Conducting Comparative Effectiveness Research in the Real World: An Anthropologic Perspective

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Topic Areas: Anthropologic Perspective

- Background: Anthropology, Practical Clinical Trial-PCT/CER, Interprofessional collaboration (our culture)
- NIH R34 CER: Approach (medical, behavioral, cultural)
- NIH R34 CER: Process results
- Lessons learned
Anthropologic Perspective

• Anthropology is the study of humans
• Culture: “how do things work around here?”
• At a macro-level
  • How we evolve (biologically & culturally)
  • How we adapt to our changing environment
  • Why some groups survive/thrive and others do not
• At a micro-level
  • How do cultures within MUSC and practices affect the process (conducting) and outcome of the CER?
  • How do beliefs and the social environment affect patient & provider adherence/compliance with the protocol?

Qualitative Data

• Comprehensive understanding of a complex problem
• Provides context: practice & patient
• Gain insights into potential causal mechanisms
• Special populations
Anthropologic Methods

• Culture:
  • Participant observation
  • Key informant interviews (individual/group – focus groups, meeting summaries)
• Surveys
• Analysis of extant data (CRFs, emails, etc.)
• Triangulation

Background on PCT/CER

• Explanatory vs. Pragmatic Trials
• What are PCTs/CER: CER is a type of PCT.
• How did they evolve?
• Current thinking
• Various types of PCT/CER
Explanatory vs. Practical/Pragmatic RCT

Pragmatic trials

- High external validity
- Large sample size
- Simple design
- Diverse settings
- Mostly phase IV

Explanatory trials

- High internal validity
- Smaller sample size
- Sophisticated design
- Controlled environment
- Mostly phase II-III

Patsopoulos N. A pragmatic view on pragmatic trials. www.dialogues-cns.org

Proposal for the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) – 9 Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Explanatory</th>
<th>Pragmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria</td>
<td>Many restrictions (screen out patients not likely to benefit or comply with protocol)</td>
<td>Few restrictions (include all subjects with condition – except for safety reasons)</td>
</tr>
<tr>
<td>Flexibility in delivery of Intervention</td>
<td>Strict protocol and monitoring with measures to improve compliance.</td>
<td>Specific direction on intervention but &quot;usual encouragement to adhere.&quot;</td>
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<tr>
<td>Follow up</td>
<td>High intensity</td>
<td>&quot;Usual follow-up&quot;</td>
</tr>
<tr>
<td>Organization</td>
<td>Restricted to experienced clinicians in resource-rich environment.</td>
<td>Any licensed clinician can be involved; may be severely under-resourced.</td>
</tr>
<tr>
<td>Participants’ adherence</td>
<td>Rigorous with strategies to improve adherence</td>
<td>Flexible to learn how &quot;real people&quot; behave in the &quot;real world.&quot;</td>
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Thorpe K, et al. CMAJ. 2009;180:4/-45/
Background: PCTs/CER

- Need for PCT/CER:
  - IOM Report 2009 – over half of treatments delivered today lack clear evidence of effectiveness; many evidence-based treatments are not used.
  - Explanatory trials are not representative of “real world” of primary care & diverse patients.
  - Lack input from providers and consumers
  - PCTs are needed to assess effectiveness of efficacious treatments.

Definition CER

- IOM – “CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.”
Practical Clinical Trial vs. CER

- CER is a type of PCT
- Both conducted in the “real world” to determine effectiveness.
- Both: multiple outcomes important to decisions and policy makers.
- PCTs can include control/comparison group, e.g. standard of care, or usual care.
- CER must compare two or more efficacious treatments or approaches to treatment/delivery of care. “head-to-head comparison”

Key Milestones in CER

- 1960s with expansion of Medicare/Medicaid
- 1980s – CMS & Nat. Center Health Services Research → AHRQ
- 2003 Medicare Prescription Drug Improvement & Modernization Act funded AHRQ to do CER
- Stimulus Bill of 2009 (ARRA) AHRQ, NIH, HHS
- ACA in 2010 funded PCORI
Concerns about CER

- Pharma: Cost drives decisions limiting treatment options. Gov’t and payers determine treatment options.
- Physicians: Intrusion into Dr.-Patient relationship. May impede providing patients with the best care.
- Researchers: CER might stifle innovation if cost is required early in development process.

