New Methodological Directions in: Harvesting the Scientific Investment in Prevention Science to Promote Children's Cognitive, Affective, and Behavioral Health

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Outline

- Advances in Prevention Methodology
  - NRC-IOM 2009 report, Chapter 10
- Expanded portfolio of study designs to address broadened array of research questions
- Mixed methods
- Advances in technology
- “Small data” applications for implementation, dissemination, and quality improvement
- Discussions

Advances in Prevention Methodology

- Preventing Mental, Emotional, and Behavioral Disorders Among Young People: Progress and Possibilities, NRC-IOM (2009), Chapter 10:
- Advances in statistical methodologies have contributed to improved interventions, etiological theories, and theories of change
- Methodologies to evaluate approaches to implementation and dissemination are less well developed than methodologies related to efficacy and effectiveness

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Study Design and Research Q's

- Standard two-armed RCT is suitable for efficacy research
- Alternative designs are needed for research questions in comparative effectiveness research, implementation and dissemination research, quality improvement, etc.
  - Pragmatic trial
  - Factorial trial
  - Sequential multiple assignment randomized trial

Pragmatic Trial for Comparative Effectiveness Research

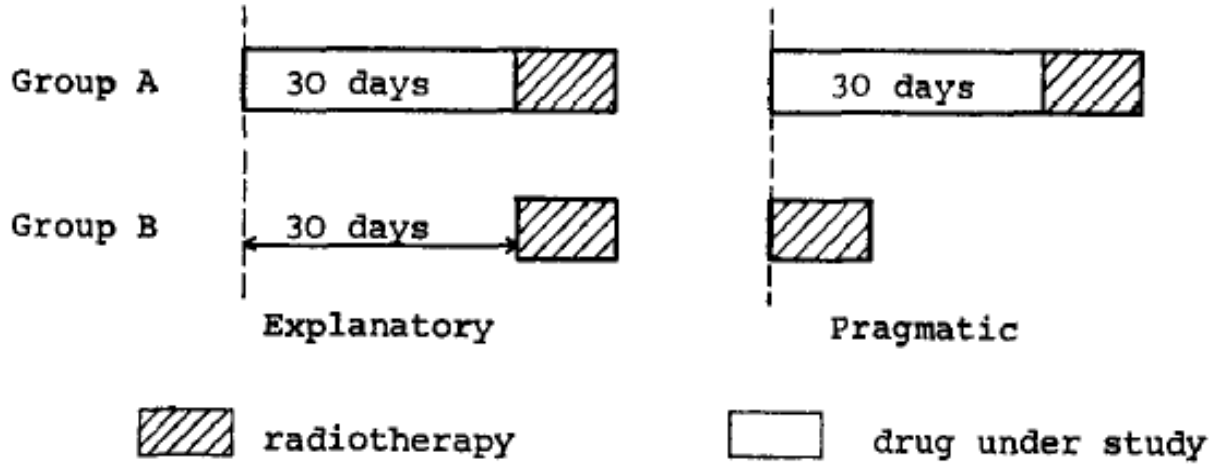
- Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis. 1967 Aug;20(8):637-48. Republished: J Clin Epidemiol. 2009 May;62(5):499-505.
- Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003 Sep 24;290(12):1624-32.

1.1. *"Equalized" or "optimal" conditions*

Consider a trial of anti-cancer treatments in which radiotherapy alone is to be compared with radiotherapy preceded by the administration of a drug which has no effect by itself but which may sensitise the patient to the effects of radiation. Suppose the drug is to be administered over a 30-day period. The "radiotherapy alone" group may then be handled in two different ways (Fig. 1):

(a) radiotherapy may be preceded by a blank period of 30 days, so that it is instituted at the same time in each group;

(b) radiotherapy may be instituted at once, thereby carrying it out at what is most probably the optimal time.



Is There an Attention Bias? (I)

- Medication vs. Therapy
  - More intensive contact with clinician among therapy patients
- Explanatory trial
  - Difference in attention intensity considered a confounding factor
    - There is an attention bias
  - Control/equalize all contextual factors
    - Impose non-therapeutic clinician contact among medication patients?

