



Fusing RCTs with EHR 'Big Data'

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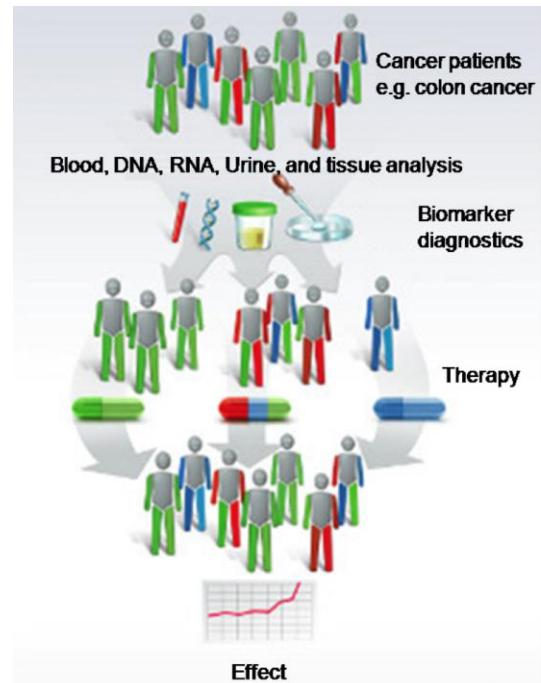
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The post-approval world ...

- 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



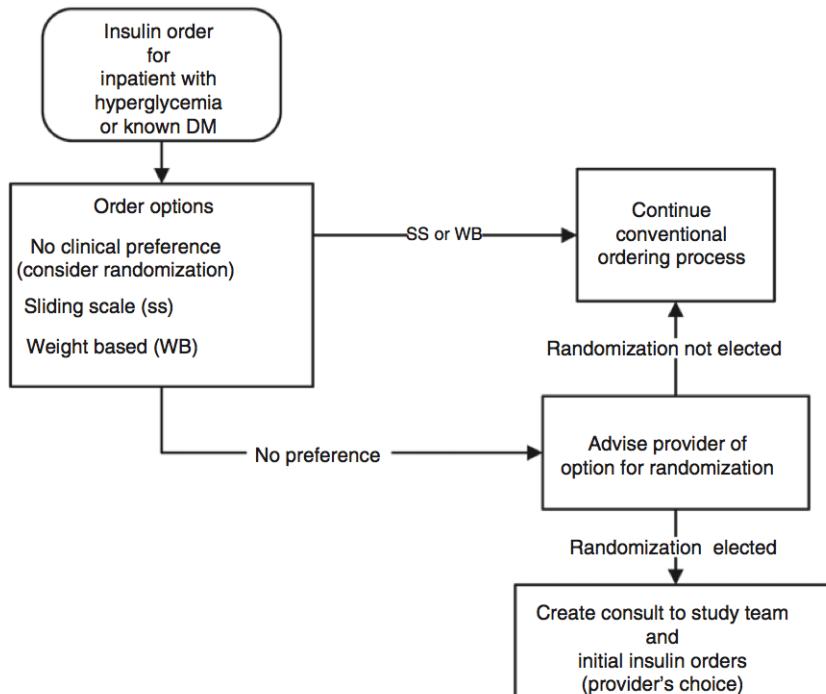
Evidence Generator Report Card

Feature	'Big Data' Analytics
Leverage the EHR	✓
Low incremental costs	✓
Real-world 'effectiveness' estimates	
'Personalized' treatment estimates	✓
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

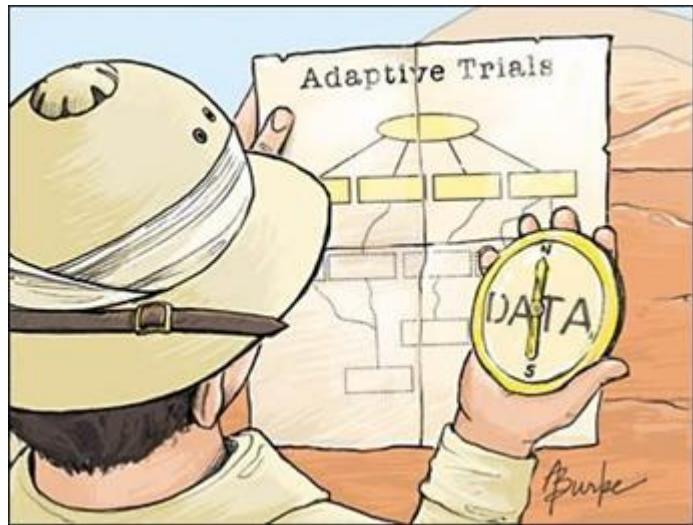
- Targeting the large ‘pragmatic’ trial arena
 - 2 thiazide diuretics in >13k high BP Veterans (NCT02185417)
 - 2 aspirin doses in 20k CVD patients (ADAPTABLE) (PCORI)

