U.S. Department of Health and Human Services

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

PRECIS Tool: Understanding your Research Intentions, the Pragmatic-Explanatory Continuum

Presented By:
Kevin E. Thorpe, MMath

Moderated By:
Rebecca Roper, MS, MPH, Director, Practice-Based Research Network Initiative,
Agency for Healthcare Research and Quality

Sponsored by the AHRQ PBRN Resource Center
December 11, 2014

Agenda

- Welcome and introductions
- Presentation
- Q&A session with presenter
- Instructions for obtaining CME credits

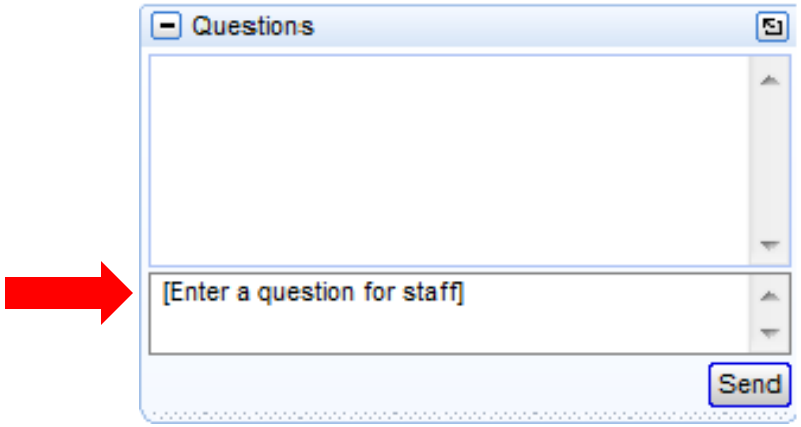
Note: After today's webinar, a copy of the slides will be e-mailed to all webinar participants.

Disclosures

- Today's presenter does not have any financial relationships to disclose.
- Today's presenter will not discuss off label use and/or investigational use of medications in his presentation.

How to Submit a Question

- At any time during the presentation, type your question into the “Questions” section of your GoToWebinar control panel.
- Select “Send” to submit your question to the moderator.
- Questions will be read aloud by the moderator.



Today's Presenter

A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

Kevin E. Thorpe, MMath
Assistant Professor, Dalla Lana School of Public Health,
University of Toronto;

Head of Biostatistics, Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute, St. Michael's Hospital and the University of Toronto.

A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

Prof. Kevin E. Thorpe

Dalla Lana School of Public Health
University of Toronto
Applied Health Research Center at the Li Ka Shing Knowledge Institute
St. Michael's Hospital

December 11, 2014

Outline

1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

Outline

1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

Introduction

- Randomized trials have traditionally been broadly categorized as either an effectiveness trial or an efficacy trial.
- In 1967, Schwartz and Lellouch describe these two approaches to clinical trials and coined the terms *pragmatic* and *explanatory* which we prefer.
- These terms relate to the purpose of a clinical trial.
- These authors clearly linked a trial's purpose with it's structure.

Introduction

Definitions

Definition (Pragmatic Trial)

A *pragmatic trial* seeks to answer the question, "Does an intervention work under usual conditions?"

Definition (Explanatory Trial)

An *explanatory trial* seeks to answer the question, "Can an intervention work under ideal conditions?"

Introduction

Why does the distinction matter?

- One important reason is the "type" of trial matters for the interpretation of the trial's results.
- A "positive" explanatory trial is not proof that its intervention will work in usual practice, whereas a "negative" explanatory trial very strongly suggests that its intervention would not work in usual practice.
- Similarly, a "positive" pragmatic trial strongly suggests its intervention would also work in an ideal setting, whereas a "negative" pragmatic trial does not mean its intervention cannot work in an ideal setting.

Introduction

The problem with labels

- Labels such as pragmatic or explanatory are an over-simplification and erroneously imply a dichotomy.
- In reality, there is a continuum of options between the extreme cases of either type.
- Moreover, since many design decisions are made for a given trial, we are really faced with a multidimensional continuum of possibilities.