Is There an Attention Bias? (II)

- Pragmatic trial
  - Difference in attention intensity is natural for the way each treatment is delivered
  - Compare treatment bundles, not isolated treatment ingredients
    - "Medication + low attention" vs.

      "Therapy + high attention"
  - There is no attention bias
  - Incorporate/optimize all contextual factors

Distinct Research Questions Neither Right Or Wrong

- Explanatory trial informs development of new treatment, "provides information on the effects of the key component"
  - Lab condition
  - Control for contextual factors – "everything being equal…"
- Pragmatic trial informs clinical and policy decision-making, "compares two complex treatments as a whole under practical conditions"
  - Naturalistic condition
  - Incorporate contextual factors – treatment bundle

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Factorial Trial to Inform Design and Optimization of Multi-Component Interventions

- Robust parameter design
  - Nair VN, et al. *Technometrics*. 1992;34(2):127-161.
  - Duan et al. Psychiatric Services. 2001;52:413.
- Multiphase optimization strategy (MOST)
  - Collins et al. Ann Behav Med. 2005;30(1):65-73; Am J Prev Med. 2007;32(5 Suppl):S112-8; Ann Behav Med. 2011;41(2):208-26; Collins, Murphy, Strecher. Am J Prev Med. 2007;32(5 Suppl): S112-8; Chakraborty et al. Stat Med. 2009;20;28(21):2687-708
  - methodology.psu.edu/ra/most

Factorial Trial to Assess Consumer Preference

- Integrate business models into prevention to address consumer needs from the beginning
  - Rotheram-Borus & Duan. J Am Acad Child Adolesc Psychiatry. 2003;42(5):518-26.
- Conjoint Analysis
  - Factorial trial imbedded in consumer survey to assess consumer preference for alternative configurations of multi-component products
  - Green & Srinivasan. *J of Consumer Research*, 1978;5:103–123
  - Lee et al. Int J STD AIDS. 2012;23(4):235-41.

Sequential Multiple Assignment Randomized Trial (SMART)

- Development and evaluation of dynamic treatment regimes (a.k.a. adaptive treatment strategies) to inform multi-stage treatment decisions
  - Murphy. J. R. Stat. Soc. B. 2003;65(2):331-366; Stat. Med. 2005;24:1455–81; Collins, Murphy, Strecher. Am J Prev Med. 2007;32(5 Suppl):S112-8; Chakraborty & Murphy, Annu. Rev. Stat. Appl. 2014. 1:447–64
  - dept.stat.lsa.umich.edu/~samurphy/
  - methodology.psu.edu/ra/adap-inter/projects

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Mixed Methods

- Green et al. Approaches to Mixed Methods Dissemination and Implementation Research: Methods, Strengths, Caveats, and Opportunities. Adm Policy Ment Health. 2014 Apr 11. [Epub ahead of print]
- Optimal Design and Purposeful Sampling
  - Duan, Bhaumik, Palinkas, Hoagwood. Optimal Design and Purposeful Sampling: Complementary Methodologies for Implementation Research. Manuscript.

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Advances in Technology

- Information and sensing technologies facilitates intervention delivery and data acquisition/processing/analysis
- Distributed ownership of technologies allows customization of objectives and procedures

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“Small Data” Applications for Implementation, Dissemination, and Quality Improvement

- “Small data”
- Heterogeneity of treatment effects
- Methodology for local investigations
- Single patient (n-of-1) trials

“Small Data Is the Real Revolution”?