Evidence Generator Report Card

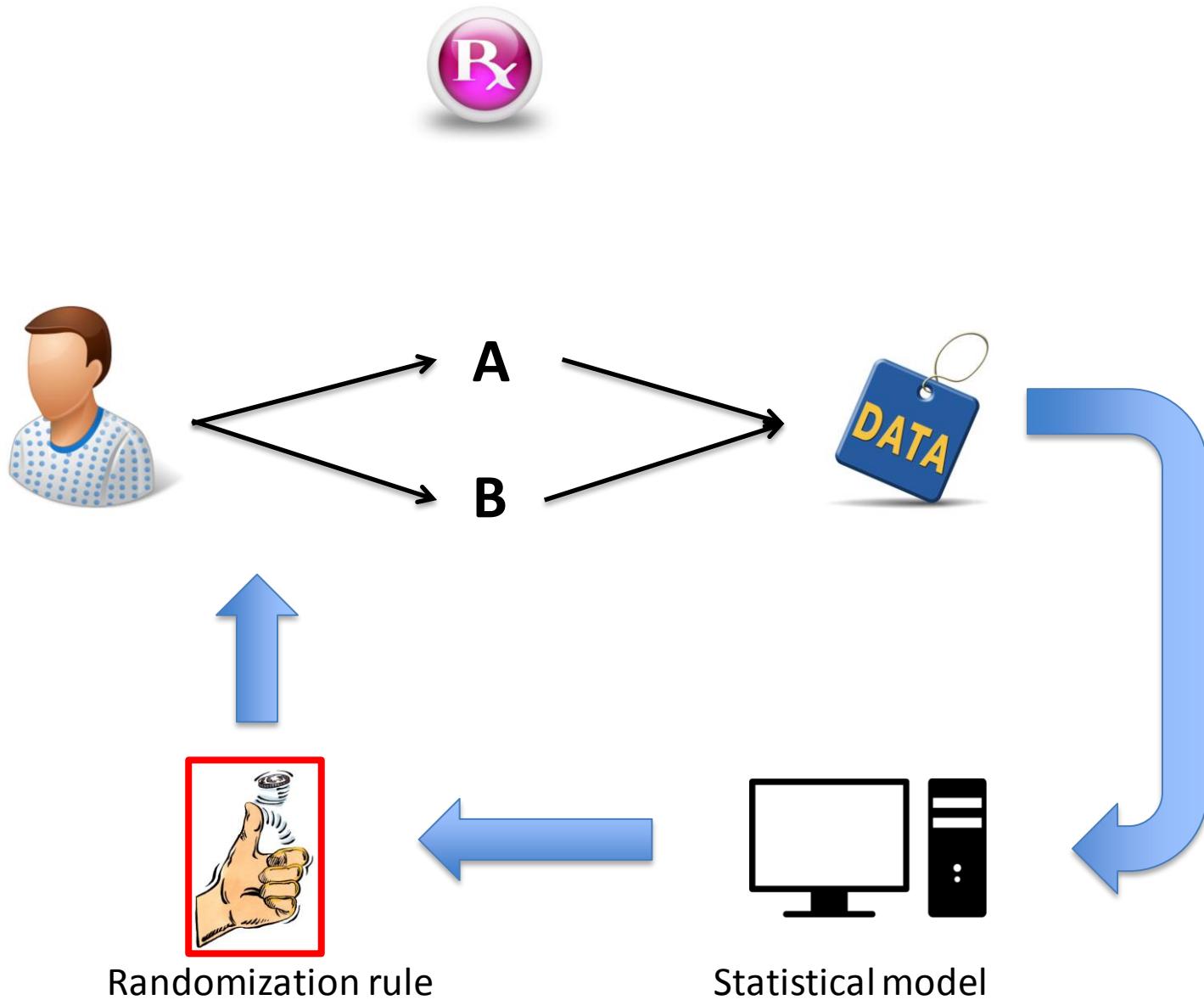
Feature	'Big Data' Analytics	POC Trials
Leverage the EHR	✓	✓
Low incremental costs	✓	✓
Real-world 'effectiveness'	✓	✓
Consider multiple therapies	✓	✗ / ✓
'Personalized' estimates	✓	✗
Offer 'live' tailored options	✓	✗
Robust causal inference	✗	✓

