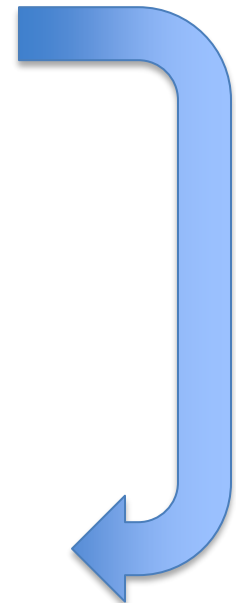
Odds weighted  
towards best RX



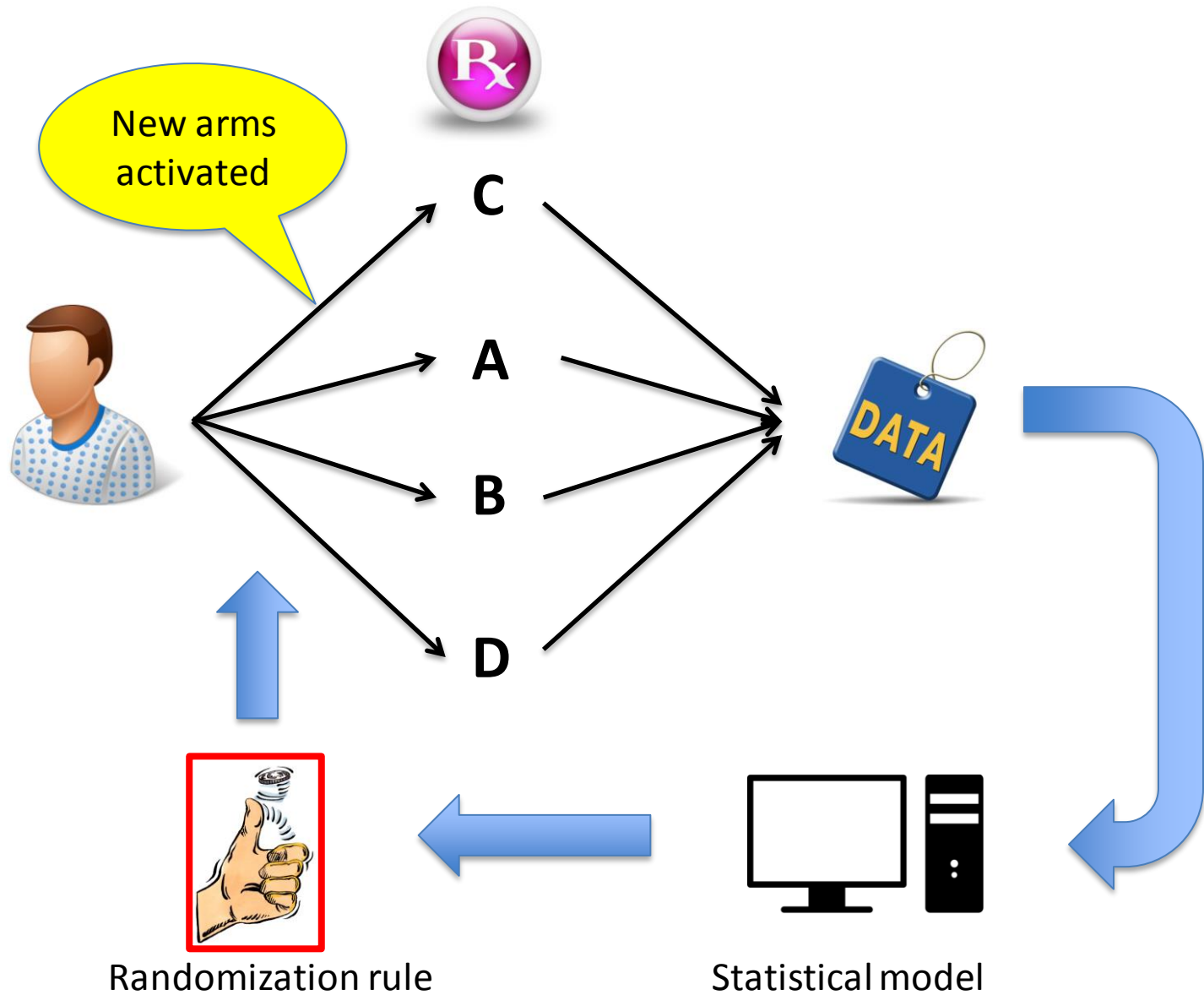
Randomization rule



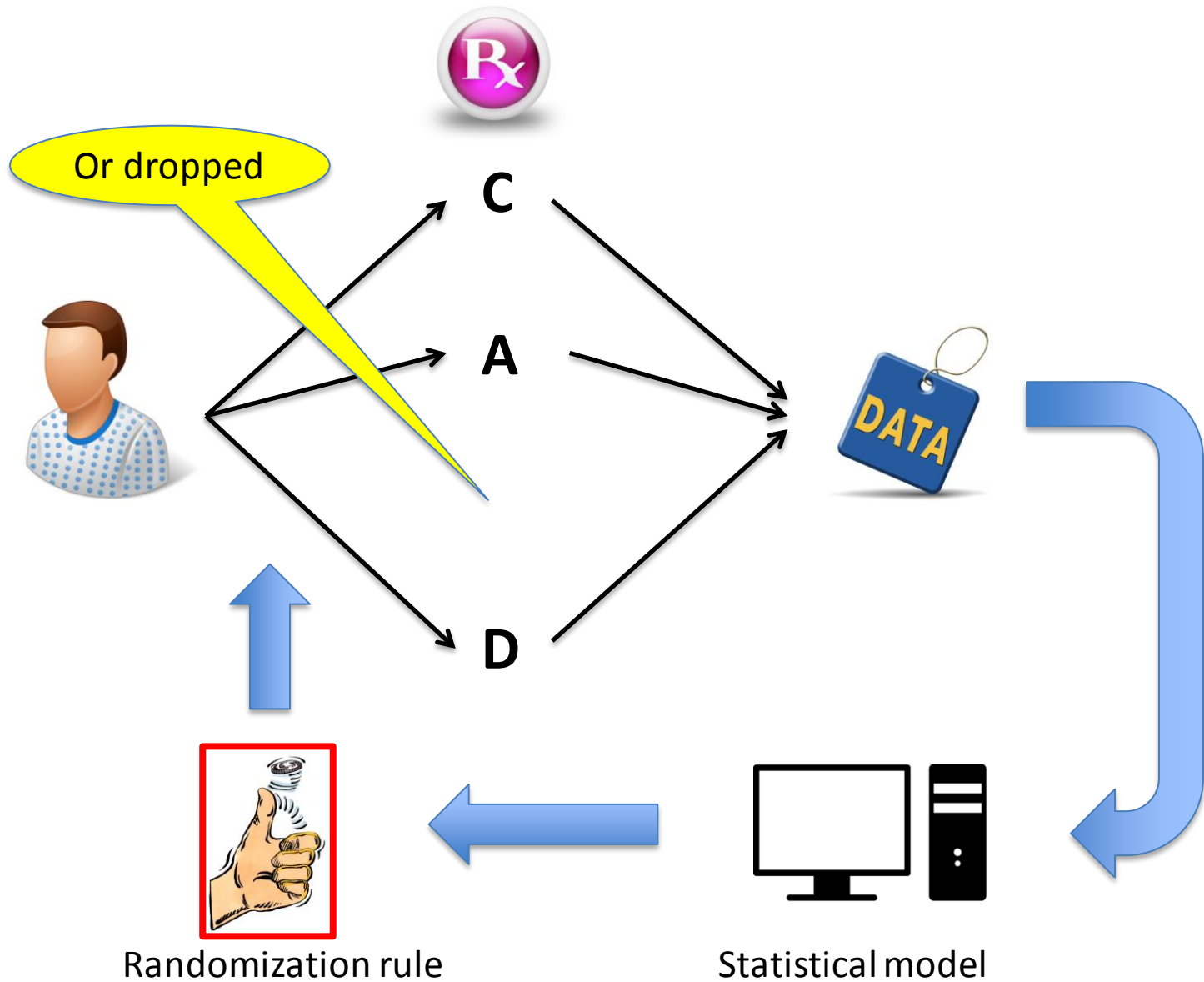
Statistical model