Introduction

PRECIS in brief

The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) describes ten domains in which trial decisions are made that affect the degree to which a trial is pragmatic or explanatory.

1. Participant eligibility criteria
2. Experimental intervention flexibility
3. Practitioner expertise (experimental)
4. Comparison intervention
5. Practitioner expertise (comparison)
6. Follow-up intensity
7. Primary trial outcome
8. Participant compliance
9. Practitioner adherence
10. Analysis of primary outcome

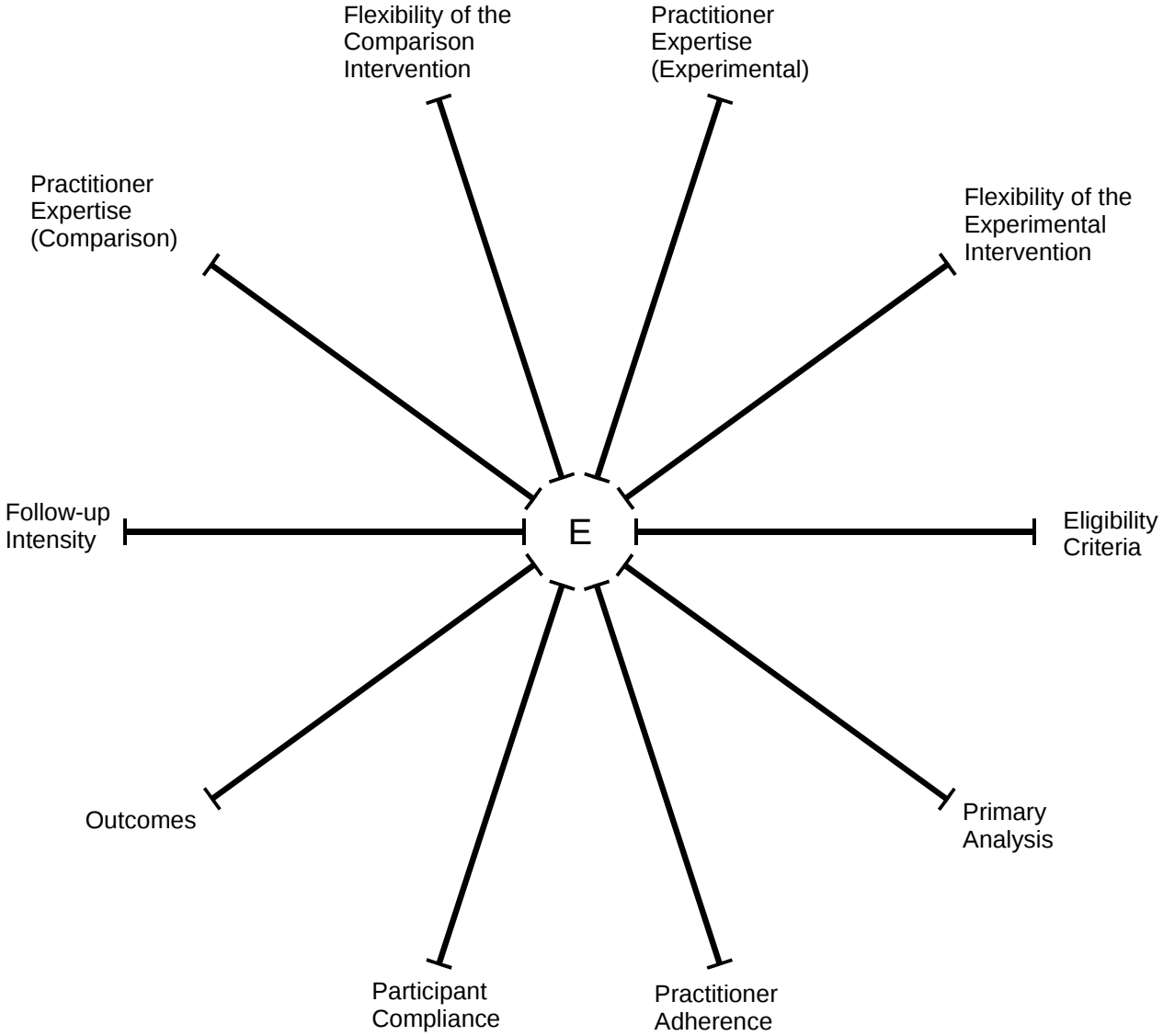
Outline

1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

PRECIS in detail

Four steps of trial design

1. Declare whether the purpose of the trial is pragmatic or explanatory.
2. Specify the settings or conditions for which the trial is intended to be applicable.
3. Specify the design options at the pragmatic and explanatory extremes of each domain.
4. Decide how pragmatic or explanatory the trial is in relationship to those extremes for each domain.
   - This is done by considering the addition/removal of restrictions that shift the trial's position along the continuum for a given domain.
   - The result of this assessment can be displayed graphically.


Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
Flexibility of the Experimental Intervention
Follow-up Intensity
E
Eligibility Criteria
Outcomes
Primary Analysis
Participant Compliance
Practitioner Adherence

PRECIS in detail

Participant eligibility criteria

- The most extremely pragmatic approach to eligibility would seek only to identify study participants with the condition of interest from as many sources (e.g. institutions) as possible.
- The study populations is restricted as a more explanatory approach is taken.
  - excluding participants not known/shown to be highly compliant to the interventions under study
  - excluding participants not known/shown to be at high risk for the primary trial outcome
  - excluding participants not expected to be highly responsive to the experimental intervention
  - using a small number (or even one) of sources for participants

PRECIS in detail

Experimental intervention flexibility