Platform Trials

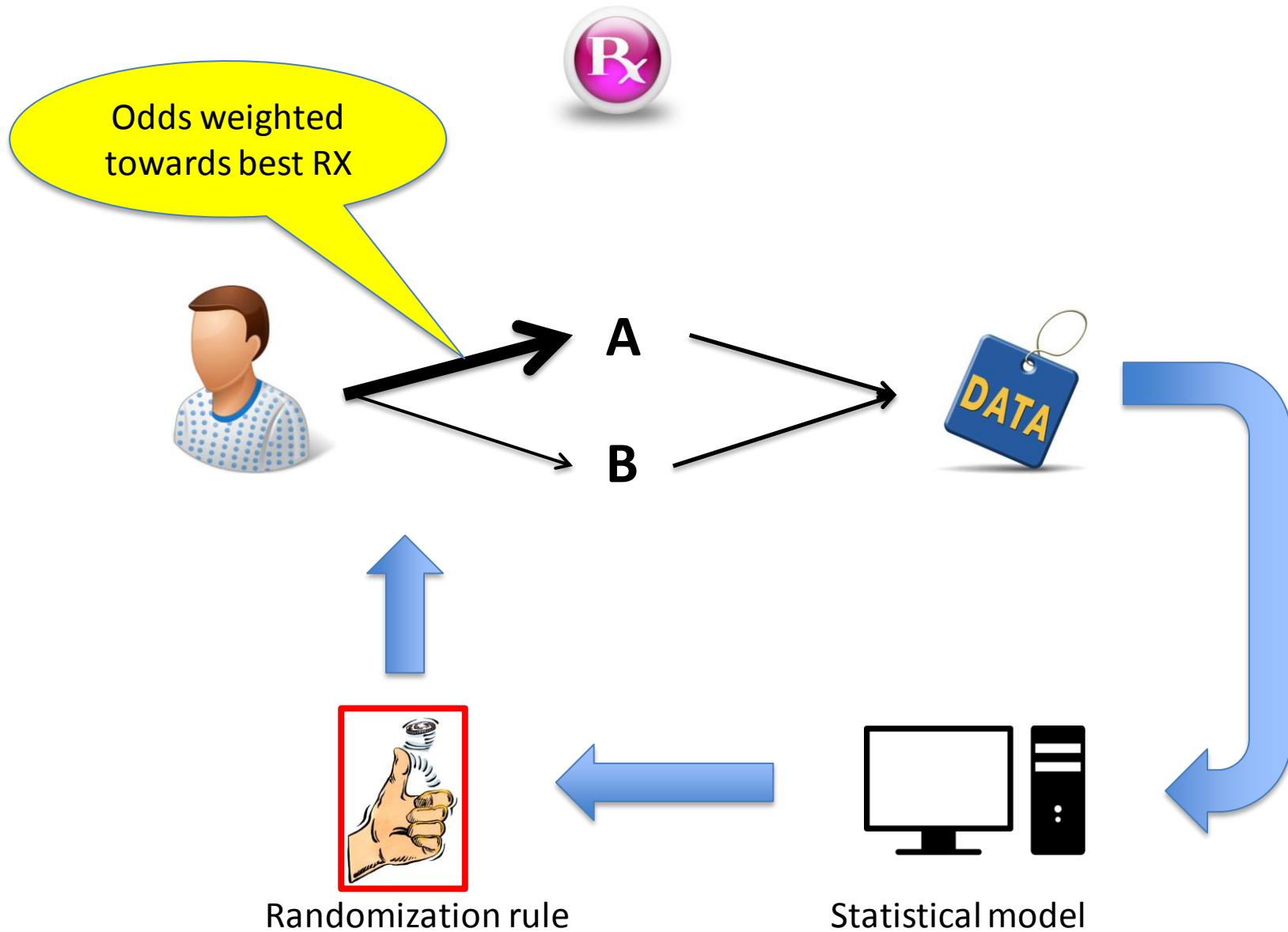
- **Adaptive trials**
 - Focus on disease, not a particular Rx
 - Multiple interventions (arms)
 - ‘Perpetual’ enrollment
 - Tailor choices over time
 - Response-adaptive randomization (RAR)
 - Biomarker-based ‘enrichment’ strategies
- **Focus on pre-approval space**
 - Emphasis on efficiency with (very) 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



