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Training Institute for Dissemination and Implementation Research in Health
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Design Principles for Comparative Effectiveness Research and Pragmatic Trials

The Case of Hypertension Treatment

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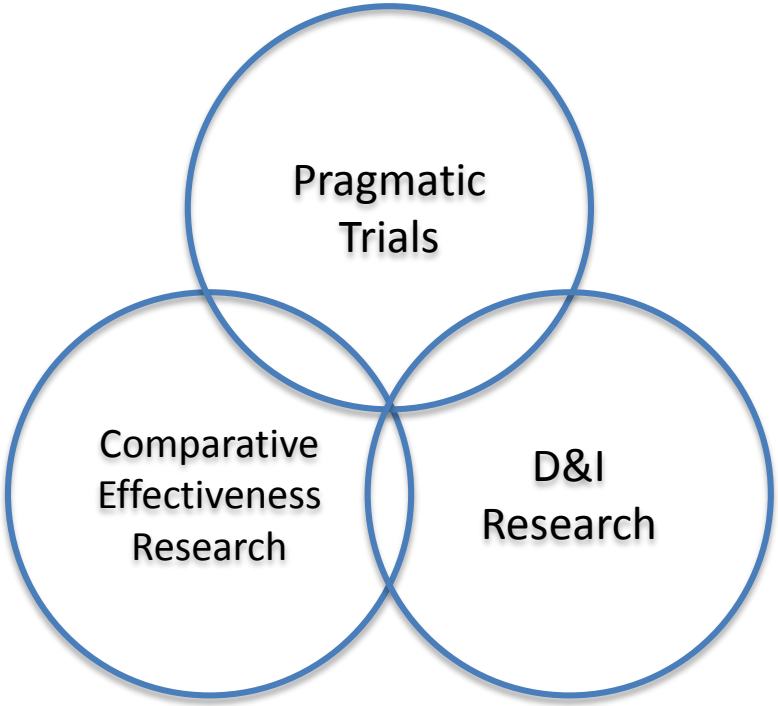
Overview of Session

- Key definitions and context for CER, D&I and Pragmatic Trials
- Brief overview of research designs
- Guidelines to disseminate research findings: hypertension as an example
- Observational CER example
  - Guideline implementation
- Pragmatic trials: the PRECIS tool
  - Examples from hypertension studies
- Test what you've learned: make an RCT pragmatic

Today's Talk Will Focus on D&I Research for CER and the Role of Pragmatic Trials



CER Informs What Works In the Real World, D&I Informs How to Get What Works Done

RCTs

Pragmatic Trials
Observational Studies

QI Studies
D&I Studies

What Works in Controlled Studies? → **What Works in the Real World?** → **How Can We Reliably Do What Works?**

CER

- Head-to-head comparisons
- Subgroups of patients
- Outcomes that matter to patients

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D&I Research as Defined by NIH

- Dissemination Research
  - Study of how and when research evidence spreads throughout agencies, organizations and front line workers
  - “Help it happen”
- Implementation Research
  - Scientific study of how to move evidence-based interventions into healthcare practice and policy
  - “Make it happen”

Some Features of Research Designs

Method	Features
Randomized Controlled Trials	• Patients (individual) or groups (cluster) are randomly assigned to receive (treatment) or not receive (control) the intervention • **The intervention is highly standardized and delivered consistently, usually in a controlled setting** • Analysis is typically done comparing the assigned groups (intention to treat) • Differences are attributable to the intervention
Pragmatic Trials	• Random assignment similar to RCTs • **Intervention may vary, settings are usual care, providers and patients are more heterogeneous** • Data collection may rely on what is obtained in usual care delivery • Differences are attributable to the intervention
Quasi-experiments	• Sometimes called natural experiments – take advantage of a policy change • Assignment to groups is not random • Analysis similar to before-after designs (with or without a control group)

Some Features of Research Designs (cont.)