- The pragmatic approach leaves the details of how to implement the experimental intervention up to the practitioners and would not dictate which co-interventions were permitted or how to deliver them.
- Flexibility may be restricted in the following ways.
  - specific direction for the administering the intervention (e.g. dose, dosing schedule, surgical tactics, educational material and delivery)
  - timing of intervention delivery is designed to maximize the intervention effect
  - restrictions in the number and permitted types of co-interventions, particularly if excluded co-interventions would dilute any intervention effect
  - specific direction for applying permitted co-interventions
  - specific directions for managing complications or side-effects from the primary intervention

PRECIS in detail

Practitioner expertise (experimental)

- A pragmatic approach would put the experimental intervention into the hands of all practitioners "treating" the study participants.
- Practitioner choice can be restricted.
  - practitioners could be required to have some experience, defined by length of time, in working with the subjects like the ones to be enrolled in the trial
  - some specialty certification appropriate to the intervention could be required
  - for an intervention that has been in use (e.g. surgery) without a trial evaluation, experience with the intervention itself could be required
  - only practitioners who are deemed to have sufficient experience in the subjective opinion of the trial investigator would be invited to participate

PRECIS in detail

Comparison intervention

- A pragmatic trial would typically compare an intervention to "usual practice" or the best available alternative management strategy (as per guidelines), but not otherwise dictate the details of the intervention.
- Explanatory restrictions similar in nature as for the experimental intervention would be possible.
- There are times when an explanatory trial may use a placebo rather than the best alternative management strategy as the comparator.

PRECIS in detail

Practitioner expertise (comparison)

- The pragmatic approach would accept the usual practitioners in the setting of interest.
- Restrictions would follow a similar path as for the experimental intervention with the aim of a clean comparison.

