Building an Evidence Base for Clinical Practice: Role of Pragmatic Trials

Gary E. Rosenthal, MD

Roy J. Carver Chair in Internal Medicine Professor and Interim Chairman, Department of Internal Medicine
Director, University of Iowa Institute for Clinical and Translational Science

November 7, 2014
Clinical Practice in the US: Biopsy

- Total expenditures of $2.9 trillion in 2013 (18% of GDP)
- Per capita expenses **50% higher** than next most expensive nation (Norway) & **2.5 times higher** than median for other industrialized nations
- Comparative study of 7 nations (US, UK, Australia, NZ, Canada, Germany, & Netherlands) → **US ranked last or next to last** on measures of access, safety, efficiency, care coordination, & equity (*Commonwealth Fund*)
- Significant variation in costs across US → **Higher costs do not yield higher quality**
State Rankings for 24 Quality Measures & Medicare Spending
(Baicker & Chandra, Health Affairs 2004)
Inescapable Diagnosis:
Little Bang for the Buck

- Recent estimates:
  - 30% of Medicare spending could be avoided without worsening patient outcomes (Dartmouth Institute)
  - 1/3 of healthcare expenditures is wasteful (Berwick, 2012)
Little Bang for the Buck: Lack of High Quality Evidence

- Underlying factors complex but include the lack of high quality clinical evidence on what works in healthcare

✓ *Less than 20% of interventions used in common clinical practice based on evidence from RCTs*

✓ *Many RCTs study homogeneous populations → limits generalizability to large percent of patients in routine practice, including those with multiple comorbidities who drive substantial healthcare spending.*
How Can We Build the Necessary Evidence Base to Improve Clinical Practice?

- Traditional multi-site RCTs are expensive → $50 to 250 million
- Thus, new paradigms urgently needed to create high quality evidence to inform clinical decision making
  - Learning Health Systems
  - Practice-based pragmatic trials
Overview of Presentation

- Present working definitions of a learning health system and a practice-based pragmatic clinical trial
- Contrast differences between pragmatic trials and traditional clinical trials
- Review methodological and cultural issues that must be addressed to:
  - Advance agendas in pragmatic trials and practice-based research and
  - Enable creation of high value learning health systems
Learning Health System: What is It?
(Institute of Medicine, 2007)

A delivery system in which ...

“science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”
Learning Health System *(Green, 2012)*

**Evaluate**
- Collect data and analyze results to show what works and what doesn’t.

**Adjust**
- Use evidence to influence continual improvement.

**Implement**
- Apply plan in pilot and control settings.

**Design**
- Design care and evaluation based on evidence generated here and elsewhere.

**Disseminate**
- Share results to improve care for everyone.

**Internal and External Scan**
- Identify problems and potentially innovative solutions.

In a learning health care system, research influences practice and practice influences research.
Learning Health System: What’s Different?

1. Tight integration between research and practice such that research findings directly inform practice and key issues faced by practitioners become the focus of future research projects

2. Research is conducted in routine practice settings with modest research infrastructures

3. Health system resources, such as the EMR, are an integral part of the infrastructure
Pragmatic Clinical Trials

- Term first used by Schwarz and Llellouch in 1967 (J Chron Dis 1967; 20: 637-648)
- Distinguished between trials that were explanatory in orientation and trials that were pragmatic
- **Explanatory**: aimed at mechanistic understanding → discover if a difference exists between two treatments that are specified by strict definitions
- **Pragmatic**: aimed at clinical decision-making → discover which treatment would be preferred as the treatments would be administered in clinical practice
Differences in Explanatory & Pragmatic Approaches to Trial Design \textit{(Schwarz & Lellouch, 1967)}

- Possible study comparing XRT alone and XRT plus sensitizing drug administered 30 days prior to XRT

- **Explanatory** approach to control group
  - XRT preceded by 30-day period in which no Rx given
  - XRT + drug group and XRT alone control group receive XRT at same time

- **Pragmatic** approach to control group
  - XRT given right after decision to use XRT is made
  - XRT + drug and XRT alone groups control receive XRT at different time
Differences in Study Populations

- Explanatory trials often enroll homogeneous patients with few comorbid conditions to reduce response variation.
- PCTs have fewer patient selection criteria & seek to enroll more heterogeneous populations → may have higher external validity but lower internal validity.
- PCTs may require larger sample sizes because of patient heterogeneity.
Differences Between Pragmatic and Explanatory Trials (cont.)