Method	Features
Stepped Wedge	• **Sequential roll out of intervention over time** • By end of study everyone has received intervention • Randomizing order of roll out enhances rigor • Data collected & outcomes measured each time a new group receives intervention • Pre-receipt time period serves as control
Time Series	• **Compares results over time to distinguish secular trends from intervention-related trends** • Data collected & outcomes measured at several points before and after intervention is introduced • Intervention may be stopped (interrupted) and restarted or implemented just once

Some Features of Research Designs (cont.)

Method	Features
Controlled before-after	• Identify a control group that is similar to the planned intervention group (before the intervention!) • Data are collected both before and after intervention is introduced and changes compared to a group with no intervention • Differences between the control and intervention group are assumed to be attributable to the intervention
Before-after (no control)	• Outcomes are measured before and after the intervention in the same study setting • Observed differences are assumed to be attributable to the intervention

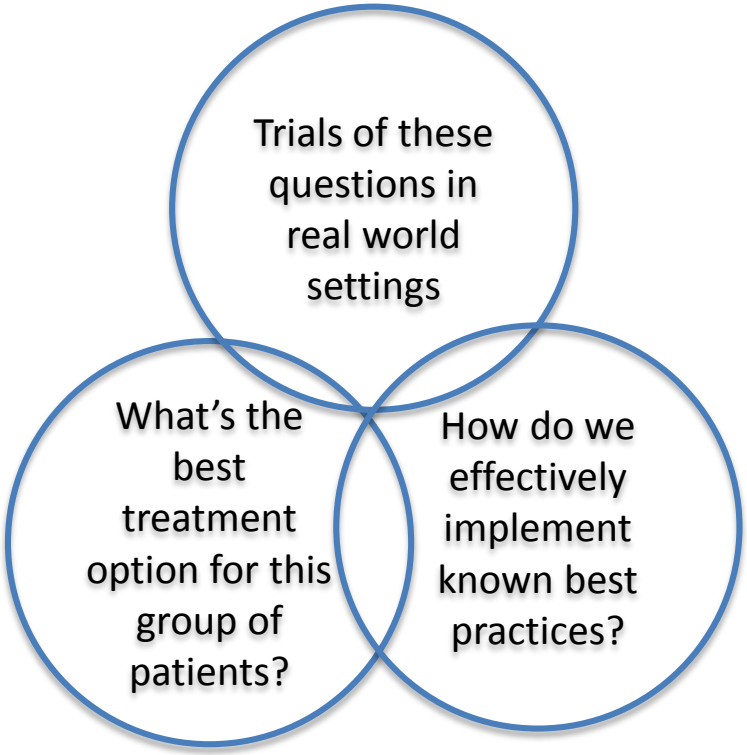
Qualitative Methods

Method	Features
Interview-based	• This can be a quantitative or qualitative method (depends on approach, numbers, nature of interview) • Can involve individuals or groups • Different modes (face-to-face, written, telephone) may produce different responses • Interviews may vary in level of structure • Useful in both design and evaluation • **Provides context and information to interpret findings**
Observation	• Can be structured (process map) or unstructured • **Provides an independent perspective on how some interventions are being implemented** • May reveal aspects of intervention that would otherwise have been missed (e.g., work arounds)
Ethnography	• Incorporates sensitivity to cultural differences • We often use video (more objective capture of what happened) • Researcher typically interacts with study participants

Mixed Methods

- Refers to the use of both quantitative and qualitative methods
  - Quantitative methods capture magnitude and frequency of key dimensions
  - Qualitative methods capture meaning and understanding
- But the way in which each method is used is planned in advance and approaches to integrate findings are specified
- Useful for areas of inquiry where context is critical to interpreting findings (D&I research is an example of this area)

Pragmatic Trials Are A Key Method for Answering CER & D&I Questions



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Guidelines Are A Mechanism for Summarizing and Disseminating What's Known About Best Practices: JNC 8 Hypertension Guideline As An Example

