What is the best approach to generating evidence: registries, trials or both?

Andrew D. Althouse, PhD
University of Pittsburgh
Center for Research on Health Care Data Center
Center for Clinical Trials and Data Coordination

Randomized Trials

- Advantages
  - Inherently prospective; allows us to make sure the key data elements are collected in systematic, routine fashion
  - Randomization removes bias (patient and/or provider preference) from treatment assignment
  - Estimation of treatment efficacy from RCT's easier (**a lot easier**) than trying to estimate from observational data with potential confounders and biases in treatment decision
- Disadvantages
  - Costly; requires separate infrastructure from routine clinical care
  - Need sites willing to participate
  - Need clinicians willing to randomize
  - Need patients willing to be randomized
  - Need dedicated research staff to consent / enroll / follow-up patients and record research data

Registries*

- Advantages
  - Ideally, leverages data collected in routine clinical practice (which can result in larger available sample size)
  - Can collect data on outcomes for patients or physicians not willing to participate in randomized trial
  - Excellent for post-marketing surveillance and assessment of long-term outcomes “in the real world”
  - Still costly, but doesn’t require full infrastructure of RCT’s, nor does it require physicians and patients willing to be randomized
- Disadvantages
  - If reliant on “routine clinical data” (EHR) may have a lot of missing or inconsistency; less control exercised for systematic collection of data, routine follow-up, or ascertainment of outcomes
  - Much harder to accurately estimate treatment efficacy due to biases in choice of treatment (which is kind of important when you’re trying to learn whether treatments work…)

Both…Living Together?

- High-quality evidence requires both RCT (assessment of treatment efficacy before bringing things to market) and registries (surveillance, understanding of utilization & prevalence, ongoing cost-effectiveness & economic analyses, safety monitoring for rare adverse events that may not have emerged in RCT's, hypothesis generation for future RCT's)
- Even when RCT are used to test therapies before wide adoption, we still use registries or "real world" data for many other useful research purposes…
- So if we create them anyway, shouldn't it be possible to conduct randomized trials within the framework of those big registries?

The Dream: **REMAP** Trial

Randomized	Avoids bias in treatment assignment due to patient and/or physician preference that might systematically bias results in favor of one treatment
Embedded	Leverages modern EHR to decrease burden of finding the patients, recruiting, & collecting data; potentially "embed" inclusion criteria to automatically flag eligible patients and enroll them (somewhat) seamlessly
Multifactorial	Allows consideration of multiple treatment combinations (different combinations of strategies / drugs / MCS devices) in a single trial framework; efficient for very hard-to-recruit populations, consider interaction between treatments
Adaptive	Randomization probabilities varied by accruing data; keeps benefit of randomization (unbiased estimates of treatment efficacy) while making it safer to be "in" the trial rather than outside it
Platform	Once infrastructure is in place, trial can be run for indefinite period of time; newer treatment options can be "added" to trial, options that are known to be inferior may be dropped

REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

- https://clinicaltrials.gov/ct2/show/NCT02735707
- Currently enrolling at 37 sites worldwide
- REMAP-CAP has been designed to:
  - Test several treatments, at the same time, in the same patient.
  - Look at the results as it goes and uses these results so that new patients in the study have a better chance of getting better treatments
  - Drop treatments if they are shown to be less effective than others
  - Add new treatments to the study as those that have undergone testing complete their evaluation

“Closer to Real Care Decisions”

“Should my severe CAP patient receive IV hydrocortisone?”

- **Depends on whether:**
  - shock is present
  - underlying cause is viral or not
  - an anti-viral is being administered
  - other strategies are being used that may minimize lung injury

- **REMAP trials take this information into account, then use accruing trial data to generate estimated probabilities of success of treatment options combined with response-adaptive randomization**

- **Separate probability estimates computed for each consideration:**
  - Trial continues until predefined level of certainty reached
  - When one question hits threshold, answer is announced for that question; however, trial framework carries on answering other questions

Issues For “REMAP-CS”

- Overcoming Inertia: “This Is The Way We’ve Always Done It”
- Funding & Large, Multi-Institutional Coordination
- Integration of EHR’s (screening / consent / randomization)
- Data Quality in EHR’s (if used to capture outcome data)
- Who Should Be Eligible for Trial?
- What Treatments / Combinations Should Be Studied?
- What Patient Profiles / Subgroups Of Special Interest?
- Statistical Complexity (REMAP-CAP led by Berry Consultants)
- Funding Sources Willing To Sustain REMAP trials (???)