Differences in Treatment & Control Groups

- Explanatory trials often compare new treatments to placebo treatments and may not compare a new treatment to existing treatments.

- PCTs typically compare two or more ‘standard of care’ treatments, often for which there is clinical equipoise.

- In PCTs, patients & clinicians typically not blinded to treatment assignment \(\Rightarrow\) however, allocation to study groups should be random and assessment of outcomes should be blinded.
Differences Between Pragmatic and Explanatory Trials (cont.)

Differences in the Intervention Being Tested

- Explanatory interventions typically delivered by specialized practitioners in highly controlled settings to maximize intervention fidelity

- Pragmatic interventions:
  - delivered in routine practice settings with modest infrastructures to support delivery of intervention
  - incorporate flexibility to account for the individual needs of patients & capabilities of delivery settings
Differences Between Pragmatic and Explanatory Trials (cont.)

Other Important Issues

- PCTs may require longer follow-up to track outcomes reflecting “real life” concerns of patients & may be better suited to study chronic conditions that require treatment over many years

- Analysis typically based on “intention-to-treat” approach recognizing that treatment cross-over may be more common than in explanatory trials
Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) (Thorpe, CMAJ 2009)
Classification of Trials Using PRECIS

1. Self-Administered vs. Observed TB Rx
2. North American CEA Trial
3. Low Dose ASA Study in Pregnancy
4. ASA in Pre-eclampsia
Pragmatic Trial Example:
Night Time Dosing of Antihypertensives

Goal of Study

- Examine the impact of nighttime dosing of antihypertensive medications by comparing rates of adverse CV events in patients randomized to take their once daily BP medications either in the morning or at night.
Rationale for Night Time Dosing Trial

- BP exhibits circadian variability → lower during sleep ("nighttime dipping") with increase on arising (may explain excess risk of AMI during early am)
- Sleep BP stronger predictor of CV risk than daytime BP
- Lack of nighttime dipping associated with excess CV risk
- Many q day BP meds do not sustain plasma levels for full 24 hours and when taken in AM, may not promote nighttime dipping or protect against AM surge in BP
- 3 recent RCTs trials found that patients taking 1 or more BP meds at night had a 65% reduction in CV events
Why is Nighttime Dosing an Ideal Topic for a Pragmatic Trial?

- HTN is common problem & major CV risk factor
- Eligible patients can be identified through EMR
- Key endpoints (adverse CV events) can be captured through the EMR and other extant data sources
- Nighttime dosing can be implemented in practice without the need for sophisticated infrastructure
- Intervention has high potential for sustainability if pragmatic trial confirms prior clinical trials
Night Time Dosing: Overview of Trial Design

- Eligibility Criteria
  - Age 50-85 years with HTN & ≥ 1 comorbid condition that increases cardiovascular risk
  - 2 or more ambulatory visits in past 12 months to General Medicine or Family Medicine clinics
  - Prescriptions for ≥ 1 once-daily anti-hypertensives (excluding diuretics)

- Informed consent obtained using online interactive consent module or mailed consent letter
- Patients followed for 36-42 months with f/u contacts every 6 months via online portal or paper survey
Night Time Dosing: Overview of Trial Design (cont.)

- CV events obtained from EMR, online or paper surveys, & extant data (*Medicare claims & death certificates*)
  - Death
  - *Hospitalizations for AMI, IHD, CHF, stroke*
  - *coronary, cerebral, or peripheral revascularization*

- Sample size $\rightarrow$ ~ 20,000 patients (8-9 sites) to detect 10-15% difference in event rates for composite endpoint of the above CV events

- Estimated Cost: $10 million ($500 patient) $\rightarrow$ 10-15% of cost of traditional multi-site hypertension trial
Pragmatic Trial Example: Targeted versus Universal Decolonization to Prevent ICU Infection

(Huang SS et al, New Engl J Med 2013; 368:2255-65)

Goal of Study

- Compare targeted decolonization and universal decolonization strategies to prevent healthcare associated MRSA infections in ICU patients
Targeted versus Universal Decolonization: Overview of Trial Design

- Cluster-randomized trial of 74,256 patients in 74 ICUs in 47 HCA hospitals
- Hospitals randomly assigned to 1 of 3 strategies
  1. *Universal MRSA screening with isolation of all MRSA carriers*
  2. *Targeted decolonization (universal screening with isolation, and decolonization of MRSA carriers)*
  3. *Universal decolonization (i.e., no screening, and decolonization of all patients)*
Targeted versus Universal Decolonization: Overview of Trial Design (cont.)