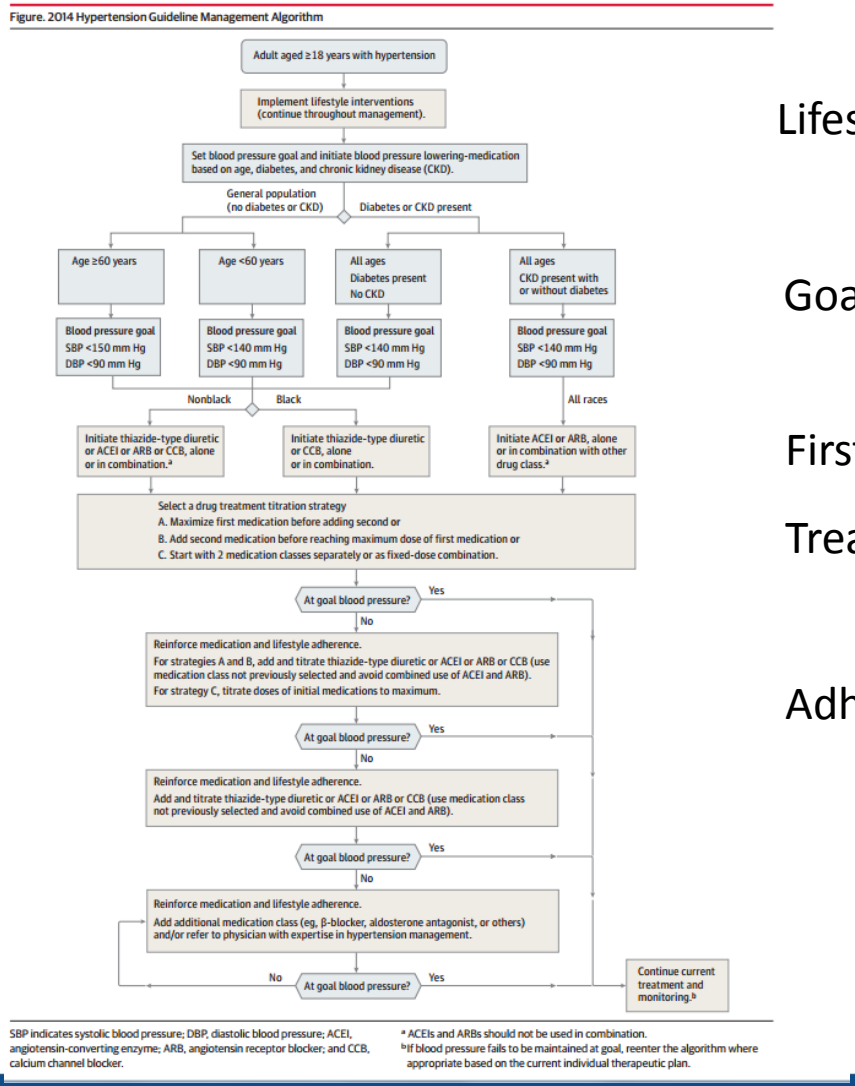
WHO/HOW

Patients

Providers

Tools

Systems



WHAT

Lifestyle modification

Goal setting

First-line medication

Treatment intensification

Adherence to treatment

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KP Approach to Implementation of Hypertension Guideline

"Intervention"	KPNC	KPSC
Disseminate guidelines, tx algorithm	2001	2003
Create a hypertension registry	2001	2004
Physician feedback on performance	2001 (med ctr)	2004
Engage teams (pharmacy, nursing)	x	x
Promote fixed-dose combination drug	2005	2005
Standardize BP measurement	2007	2005
Create new visit type (BP check; no copay)	2007	2010
Incorporate into point of care (POC) reminders	x	2007
Pt-MD language concordance enhanced		2008
MD given POC information on med adherence		2009
Patient education		x