Consensus Guidelines CER

- Compare one or more efficacious treatments
- Conducted in the “real world”
- Providers, patients and other stakeholders involved in design/conduct and/or evaluation
- Large sample of diverse provider types and patients to understand diversity
- No cost-effectiveness (QALYs)*
Types of CER

- Synthesis of existing data (systematic reviews, decision modeling)
- Analysis of observational data: (claims, EHRs, registries, case control studies)
- RCT – Gold Standard

Summary of PCT/CER

- Evolving concept and methods.
- Increase in popularity and funding.
- Must occur in the “real world” with “real patients.”
- CER: Must compare two or more efficacious interventions.
- Read the review funded studies, read the PA carefully and/or contact program officer to understand the cultural rules.
Collaboration at MUSC

- Inter-professional
- Culture of collaboration across 6 Tribes & “tribal elders”
- 3 disciplines, 2 different tribes, different personalities
- Established rules of collaboration
  - Share resources
  - Equal voice
  - Share benefits
  - Trust

R34 - Pilot CER

- R34 – pilot test approaches, team, and environment
- NHLBI R34 submitted 2010; started 6/2011
  - AIMS
  - Assess the feasibility, safety, and preliminary (comparative) effectiveness in a diverse group of patients and clinical settings of four evidence-based treatment strategies for TRH.
  - Learn from the experience and insights of all stakeholders including practices, providers, staff and patients participating in the trial to inform the design of the subsequent cluster-randomized demonstration study.
Treatment Resistant Hypertension

- Blood Pressure is above goal when the patient is taking 3 or more BP medications at 50% of maximum approved FDA dose.
- Blood pressure is a “vital sign.” Accurate and representative -
  - Not according to AHA guidelines
  - Office/white coat hypertension
  - Physicians not believe the BP measurement

R34 - Design

- Cluster-randomized (by practice), pilot clinical trial in TRH.
- We used a factorial, mixed-methods design.
  - RCT of 4 efficacious treatments for TRH in 8 practices
  - Pre-post focus groups with providers/staff
  - Surveys and interviews with patients
  - Participant observation in practices
  - Field notes (calls, meetings, comments in CRFs, etc.)
Approach

• RCT: 4 arms –
  1) aldosterone antagonist (AA),
  2) Renin-treatment guided therapeutics (RTGT),
  3) clinical hypertension specialist (CHS)
  4) RTGT & CHS.
• Two screening visits and four treatment visits < one month apart.
• Experiences and perceptions of providers/staff and patients.
• Intention-to-treat; 36 patients/ARM.

Inclusion Criteria:
  two separate visits

• No diabetes mellitus or chronic kidney disease
  AND
• BP ≥135 and/or ≥85 by the average of the 2nd – 6th BpTRU seated reading

  OR

• Diabetes mellitus and/or chronic kidney disease.
  AND
• BP ≥125 and/or ≥75 by the average of the 2nd – 6th BpTRU seated reading
Accurate & Representative Blood Pressure: BpTru Device

- Takes 5 recordings one minute apart and averages.
- “A” rating for accuracy from British HTN Society.
- Approximates the daytime ambulatory BP.
- Eliminate “white coat” effect.
- Adds time and effort - workflow

Qualitative Data

- Focus group discussions (content analysis – pre-determined categories/domains followed by grounded – bottom-up approach emanating from experiences of participants)
- Patient surveys – Likert scales and narrative (satisfaction, understanding, adherence, etc.)
- Patient interviews – lived experience of being a research subject with TRH
- Participant observation/field notes/CRFs
Results of Process Variables

• Practices
• Address potential barriers
• Research coordinators
• IRB
• Recruitment
• Clinician & patient adherence/compliance
• Clinician/research coordinators’ experience
• Subjects’ experience

8 Practices

• Most under-resourced
• All practices saw patients that varied by race/ethnicity, SES, gender, age, insurance.
• Varied in size, organization and location
  • FQHC; 2 Family Medicine Training Programs; 3 solo; hospital-owned with clinical trials research staff; part of large physician-owned practice network.
  • 4 urban, 4 rural
• All had some experience with clinical trials
Facilitating RCT in Practices

- We are guests in their “home.”
- Respectful of the realities of busy, stressful practices.
- Provide some flexibility – clinical judgement
- Trained lead physicians and staff together and apart.
- Review practice redesign issues and resolve (BpTRU, monthly visits – “good luck changing that in this practice!”).
- Simplify CRFs (reviewed by lead MDs).
- Site visits.
- Phone calls/emails.
- Conference calls with lead MDs.