PRECIS in detail

Follow-up intensity

- The pragmatic position would be not to seek follow-up contact with the study participants in excess of the usual practice for the practitioner (most extreme could be no contact).
- The extent to which increased follow-up intensity could lead to increased compliance or improved intervention response, follow-up intensity moves toward the explanatory end.
  - follow-up visits (timing and frequency) are pre-specified in the protocol
  - follow-up visits are more frequent than typically would occur outside the trial (i.e. under "usual" care)
  - un-scheduled follow-up visits are triggered by a primary outcome event
  - un-scheduled follow-up visits are triggered by an intervening event that is likely to lead to the primary outcome event
  - participants are contacted if they fail to keep trial appointments
  - more extensive data are collected, particularly intervention related data, than would by typical outside the trial

PRECIS in detail

Primary trial outcome

- The explanatory approach would consider a primary outcome that the experimental intervention is expected to have a direct effect on.
- There may well be central adjudication of the outcome or assessment of the outcome may require special training or tests not normally used to apply outcome definition criteria.
- The pragmatic approach would consider patient-important outcomes that can readily be measured in usual care and not use central adjudication.
- A pragmatic trial may often consider much longer follow-up periods for outcome measurement in its quest to determine if the intervention works.

PRECIS in detail

Participant compliance with "prescribed" intervention

- Since measurement of compliance may have the possibility of altering compliance, the pragmatic approach in a trial would be not to measure or use compliance information in any way.
- The more rigorous a trial is in measuring and responding to non-compliance of the study participants, the more explanatory it becomes.
  - compliance measured (indirectly) purely for descriptive purposes at the conclusion of the trial
  - compliance data measured and fed back to providers or participants during follow-up
  - uniform compliance-improving strategies are applied to all participants
  - compliance-improving strategies are applied to participants with documented poor compliance

PRECIS in detail

Practitioner adherence to study protocol

- A purely pragmatic approach would not be concerned with how practitioners vary or "customize" a trial protocol to suit their setting.
- By monitoring and (especially) acting on protocol non-adherence, a trial shifts towards being more explanatory.
  - adherence measured (indirectly) purely for descriptive purposes at the conclusion of the trial
  - adherence data measured and fed back to practitioners
  - uniform adherence-improving strategies are applied to all practitioners
  - adherence-improving strategies applied to practitioners with documented poor adherence

PRECIS in detail

Analysis of primary outcome

- The pragmatic approach to the primary analysis would typically be an intention-to-treat analysis of an outcome of direct relevance to the study participants and the population they represent.
- Although the intention-to-treat analysis is also the norm for explanatory trials, there are various restrictions that may (additionally) be employed to address the explanatory question, "Can this intervention work under ideal conditions?"
  - exclude non-compliant participants
  - exclude patients found to be ineligible post-randomization
  - exclude data from non-adherent practitioners
  - multiple sub-group analyses planned for groups thought to have the largest treatment effect

Outline

1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

Examples

DOT ...

- The first example uses the trial of self-supervised and directly observed treatment of tuberculosis (DOT).
- Its question was, "Among South African adults with newly diagnosed pulmonary tuberculosis, does five times weekly direct observation of pill swallowing by a nurse in the clinic, compared to self-administration, increase the probability that patients will take >80% of doses within 7 months of starting treatment, with no interruptions of >2 weeks?"
- The experimental intervention was self-administration and the comparison intervention was DOT, which was widely used in South Africa.

Examples

...DOT...

- Participant eligibility criteria
  - all-comers receiving care for newly diagnosed tuberculosis at two clinics
  - extremely pragmatic, but since only two clinics were studied it is not at the extreme edge
- Experimental intervention flexibility
  - method of self-administration was left to the individual patient, who could delegate weekly drug collection visits to a family member
  - extremely pragmatic

Examples

...DOT...

- Practitioner expertise (experimental)
  - all clinic nurses were involved, with no particular specialization or additional training and patients were self-treating with no special training
  - extremely pragmatic
- Comparison intervention
  - clinics already had the direct observation intervention in place, and this was not altered
  - extremely pragmatic

Examples

...DOT...

- Practitioner expertise (comparison)
  - all clinic nurses were involved, with no particular specialization or additional training
  - extremely pragmatic
- Follow-up intensity
  - no extra clinic visits were scheduled
  - in the experimental arm, no visits whatsoever were required since even the weekly drug collection could be delegated to a family member
  - this was the most extreme pragmatic approach

Examples

...DOT...