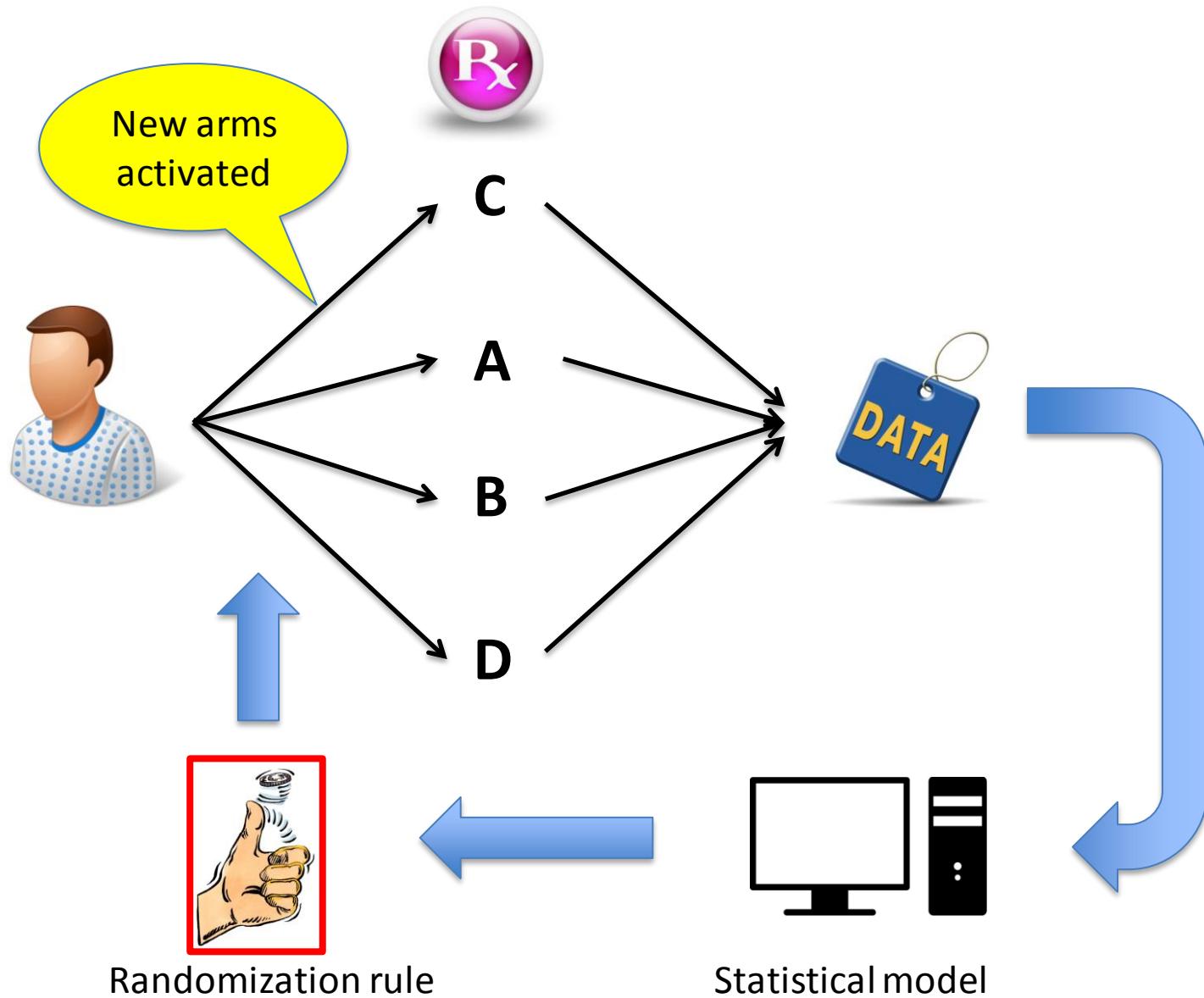
Response-adaptive randomization



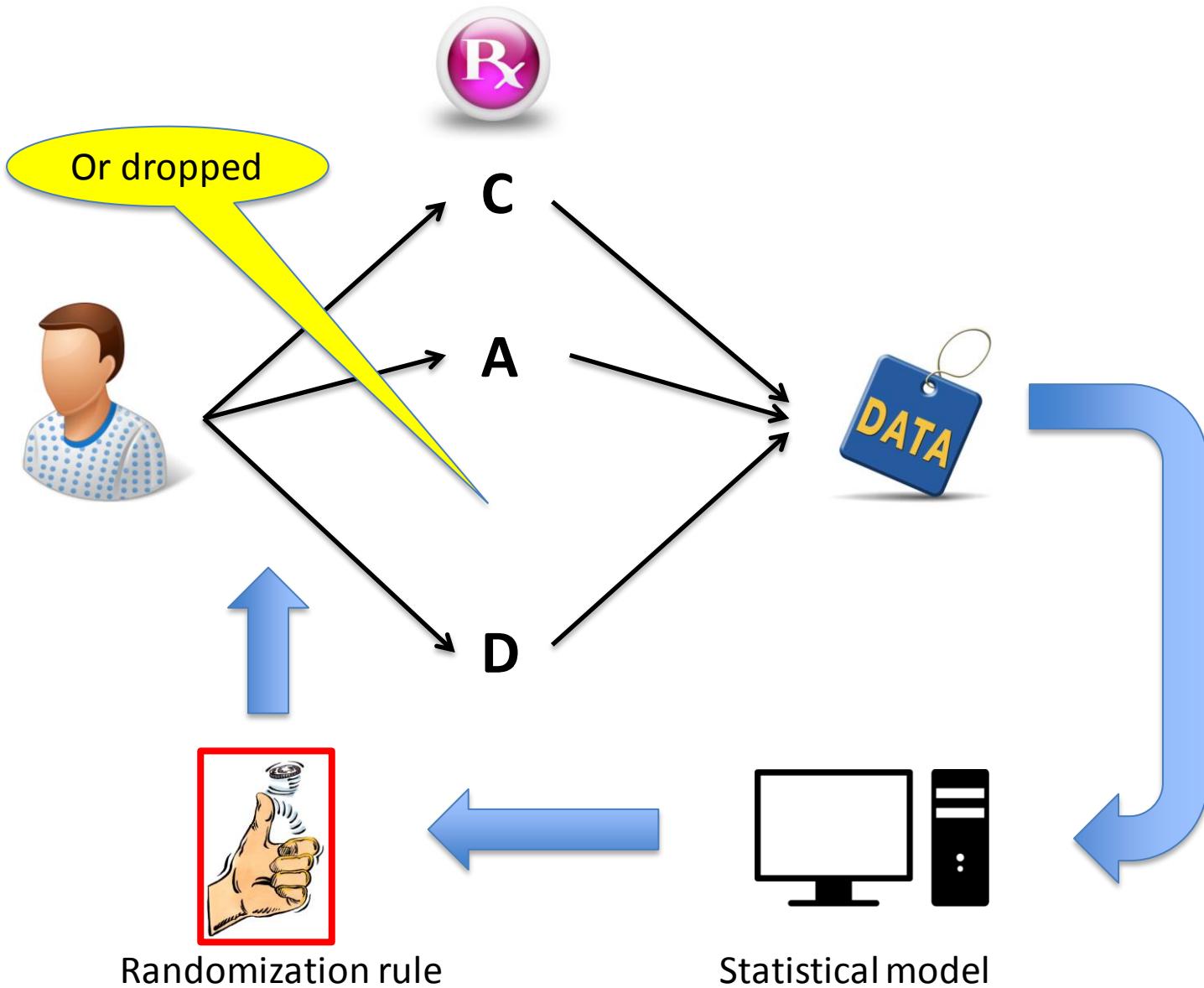
Response-adaptive randomization



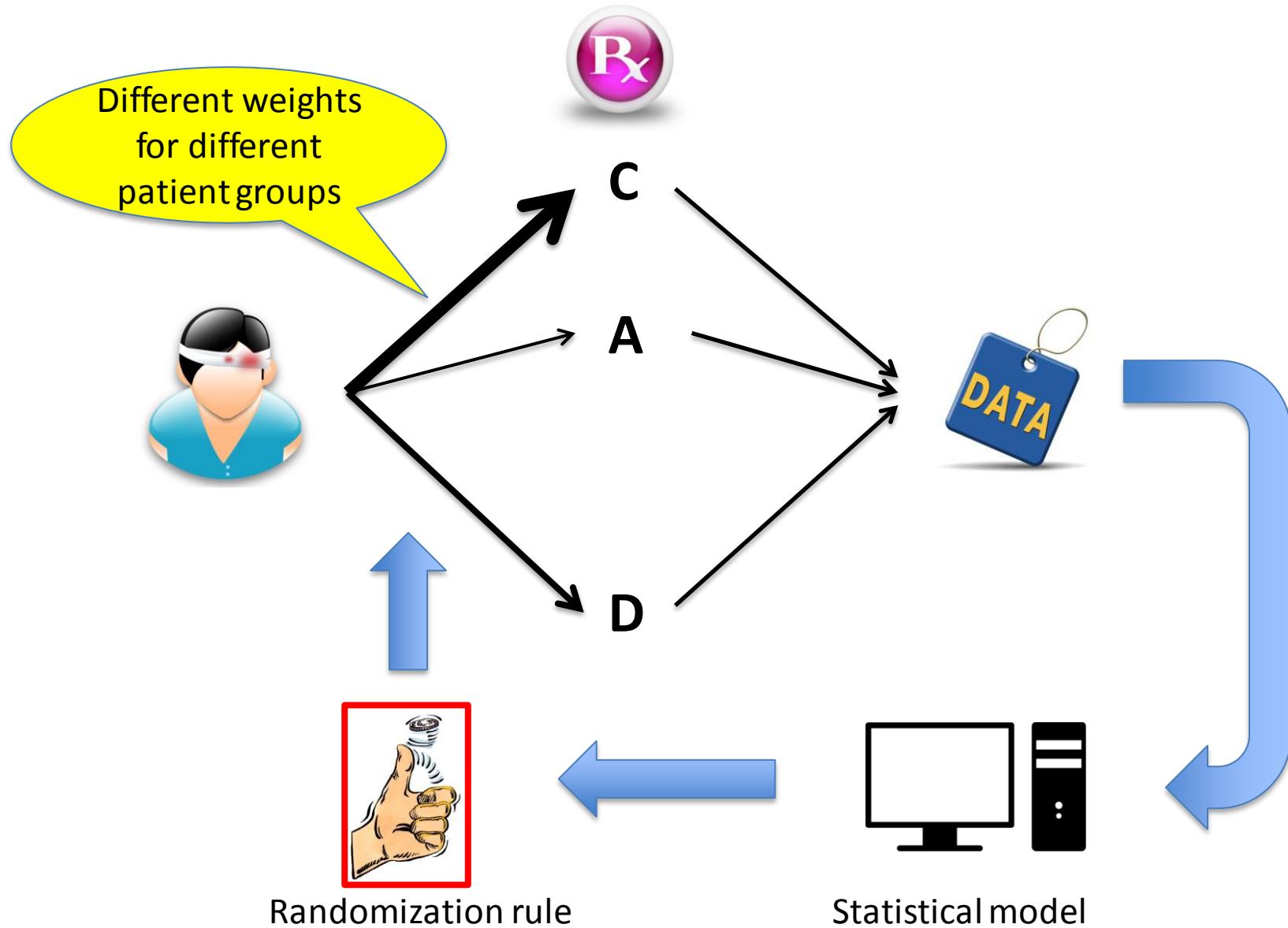
Response-adaptive randomization



Response-adaptive randomization



Response-adaptive randomization



Evidence Generator Report Card

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Leverage the EHR	✓	✓	✗
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Real-world 'effectiveness'	✓	✓	✗
Consider multiple therapies	✓	✗ / ✓	✓
'Personalized' estimates	✓	✗	✓
Offer 'live' tailored options	✓	✗	✓
Robust causal inference	✗	✓	✓