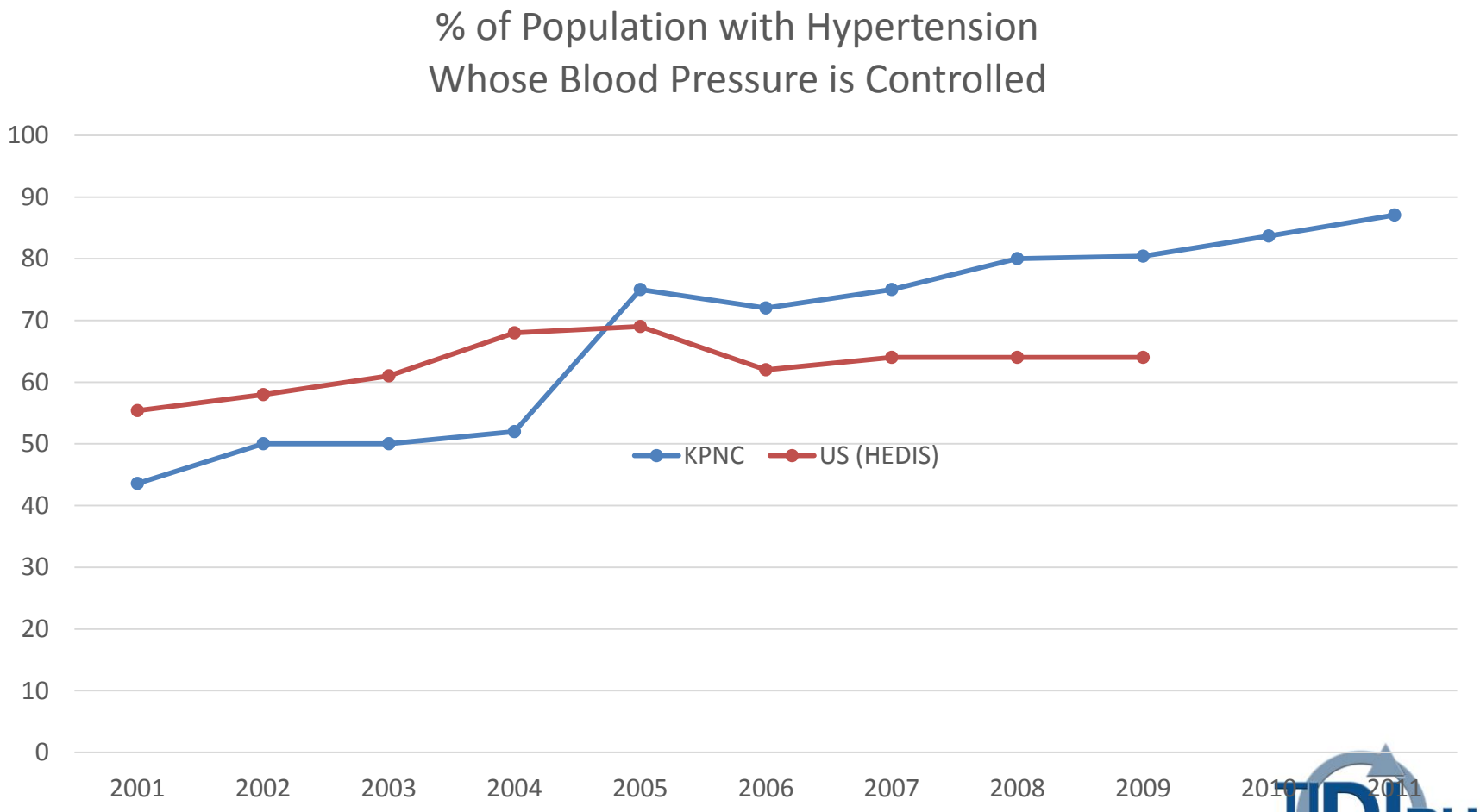
So, How Would You Study Whether This Approach to Implementation Worked?

- Who do you think the audience for this study might be?
- What study design seems best?
- Over what time period (start, end) would you do the study?
- Would you study one or both regions? Other comparisons?
- Would you study all interventions or not?
- Which patients would you include?
- Which physicians would you include?
- What would worry you the most about this study?
- What do you think people would be most interested in?

Improvement in Detection & Control of Hypertension in KPSC, 2004-2010

Sim JJ et al. Systematic implementation strategies to improve hypertension:
The Kaiser Permanente Southern California experience. 2014. Can J Card, 30:544-552.