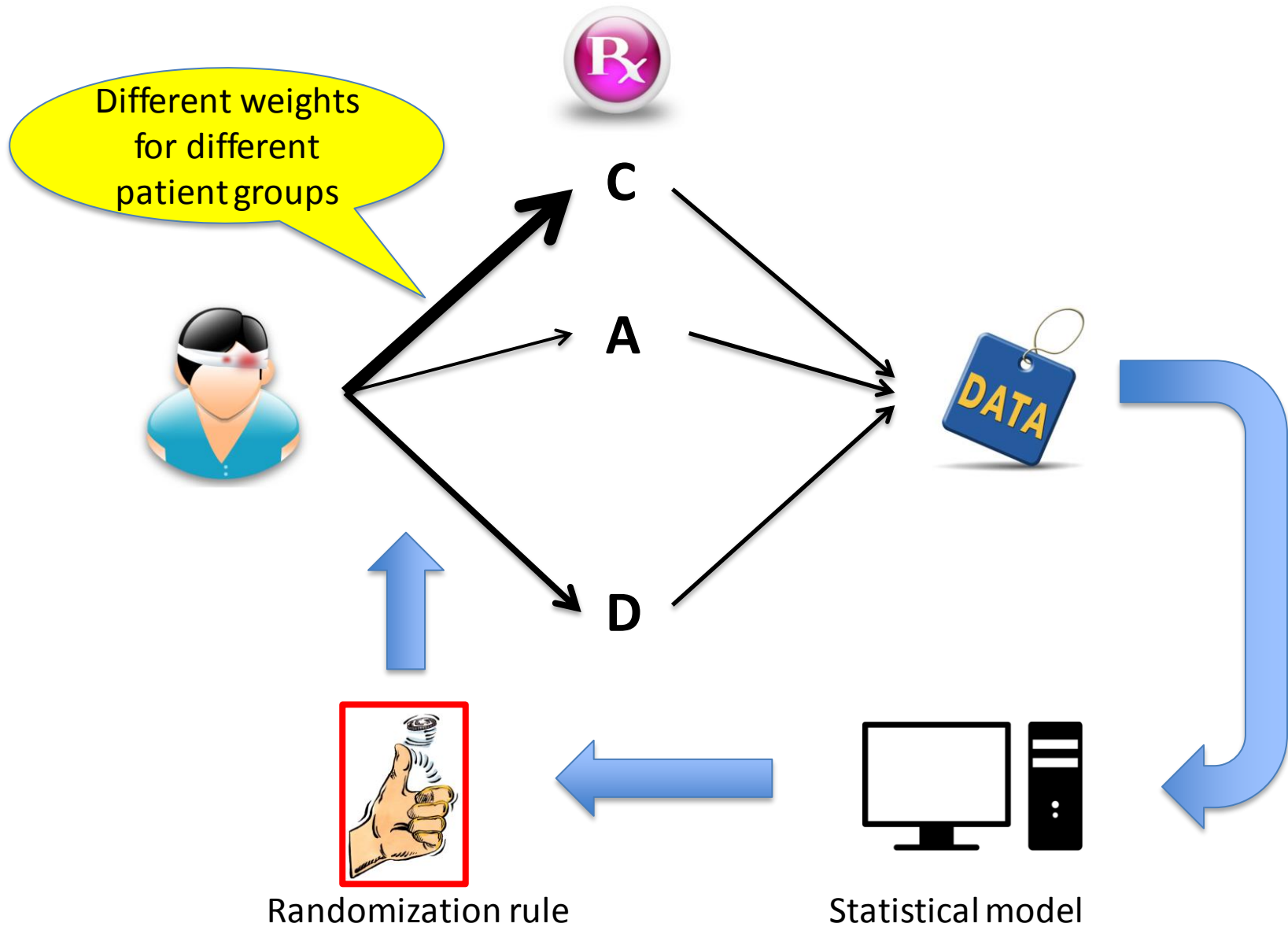
# Response-adaptive randomization



# Response-adaptive randomization



# Response-adaptive randomization



# Evidence Generator Report Card

Feature	'Big Data' Analytics	POC Trials	Platform Trials
Leverage the EHR	✓	✓	✗
Low incremental costs	✓	✓	✗
Real-world 'effectiveness'	✓	✓	✗
Consider multiple therapies	✓	✗ / ✓	✓
'Personalized' estimates	✓	✗	✓
Offer 'live' tailored options	✓	✗	✓
Robust causal inference	✗	✓	✓

