Fusing RCTs with EHR ‘Big Data’

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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

<table>
<thead>
<tr>
<th>Feature</th>
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For causal inference, randomize!
Point-of-care (POC) Clinical Trials

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

• 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

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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

Berry et al JAMA 2015
Response-adaptive randomization

Randomization rule

Statistical model
Response-adaptive randomization

Odds weighted towards best RX

Randomization rule

Statistical model
Response-adaptive randomization

- New arms activated

C

A

B

D

Randomization rule

Statistical model

Response - adaptive randomization
Response-adaptive randomization

Randomization rule

Statistical model

Or dropped
Response-adaptive randomization

- Different weights for different patient groups
- Randomization rule
- Statistical model

- C
- A
- D
- Rx

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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

Angus DC. JAMA 2015
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

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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!!!!