KPNC Showed Similar Increases Compared to US Rates (HEDIS Reports)



Jaffe et al. Improved blood pressure control associated with a large-scale hypertension program. 2013. JAMA. 310:699-705

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Which Beta-Blocker Is Best? (A Classic CER Question)

- Beta-blockers (used to be) the first line treatment for hypertension based on evidence from placebo controlled trials
- 2 large trials found that atenolol regimens were less effective than other antihypertensive drugs, so beta-blocker role in first line therapy questioned; inferiority results from meta-analysis largely related to stroke prevention
  - But data were fairly sparse for drawing conclusions
- Unlikely that a head-to-head RCT would be conducted
  - Can an observational study address the question?

Observational Study Flow Diagram

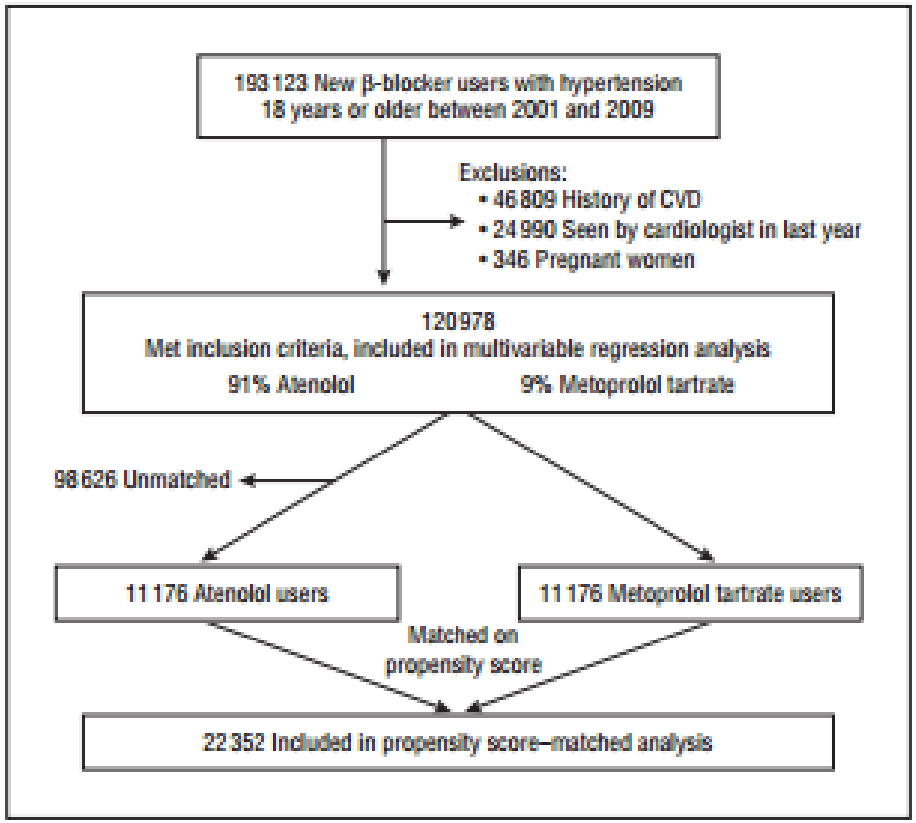


Figure. Selection of patients for analyses. CVD indicates cardiovascular disease.