# Evidence Generator Report Card

Feature	'Big Data' Analytics	POC Trials	Platform Trials	???
Leverage the EHR	✓	✓	✗	✓
Low incremental costs	✓	✓	✗	✓
Real-world 'effectiveness'	✓	✓	✗	✓
Consider multiple therapies	✓	✗ / ✓	✓	✓
'Personalized' estimates	✓	✗	✓	✓
Offer 'live' tailored options	✓	✗	✓	✓
Robust causal inference	✗	✓	✓	✓

# A novel blend of 'POC' + platform designs

- **REMAP**

- Randomized
- Embodied
- Multifactorial
- Adaptive
- Platform trial



- **Ex: REMAP Severe Pneumonia**

- EU FP7 PREPARE WP 5 program
- (Australian NHMRC 'OPTIMISE' program)
- >6,000 patients admitted to ICU with severe CAP
- Simultaneously test
  - Different anti-microbial strategies
  - Different host immunomodulation strategies
  - Different ventilation strategies
- Separate RAR and stopping rules for multiple potential subgroups



# Key REMAP design features ...

- **Embedded**
  - Clinical 'moment' to trigger trial activation
- **Multifactorial**
  - Multiple domains of interventions
  - Multiple subgroups
- **Adaptive**
  - Response-adaptive randomization
  - Enrichment
- **Patients are preferentially assigned to best performing arm**
  - Allocation is random, but NOT 50:50
  - Odds of assignment proportional to odds of success
  - Not a guinea pig!



# REMAP severe pneumonia

- **Embedded**
  - ICU admission orders
    - Approved in Netherlands with delayed consent
- **Multifactorial**
  - 12 regimens (3 x 2 x 2)
  - 4 subgroups
  - 48 estimates of treatment effect

The image shows a medical order form from Methodist Le Bonheur Healthcare. The title is 'Physician Orders - ADULT Order Set: Ventilator Bundle- Sedation and Analgesia Orders'. It includes fields for patient information (Name, MRN, Room, Bed, Date, Time, Weight, Height, Allergies) and checkboxes for various orders. The form is divided into sections: 'Patient Care', 'Respiratory Care', 'Sedation/Analgesia', and 'Ventilator Bundle'. It includes several 'NOTE' boxes with instructions for use. At the bottom, there are fields for Date, Time, Physician's Signature, and MD Number, along with a barcode.

$$Z = [g] + [R] + [Time] + [Interv] + [Inter, Shock] + [Interv, Hypox] + [Interv, Interv]$$

	Antimicrobial	Immunomodulation	Ventilation
Factor 1	A-1	B-1	C-1
Factor 2	A-2	B-2	C-2
Factor 3	A-3		

# Ok, but ...

- **Data**

- Quality and integration of EHR within large systems or across consortia
- Standardized point-of-care clinical ‘moments’

- **Institutional commitment**

- Leadership, financial support, and appropriate incentives

- **Ethics**

- Part of the ‘comparative effectiveness’ debate

- **Statistics and design**

- Power and alpha error
  - Bayesian plus simulation vs. closed form frequentist solutions

# Ok, but ...

- **Reporting and dissemination**
  - Rules for 'graduating' winners and losers by subgroups
- **Funding**
  - Who pays for interventions?
  - Who funds overall trial design?
- **Oversight**
  - What should be studied? In what order?
    - Framed as a VOI exercise
  - Who should be in charge?
- **Integration with other clinical research programs**



# Conclusions

- **The post-approval space is a mess**
- **Conflating the EHR with 'Big Data' analytics could make things worse**
  - The allure of Big Data should not thwart efforts to randomize
- **But, huge barriers to randomizing in the post-approval space**
  - Answers are too broad and too narrow
  - No one wants to be a guinea pig
- **The EHR 'could' provide an opportunity for a novel RCT design**
  - 'POC-CTs' + 'Platform' trials = REMAP trials
  - Mimics 'best choice' for patient
    - Safer in the trial than out of it
  - Serves as a continuous quality improvement engine for a HC system
- **But, a not inconsiderable set of challenges!!!!**