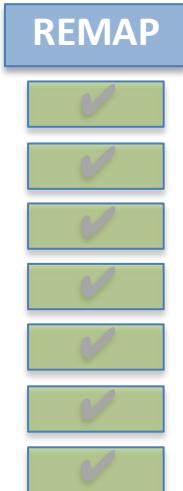
Evidence Generator Report Card

Feature	'Big Data' Analytics	POC Trials	Platform Trials	???
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Consider multiple therapies	✓	✗ / ✓	✓	✓
'Personalized' estimates	✓	✗	✓	✓
Offer 'live' tailored options	✓	✗	✓	✓
Robust causal inference	✗	✓	✓	✓

A novel blend of 'POC' + platform designs

- **REMAP**

- Randomized
- Embedded
- 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

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

Physician Orders - ADULT		attach patient label here
Order Set: Ventilator Bundle- Sedation and Analgesia		
Orders		
<input checked="" type="checkbox"/> will be ordered <input type="checkbox"/> T= Today; N= Now (date and time ordered) <input type="checkbox"/> Height: _____ cm. Weight: _____ kg <input type="checkbox"/> Allergies: _____ <input checked="" type="checkbox"/> No known allergies		
<input type="checkbox"/> Medication allergies <input type="checkbox"/> Lab allergies <input checked="" type="checkbox"/> Ventilator Bundle Care Track		
<input type="checkbox"/> Nursing Communication <input type="checkbox"/> T.N. Upon intubation, discontinue ALL IV analgesics, anesthetics, haloperidol and sedatives. Notify Respiratory. Contact MD for new orders re: sedation and analgesia. When extubation is documented, a nurse will need a task to fog and Pharmacy.		
<input type="checkbox"/> Indications for Usage <input type="checkbox"/> NOTE: Use only for Adult Respiratory Failure Patients requiring intubation and mechanical ventilation <input type="checkbox"/> NOTE: Day 1/24 hours post intubation, Care Track must be on patients chart and implemented by Day 2		
<input type="checkbox"/> Stress Ulcer Prophylaxis Check One <input type="checkbox"/> NOTE: Stress Ulcer Prophylaxis is indicated for patients who are intubated. <input type="checkbox"/> NOTE: Reduce Fentanyl to 20 mcg Q4h if Creatinine Clearance less than 50ml/min <input type="checkbox"/> 1. Fentanyl 20 mcg. Tab. NG set. Routine, T.N. <input type="checkbox"/> 2. Fentanyl 20 mcg. Tab. NG set. Routine, T.N. <input type="checkbox"/> 3. Fentanyl 20 mcg. Tab. NG QDay. Routine, T.N. <input type="checkbox"/> 4. Fentanyl 20 mcg. Tab. NG QDay. Routine, T.N. <input type="checkbox"/> 5. Fentanyl 40 mcg. Cap. NG QDay. Routine, T.N. <input type="checkbox"/> 6. Fentanyl 40 mcg. Injeton. IV. Puls. QDay. Routine		
<input type="checkbox"/> Ventilator Protocol- Ventilator Check One <input type="checkbox"/> VTE Prophylaxis (MEDICAL2229-17E-MEDICAL PROPHYLAXIS) <input type="checkbox"/> VTE Prophylaxis (SURGICAL2229-17E-SURGICAL PROPHYLAXIS)		
<input type="checkbox"/> Respiratory Care <input type="checkbox"/> Intubate Head of Bed T.N. all the time <input type="checkbox"/> NOTE: Elevating head of bed 30 degrees if systolic BP greater than 95mmHg is contraindicated for patients with head and neck surgery or severe skin bleeds		
<input type="checkbox"/> Respiratory Care <input type="checkbox"/> Ventilator Weaning Trial <input type="checkbox"/> Medication by RT <input type="checkbox"/> Ventilator Protocol-Ventilator T.N. Routine		
<input type="checkbox"/> Consult/Notifications <input type="checkbox"/> Notify Physician-Continuing T.N. if extubation goal is not met within 24 hours of initiation of ventilator sedation <input type="checkbox"/> Notify Physician-Once T.N. if sedation goal is not met within 24 hours of initiation of ventilator sedation <input type="checkbox"/> Sedation/Analgesia for Vent Patients Sedation/Analgesia for Vent Patients		
Date	Time	Physician's Signature
PULM Ventilator Bundle- Sedation and Analgesia 2/17/04 09572 195312 Page 1 MD Number		

	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!!!!