New users

Exclude

Propensity matching

Analytic sample

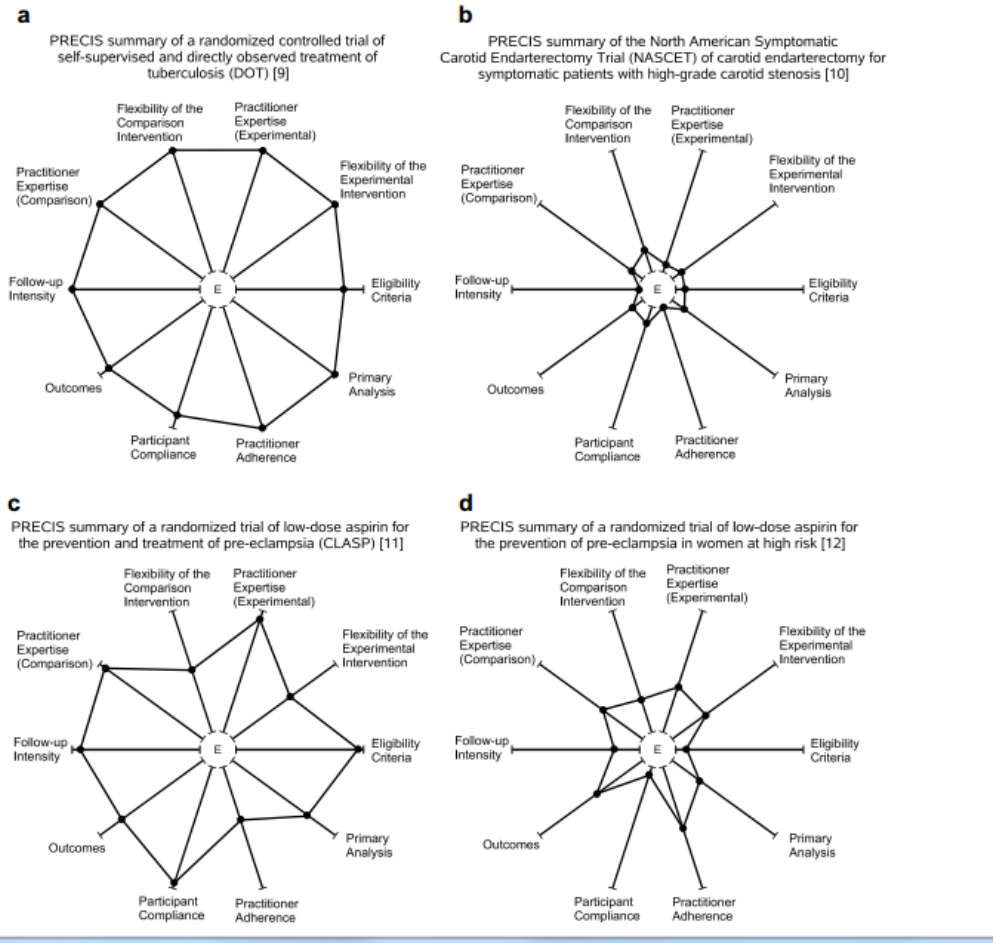
Parker ED et al. Comparative effectiveness of 2 B-blockers in hypertensive patients. 2012. Arch Intern Med. 172(18):1406-1412.

How Pragmatic Is Your Design? Components of the PRECIS Tool

- Eligibility criteria for trial participants
- Flexibility of experimental intervention
- Degree of practitioner expertise in using the experimental intervention
- Flexibility of comparison intervention
- Degree of practitioner expertise in using the comparison intervention
- Intensity of participant follow-up
- Nature of the primary outcome
- Intensity of measuring compliance by participants
- Intensity of measuring practitioner protocol adherence
- Approach to analysis of the primary outcome

Thorpe et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. 2011 J Clin Epi. 62:464-475.

Application of PRECIS Tool to Trial Designs



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Medication Adherence is a Common Chronic Disease Implementation Question

- For many chronic diseases, medication plays a key role in effective secondary and tertiary prevention
- Adherence to medication regimens is an implementation challenge
- Two examples of pragmatic trials illustrate possible approaches to improving adherence
  - Automated telephone intervention
  - Clinical pharmacist outreach

Automated Telephone Intervention to Improve Blood Pressure Control

Design Element	Description
Eligibility	Adults in a hypertension registry Most recent BP in 1 year prior to randomization >=140/90 Not on dialysis, in nursing home, hospice No valid phone number or on “do not call” list Individual randomization
Experimental Intervention	Automated phone call Invitation to have BP measured at a medical center No limits on other care provision
Provider expertise: experiment	Trained medical assistant (regular employee)
Comparison intervention	Usual care
Provider expertise: comparisons	Trained medical assistant (regular employee)

Harrison et al. A randomized controlled trial of an automated telephone intervention to improve blood pressure control. 2013. J Clin Hypertens. 15:650-654.