- Primary Endpoint → ICU-attributable, MRSA infections
- Secondary Endpoints → ICU bloodstream infections caused by MRSA and by any other pathogen
- Endpoints compared in 12-month baseline and 18-month intervention period for each of the 3 strategies
- Data Sources:
  - Census and unit location data for each patient
  - Microbiology, pharmacy, & administrative data
- Pathogens attributed to an ICU infection if collection date between 3rd day after ICU admission and 2nd day after ICU discharge
Targeted versus Universal Decolonization: Results

- **MRSA infections (Intervention to Baseline hazard ratio):**
  - Screening & Isolation → 0.92
  - Targeted Decolonization → 0.75 *
  - Universal Decolonization → 0.63 *

- **Bloodstream infections with any pathogen / MRSA:**
  - Screening & Isolation → 0.99 / 1.23 (NS)
  - Targeted Decolonization → 0.78 * / 1.23 (NS)
  - Universal Decolonization → 0.56 * / 0.72

* P<.05
Targeted versus Universal Decolonization: Why is this Study a Pragmatic Trial?

- 3 strategies compared are approaches that are commonly used to reduce ICU infections in practice
- Strategies were administered in the course of routine care by hospital nursing personnel
- Clinical cultures were obtained at the clinician’s discretion
- All data obtained from corporate data warehouses → no independent data collection
- Validation of infections based on standard CDC criteria that are used in practice to attribute infections
Key Issues in Advancing PCTs and Creating Learning Health Systems

1. Improve efficiency of subject recruitment
2. Develop reliable clinical phenotypes from EMR data and improve the quality of information captured in the EMR
3. More effective strategies for engaging healthcare systems and physicians in practice-based PCTs
4. Decrease regulatory barriers for conducting low-risk PCTs
Key Issues in Advancing PCTs and Creating Learning Health Systems

1. Improve efficiency of subject recruitment
2. Develop reliable clinical phenotypes from EMR data and improve the quality of information captured in the EMR
3. More effective strategies for engaging healthcare systems and physicians in practice-based PCTs
4. Decrease regulatory barriers for conducting low-risk PCTs
Improve Efficiency of Subject Recruitment

- Inadequate recruitment is one of the biggest challenges to the US clinical research enterprise and one of the biggest concerns of NIH
- Overall, clinical trials enrollment rates dropped from 75% in 2000 of what was initially planned to 59% in 2006, while subject retention rates fell from 69% to 48% during same period
- More than 80% of trials are delayed at least one month because of unfulfilled enrollment
Enhancing Subject Recruitment: EMR Approaches to Identifying Subjects
(Embi, Arch Int Med 2005)

- Developed clinical trial alert (CTA) in Epic for DM trial that identified patients on the basis of diagnosis, age (> 40), and HgbA1C (> 7.4%)
- Targeted to 10 endocrinologists and 104 general internists at the point of care
- CTA prompted MDs to consider additional criteria that could not be reliably obtained from the EMR
- MD could then send referral order to coordinator if patient interested in participating
EMR Approaches to Identifying Subjects: Results
(Embi, Arch Int Med 2005):

- Compared enrollment in the 12 months before and the four months after CTA was implemented.

- 12 month Control Period
  - 5 MDs referred 68 patients to study coordinator, of whom 35 were ultimately enrolled → enrollment rate of 2.9 patients per month

- 4 month Intervention Period
  - 42 MDs 238 patients, of whom 48 were ultimately enrolled → enrollment rate of 6.0 per month
EMR Approaches to Identifying Subjects: Recent UI Experience

- NIH funded randomized trial of intervention to increase visual processing speed in older adults.
- EMR-based algorithm used to identify patients in General Medicine and Family Medicine clinics who: (1) were \( \geq \) 50 years; (2) had \( \geq \) 2 clinic visits in past 12 months; and (3) didn’t have diagnosis of dementia
- Of 5743 eligible patients identified and sent single mailing, 996 expressed interest in participating
- Of these, 681 enrolled over a 6-month period.
Key Issues in Advancing PCTs and Creating Learning Health Systems

1. Improve efficiency of subject recruitment
2. Develop reliable clinical phenotypes from EMR data and improve the quality of information captured in the EMR
3. More effective strategies for engaging healthcare systems and physicians in practice-based PCTs
4. Decrease regulatory barriers for conducting low-risk PCTs
Develop More Reliable Clinical Phenotypes from EMR Data