Research Coordinators

- One: trained research RNs – ran RCTs
- One: NP who also saw patients/subjects
- One: MHA who conducted QI
- Four: LPNs with varying experience in recruitment, scheduling, BP, CRFs, and monitoring patient adherence.
- One: PCT who had assisted with research in the past.
IRB

- All lead physicians and research coordinators were Citi-certified.
- Paper copies of Citi; Net-IDs for Citi-updates
- eIRB: Institutions vary in requirements and some lead MDs and staff had to take multiple versions of Citi training
- Annual IRB review – consent forms with new stamped date sent to practices with request to destroy old forms.

Recruitment

- Great enthusiasm for all four ARMs, easy to comply with protocol.
- BpTRU anticipated 25% loss, but screened out >50% of eligible TRH patients first screen.
- Additional approx. 10% loss on second screen.
Barriers to Recruitment

- Flu season/school physicals
- Personnel changes/illness
- Regulatory issues (NetIDs, Citi)
- BpTRU (“pseudoTRH”)
- Achieved enrollment goals (2 ARMS)

Clinician Compliance Protocol

- Practical/effectiveness trial: clinicians use clinical judgment, no special strategies to motivate clinicians to comply with protocol.
- All 8 practices complied with scheduling return appointments within one month, after some practice adjustments.
- 3 out of 4 practices assigned to CHS did not refer (“protocol deviation”). 4th practice only refer to CHS in a distant location.
- Meeting of Data & Safety Monitoring Board and Project Officer to close enrollment for 2 ARMs with CHS.
- AA and RTGT sites did comply with the protocol.
Subject Compliance

- Compliance with medication assessed by clinical interview/CRF, permission contact pharmacy, survey, interview.
- Surveys (22/128) & interviews (6) detected a low rate of missing a dose.
- Name/location of pharmacy missing >50% of CRFs.
- CRFs: approx. 15% subjects: missed some/all meds, and/or missed most appointments.

Clinician/coordinators’ experience

- Frustration with screening patients with BpTru (“The BpTru is curing my patients!”)
- Practice redesign issues: return monthly appointments & time for research.
- Felt the AA and RTGT were effective and planned to continue to use them after the study ended.
- 3/4 did not feel the CHS was needed (“I have many years experience treating HTN and don’t need a specialist to tell me how to practice.”)
- Four lead physicians are asking to participate in new research projects.
Subjects’ Experiences

• Biased sample (22 surveys, 6 interviews).
• All very concerned their HTN not controlled.
• All very satisfied with participation and improvement in HTN control (“I wish this study would not end”).
• Particularly pleased with improved monthly access to clinician (norm was 3-month follow-up). “It really bothered me that so much time went by before I could see my doctor to find out how I was doing.”
• Other health problems deemed more important to address. “I have so many other problems that my doctor focuses on those and not so much on my hypertension. I can’t blame him, but we need to focus on the most important things to me: my diabetes and my hypertension.”

Collaboration

• Shared Resources: A
• Equal Voice: A-
• Shared Benefit: C (tribal conflict)
• Trust: B
Lessons Learned

• We did a lot of things right
  • Mixed Methods
  • Flexibility
  • Diverse group of practices/patients
  • Collaboration (except shared benefit)

Lessons Learned

• “Best lessons in life are the painful ones.”
• Use of CHS was not effective in our setting (3/4 did not refer). Triangulation of data from multiple qualitative data sources revealed the reason why – focus on control, follow treatment guidelines esp. change to monthly apt.
• Too complex, underfunded.
• BPTru detected significantly more “office HTN” than reported.
• Unanticipated events and realities of “real world” practice added to length of study.
• IRB – Citi Training
• Methods to better understand patient and clinician decisions.
• Need for contract on nature of collaboration.
Final Thoughts Explanatory CT vs. PCT/CER

• Fidelity vs. flexibility
  • Protocol “deviation” – accidental or non-compliance with an intervention that does not work in the real world?
  • Protocol violations (patients’ rights, integrity of data, inclusion-exclusion, SAE, other safety issues)
  • All PCTs will involve changes in protocol to integrate efficacious intervention into practices. Some efficacious interventions will not be effective. The challenge is to find out “why.”

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