- “Forget big data, small data is the real revolution”
  - Rufus Pollock, April 2013
  - http://blog.okfn.org/2013/04/22/forget-big-data-small-data-is-the-real-revolution/
  - http://www.theguardian.com/news/datablog/2013/apr/25/forget-big-data-small-data-revolution
- “mass democratisation of the means of access, storage and processing of data”
- Not "one ring to rule them all" but "small pieces loosely joined"

“Small Data” Enterprises

- Small Data Lab @ CornellTech, Deborah Estrin
  - develops new personal data APIs and applications for individuals to harvest the small data traces they generate daily
- Small Data Group, Allen Bonde
  - provide insightful perspectives, research, and case studies for organizations looking to deliver the power of big data to *everyday work*, via targeted, consumer-style, self-service analytical tools and apps

PatientsLikeMe.com

- More than 250,000 members
- We want to democratize the process of monitoring disease progression and return the results to patients as quickly as possible, so they are empowered to make the best decisions

QuantifiedSelf.com

- Self knowledge through numbers; collaboration of users and makers of self-tracking tools; help people get meaning out of their personal data
- Dozens of meeting groups in US, Europe, Asian, Latin America (4), ANZ (3), Africa (1)
- 2014 Quantified Self Europe Conference (sixth)
  - May 2014, Amsterdam; more than 100 presentations, hundreds of attendees from Chicago, Copenhagen, Kyoto, …
    - Experiments in Self-Tracking
    - Wearable Technologies for Active Living
    - Quantifying Our Sleep…

“Small Data” Applications for Implementation, Dissemination, and Quality Improvement

- “Small data”
  - ➢ Heterogeneity of treatment effects
- Methodology for local investigations
- Single patient (n-of-1) trials

Heterogeneity of Treatment Effects

- Kravitz et al. Milbank Q. 2004;82(4):661-87.
- One size often does not fit all
- Often need to target intervention delivery
- Often need to adapt intervention to accommodate unique context in each service delivery organization
- “Small data” applications may help address those needs

“Small Data” Applications for Implementation, Dissemination, and Quality Improvement

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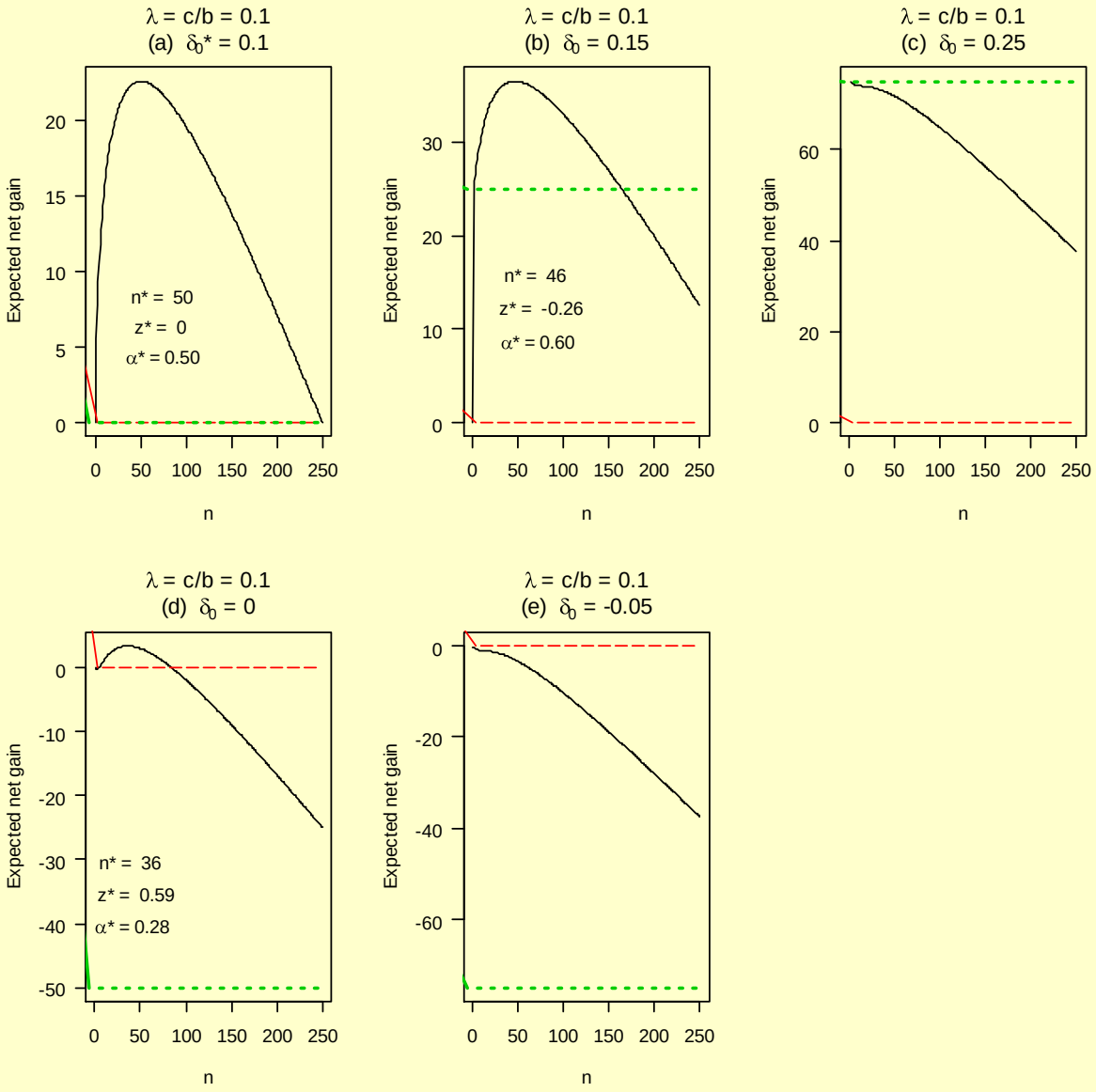
Methodology for Local Investigations