Automated Telephone Intervention to Improve Blood Pressure Control

Design Decision	Description
Intensity of follow-up	BP measurement at 4 weeks post-randomization Available from EMR data
Nature of primary outcome	BP measured in a medical center
Participant compliance	Part of what is measured (any visit, BP) but no special effort to influence compliance beyond the experimental intervention
Provider protocol adherence	No special monitoring beyond what is done in usual care (peer review of medical assistants)
Analytic approach	Excluded some patients ineligible post-randomization (those without phone numbers or on “do not call” list Primary analyses were intention to treat Sensitivity analyses excluded patients w/out f/u BP

Harrison et al. A randomized controlled trial of an automated telephone intervention to improve blood pressure control. 2013. J Clin Hypertens. 15:650-654.

Pharmacist Outreach to Improve Blood Pressure Control

Design Element	Description
Eligibility	Diagnosis of diabetes from EMR (VA & KP) Persistent poor BP control Poor refill adherence or insufficient medication intensification Cluster randomization by primary care team; prioritized random sample of patients within each team (Additional conditions to stay enrolled)
Experimental Intervention	Intake, encounters guided by a "road map" Trained pharmacists allowed to independently contact patients and adjust medications
Provider expertise: experiment	3 day training on patient-centered approaches to medication intensification for pharmacists
Comparison intervention	Usual care; no contact from study team
Provider expertise: comparisons	Usual care providers; No training in medication intensification, no access to MMT or other IT reports

Heisler M, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems. 2012. Circulation. 125:2863-2872.

Pharmacist Outreach to Improve Blood Pressure Control

Design Decision	Description
Intensity of follow-up	Usual clinical care BP measures (intervention provider BP measurements excluded)
Nature of primary outcome	Change in SBP
Participant compliance	No special intervention (no incentives) Patients "discharged" from program (but not analyses) if med adherence issues addressed, BP controlled; max meds; lost to follow up, enrolled for 6 months without achieving BP control; declined participation
Provider protocol adherence	No special intervention; Assessment of pharmacist proficiency at 6 months
Analytic approach	Intention to treat; 3-level multiple linear regression

Heisler M, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems. 2012. Circulation. 125:2863-2872.

Lifestyle Modification is First Line Therapy for Prevention and Treatment of Prehypertension & Stage 1

- What is included in lifestyle modification?
  - Weight loss (if overweight or obese)
  - Increased physical activity
  - Sodium reduction
  - Limited alcohol intake
  - Dietary recommendations (DASH or other program)
  - [Smoking cessation]
- PREMIER trial* found that patients could make multiple lifestyle changes and improve BP control
  - Average reduction in systolic BP of 3.7-4.3 mm Hg
  - Prevalence of optimal BP 30-35% in intervention groups

*Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control. JAMA. 2003. 289(16):2083-2093.

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Can You Make the PREMIER Trial More Pragmatic?

Design Decision	PREMIER	PREMIER-PT
Participant eligibility	Healthy, not taking BP meds, Systolic 120-159, Diastolic 80-95, age 25-?, BMI 18.5-45, no use of drugs that affect BP, no use of weight loss meds, no target organ damage, no diabetes, no prior CVD event, no CHF, no angina, no cancer dx or tx, no alcohol consumption > 21 drinks / week, pregnancy, planned pregnancy	
Flexibility of experimental intervention	Low (18 in-person contacts 1st 6 mo, food & activity diaries, other monitoring)	
Provider expertise with experimental intervention	High (trained in the intervention)	
Flexibility of comparison intervention	Low (One, 30 minute visit; no additional contact)	
Provider expertise with comparison intervention	High (“interventionist” – registered dietician)	

Can You Make the PREMIER Trial More Pragmatic?

Design Decision	PREMIER	PREMIER-PT
Intensity of follow-up	High (participant data collection, BP & weight measurement, random surveys, treadmill test)	
Nature of primary outcome	BP measure, hypertension status (severity)	
Participant compliance	Measured, high	
Provider protocol adherence	High	
Analytic approach	Intention to treat (secondary analyses limited to subgroups with higher compliance)	

Conclusions

- Dissemination and implementation of scientific knowledge is essential for realizing the rewards of discoveries
- Studying what works is an important scientific method
  - CER (both of the content and implementation of interventions) fills an important gap in knowledge
- There are a variety of potential approaches to these studies
  - Pragmatic trials are central to advancing the field of D&I
- Let's go get this important work done!!