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
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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

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

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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

Statistical model

Randomization rule
Response-adaptive randomization

New arms activated

Randomization rule

Statistical model
Response-adaptive randomization

Statistical model
Randomization rule

Or dropped

DATA

Copyright 

Author(s) Name
Response-adaptive randomization

Different weights for different patient groups

Randomization rule

Statistical model
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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

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

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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!!!!