Current Challenges

- Majority of information in EMRs contained in clinical notes in free text formats → difficult to extract given current limitations in NLP methods

- Variability across different EMRs in capturing diagnostic & phenotypic information → particularly problematic for diagnoses (tremendous variability even from clinic to clinic in individual institutions)

- Limited standardization of phenotypic definitions for most clinical conditions
Impact of Unreliable Phenotypes
(Abrams et al, Circulation 2009)

- Research question: What is the impact of comorbid depression on in-hospital mortality
- Sample: 21,745 consecutive admissions to VA hospitals for AMI
- 2 approaches for defining comorbid depression:
  - *Inpatient*: diagnoses recorded during the incident admission
  - *Outpatient*: diagnoses recorded during prior clinic visits
Impact of Unreliable Phenotypes
(Abrams et al, Circulation 2009)

Results:

- Prevalence of depression:
  - *Inpatient diagnoses* $\rightarrow$ 10%
  - *Outpatient diagnoses* $\rightarrow$ 24%

- Adjusted odds of death for patients with depression, relative to patients without depression (1.0)
  - *Inpatient diagnoses* $\rightarrow$ 0.89 (95% CI, 0.69 - 0.99)
  - *Outpatient diagnoses* $\rightarrow$ 1.19 (95% CI, 1.09 - 1.30)
Develop More Reliable Clinical Phenotypes from EMR Data

What’s Needed

1. Develop library of computable definitions to enable phenotyping for important clinical conditions
2. Validate definitions across different EMR systems and different institutions
3. Synthesize best practices for entering data into EMR
4. Standardize approaches used by clinicians in entering clinical data elements into the EMR (*increase use of structured data fields and flowsheets*)
Key Issues in Advancing PCTs and Creating Learning Health Systems

1. Improve efficiency of subject recruitment
2. Develop reliable clinical phenotypes from EMR data and improve the quality of information captured in the EMR
3. More effective strategies for engaging healthcare systems and physicians in practice-based PCTs
4. Decrease regulatory barriers for conducting low-risk PCTs
More Effective Strategies for Engaging Healthcare Systems and Physicians

1. Study designs & interventions that can be easily embedded into practice & not impede clinic workflow

2. Greater attention to obtaining input from front-line clinicians regarding prioritization of research topics & project implementation strategies

3. Integrating incentives into faculty reward systems (e.g., PCT involvement as factor in promotion, providing RVUs for subject recruitment)

4. Create institutional cultures that value knowledge generation
Key Issues in Advancing PCTs and Creating Learning Health Systems

1. Improve efficiency of subject recruitment
2. Develop reliable clinical phenotypes from EMR data and improve the quality of information captured in the EMR
3. More effective strategies for engaging healthcare systems and physicians in practice-based PCTs
4. Decrease regulatory barriers for conducting low-risk PCTs
Hastings Center Report (*Kass & Faden*): Research-Treatment Distinction

- Features currently used to distinguish research from practice. Research involves ...
  - *Systematic investigation to produce generalizable knowledge*
  - *Less net clinical benefit & greater risk than practice*
  - *Introduces burdens or risks that are otherwise not part of patients’ clinical management*
  - *Use of protocols that dictate which treatments patients receive*

- Systematically identifies problems with each of the 5 features and concludes that features are out of date
Hastings Center Report (Kass & Faden): Ethics Framework in a LHCS

1. Moral priority on learning → healthcare professionals & institutions have novel obligation to contribute to learning in health care

2. Similar obligation extends to patients → justified by principle of the “common good,” (i.e., members of a society have a common interest in ensuring an affordable, high quality healthcare system

3. Obligation to address unjust inequalities → LHCS has obligation to decrease inequalities in evidence base for clinical decision making & in healthcare outcomes
Take Home Points

1. PCTs hold enormous potential for decreasing the cost of answering questions about the effectiveness of interventions commonly used in clinical practice

2. The success of national agendas in PCTs will depend on innovative strategies to:
   - Improve the efficiency of subject recruitment;
   - Standardize clinical phenotypes that can be obtained from EMR data
   - Decrease regulatory hurdles to conducting practice-based research of standard of care treatments
   - Engage clinicians & reward their participation in PCTs
Take Home Points (cont.)

4. PCTs can be a central feature of true learning health systems in which ....

   “science, informatics, incentives, and culture are aligned for continuous improvement & innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”

5. Academic medical centers are uniquely positioned and have a societal obligation to drive the creation of learning health systems that generate the evidence needed to practice high value care