Single-Patient (N-of-1) Trials: A Pragmatic Clinical Decision Methodology for Patient-Centered Comparative Effectiveness Research

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Two Inter-Linked Themes

- Single-patient trial can be a useful tool for clinical decision-making
- Methodology for local investigations that aim to produce local knowledge (vs. generalizable knowledge) deserves further investigations
  - Single-patient trial being a good example of such local investigations

Outline

- Overview of Single patient (n-of-1) trials (SPT)
  - Clinical question
  - Basic protocol
  - Key features
- Implementation issues
  - Indications and contradictions
  - Blinding vs open label
  - Physical washout vs. “analytic washout”
  - Infrastructure needs
- Local investigations and local knowledge
- Discussions

Clinical Question

- Patient with chronic condition such as chronic pain
- Uncertainty Re: the comparative effectiveness of treatment options for this specific patient
  - Lack of existing research evidence
  - Potential for heterogeneity of treatment effects (Kravitz, Duan, Braslow 2004)
- Possible solution: conduct patient-centered comparative effectiveness investigation within this specific patient to inform his/her clinical decision

Basic Protocol

- Within patient multiple cross-over trials
- Assign time intervals (e.g., weeks) to alternate treatment options, say, ABBABAAB….
- Collect outcome measures over time
- Compare outcomes under each treatment option
- Select treatment option with superior performance

Key Features

- Consistent with routine clinical practice
  - Pull, not push
- Potential to improve outcomes for individual patients
  - Empirical evaluation is warranted
- Infrastructure needs
  - Application of mobile health (mHealth) technology
- Financial mechanism needs

PREEMPT Study

- Personalized Research for Monitoring Pain Treatment (PREEMPT)
- SPT using mHealth in Chronic Pain
- NINR-funded
- Infrastructure development (IT, Statistics)
- RCT to compare patients randomized to SPT vs. usual care

Implementation Issues

- Indications and contradictions
- Blinding vs open label
- Physical washout vs. “analytic washout”
- Infrastructure needs

Indications and Contradictions

- Duan, Kravitz, and Schmid (2013), Table 1
- Chronicity and stability
  - On-going treatment for chronic conditions
  - Stable treatment effects
- Need for personalized knowledge
  - Lack of adequate evidence
  - Heterogeneity of treatment effects, one size might not fit all
- Quick effect onset and extinction, but…
  - Quick onset of treatment effect
  - Negligible carry-over effect, no irreversible effects
- Examples: fibromyalgia, chronic pain, attention deficit-hyperactivity disorder, insomnia, asthma, chemotherapy-associated nausea and vomiting, allergic rhinitis…

Blinding or Open Label?

- Blinding (when feasible) is often important for parallel group trials that aim to produce generalizable knowledge for future patients
  - Expectancy among trial participants might not generalize to future patients
- Concern might not apply to SPT that aims to inform future treatment decision for the patient undergoing trial
  - Expectancy might persist from trial period into "consumption period"

Physical Washout or "Analytic Washout"?

- Washout period often inserted between treatment periods to eliminate/reduce carryover effect
- Does not address time required for onset of new treatment effect
- Might prolong transition between treatment period
- Problematic for comparative effectiveness investigations with active treatments
- "Analytic washout" models outcome trajectory, attempting to project long term treatment effect, without physical washout
  - Requires frequent outcome measurements, say, daily within weeklong treatment period

Infrastructure Needs

- IT infrastructure to facilitate trial design, implementation, data collection…
- Statistical infrastructure to facilitate trial design, data analysis, feedback…
- Infrastructure development can reduce barrier to utilize trials in non-research settings

Literature (I)

- Duan N, Kravitz RL, Schmid CH. Single-Patient (N-of-1) Trials: A Pragmatic Clinical Decision Methodology for Patient-Centered Comparative Effectiveness Research. *Journal of Clinical Epidemiology*. 2013 Aug;66(8 Suppl):S21-8.
- Kravitz RL, Duan N, eds, and the DEcIDE Methods Center N-of-1 Guidance Panel (Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S). *Design and Implementation of N-of-1 Trials: A User's Guide*. AHRQ Publication No. 13-EHC122-EF. Rockville, MD: Agency for Healthcare Research and Quality; in press, www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Literature (II)

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- Zucker DR, et al. Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. *Journal of Rheumatology*, 2006. **33**(10): p. 2069-2077.
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Local Investigations and Local Knowledge

- Biostatistical methods have been dominated by human subjects research that aims to produce generalizable knowledge to be exported to consumers external to the research
- Implementation and quality improvement programs often require local investigations that address local issues and produce local knowledge for local consumption
  - Methodological developments needed
  - SPT is the most local of local investigations

Ethical Implications

- Distinction between generalizable knowledge and local knowledge is fundamental to the distinction between human subjects research and quality improvement

Is SPT Human Subjects Research?

- Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. (45 CFR 46.102(d))
- Primary objective for clinical applications of SPT is often to produce specific knowledge for individual patient, not to produce generalizable knowledge
  - Self-contained population for production and consumption of specific knowledge, not to export generalizable knowledge from trial population to consumption population
  - Generalizable knowledge might result from SPTs as a by-product, but not as the primary objective

Is SPT Quality Improvement?

- Application of SPT for quality improvement in clinical care might not be subject to regulations for human subjects research
- "Protecting human subjects during research activities is critical and has been at the forefront of HHS activities for decades. In addition, HHS is committed to taking every appropriate opportunity to measure and improve the quality of care for patients. These two important goals typically do not intersect, since most quality improvement efforts are not research subject to the HHS protection of human subjects regulations." (http://answers.hhs.gov/ohrp/questions/7281)

Local Investigations

- Implementation/QI programs often require local investigations to address specific local issues, to produce local knowledge for local consumption
  - SPT is the most local of local investigations
- Empirical investigations can be utilized more broadly to produce such local knowledge
  - Small n problem?
- How to design local investigations? For example,
  - Finite patient horizon (small N, not small n)
  - Cheung K, Duan N. Design of implementation studies for quality improvement programs: an effectiveness-cost-effectiveness framework. Am J Public Health. 2014 Jan;104(1):e23-30. Epub 2013 Nov 14.

Side Bar: CEEBIT

- Mohr DC, Cheung K, Schueller SM, Hendricks Brown C, Duan N. Continuous evaluation of evolving behavioral intervention technologies. Am J Prev Med. 2013 Oct;45(4):517-23.
- Limited shelf-life for rapidly evolving BITs
- On-going open-ended horserace, allowing new entries, and removal of inferior horses (or, adaptive assignments)

Discussions

- Single-patient (n-of-1) trials can be a useful tool for treatment decisions for on-going treatment for chronic conditions consistent with indications discussed in Duan, Kravitz, and Schmid (2013), Table 1.
- Effectiveness of SPTs in improving long term patient outcomes needs to be established empirically in studies such as PREEMPT.
- Broad implementation of SPTs requires solution of infrastructure needs and implementation issues
- Methodology for designing rigorous local investigations can facilitate wider use of such investigations in implementation/QI programs

Thank you!

- Comments? Suggestions?

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Randomization or Counter-Balance

- Objective: balance between treatment conditions in terms of potential confounding factors such as time trend
  - AAAABBBB very bad
  - ABABABAB not so good
  - ABBABAAB much better
- Blocked randomization vs. simple randomization
  - Small block size OK, no concerns about selection bias
- Counter-balance (maybe with restricted randomization) might achieve better balance
  - ABBA or BAAB provides better protection against linear time trend than ABAB or BABA

Standardize or adapt/personalize?

- Incorporate user preference?
- Selection and weighting of outcomes
- Selection of criteria and format for reporting
- CER or PCOR

Statistical Methods: Borrow from Strength

- Individual's own SPT data most informative about his/her future treatment decisions
- Caveat: individual SPT usually of limited duration, with limited precision in estimated treatment effects
- Empirical Bayes methods can be used to "borrow from strength", combining index patient's own data with aggregate data from other patients with similar conditions, to provide more precise treatment effect estimates
  - Shrinkage estimator

Methodological Development Needs

- Use of sequential stopping rules
- Use of responsive-adaptive designs with skewed randomization to incorporate partial information available
- Analytic strategies to deal with onset and carryover effects
  - Growth curve modeling with repeatedly interrupted time series)
- Effective ways to summarize SPT findings for end-users (patients and their providers)
  - Communication of uncertainty

Publications from QI Investigations

- '…the intent to publish is an insufficient criterion for determining whether a quality improvement activity involves research… Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research… (http://answers.hhs.gov/ohrp/questions/7286)