- Biostatistical methods have been dominated by *research* that aims to produce *generalizable knowledge* to be exported to consumers external to the research
- Implementation, dissemination, and quality improvement programs often require *local investigations that address local issues and produce local knowledge for local consumption*
  - "Local" context can be a practice network, an individual practice, an individual patient), etc.
  - More attention is needed to address methodological needs for such local investigations

Methodology for Local Investigations (cont.)

- Mixed methods are promising
- Statistical investigations can be utilized more broadly to produce local knowledge for local consumption
  - Small N framework, not “small n problem”
  - Cheung & Duan. Am J Public Health. 2014 Jan;104(1):e23-30. Epub 2013 Nov 14.



tegy $E(G_2)$ versus sample size at optimal z* under a variety of prior mean δ_0. The red horizontal line indicates the expected net gain for late-adopter E

“Small Data” Applications for Implementation, Dissemination, and Quality Improvement

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Single Patient (N-of-1) Trials (SPT)

- Within patient multiple cross-over trials
  - Experimental unit: time intervals within individual patient
- Systematic, balanced assignment of time intervals (e.g., weeks) to alternate treatment options, say, ABBABAAB….
- Systematic, repeated outcome assessments
  - At least once per time period, ideally more (days within weeks)
- Compare outcomes across treatment options
  - A weeks vs. B weeks
- Select treatment option with preferred performance

SPT (cont.)

- Research to produce generalizable knowledge, to inform treatment decisions for future patients
- Quality improvement to produce local knowledge, to inform treatment decision for current patient
  - Small data application that serves the need of current patient
  - Borrow from strength
    - “small pieces loosely joined”
  - Generalizable knowledge may result as a by-product

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(14)-EHC122-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2014. www.effectivehealthcare.ahrq.gov/N-1-Trials.cfm.

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

Methodological Research Needs for SPT

- Sequential stopping rules
- Adaptive treatment assignment (multilevel)
- Analytic washout
- Model selection (automated)
- Borrow from strength with similar but non-identical SPTs
- Communication with end users

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Discussions

- Advances in methodology contribute towards advances in prevention science
- Further integration and development of methodologies needed for implementation, dissemination, and quality improvement
- Recommendation for Forum to sponsor a workshop devoted to prevention methodology

Evidence Beyond Statistical Significance

- Emphasize effect size, clinical significance, and confidence interval or credibility interval
- CONSORT Statement
  - http://www.consort-statement.org/
  - Item 17a: For each primary and secondary outcome, [provide] results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
  - Although P values may be provided in addition to confidence intervals, results should not be reported solely as P values.