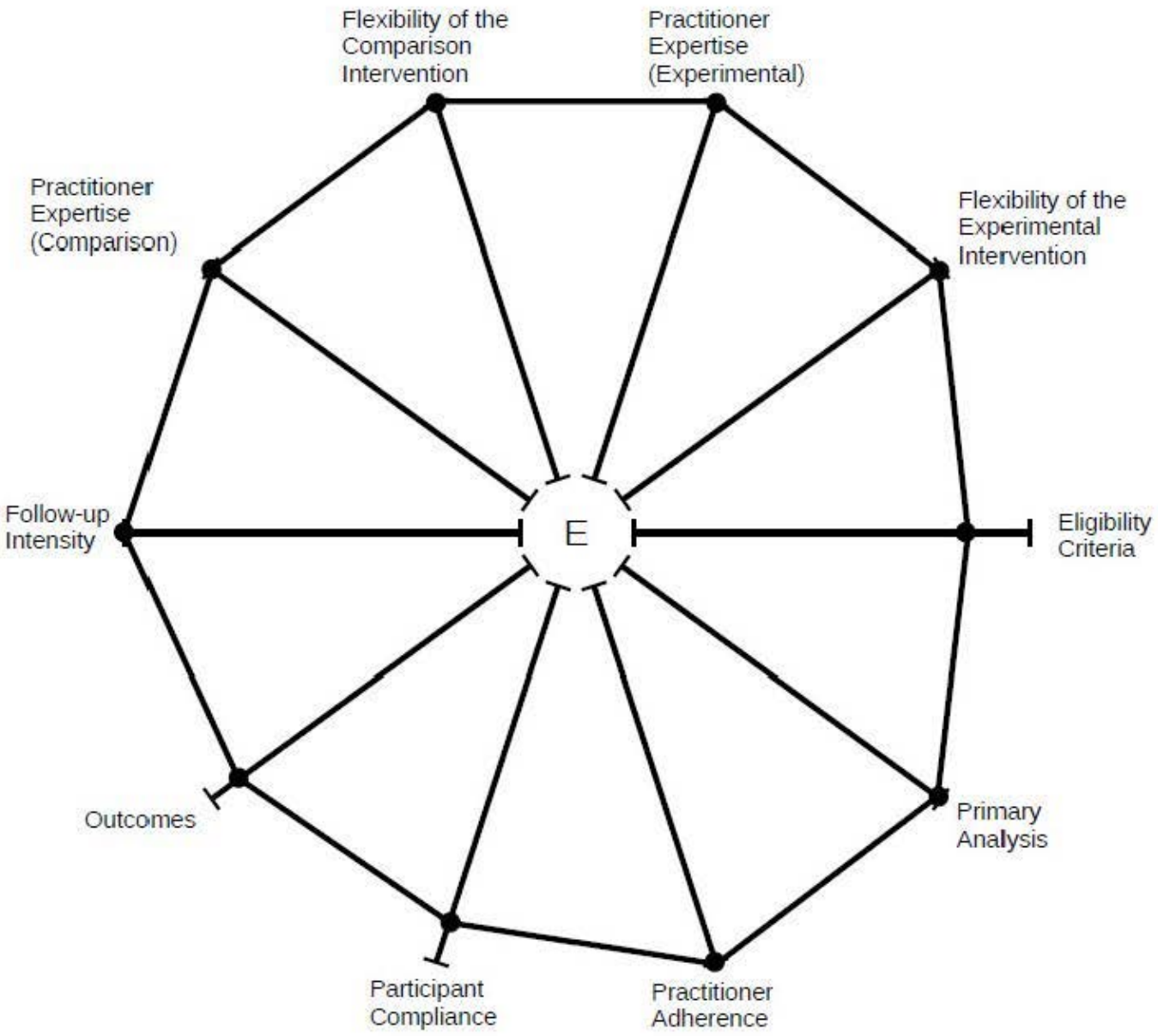
- Primary trial outcome
  - the primary outcome was "successful treatment" which included all patients who were cured and all patients who completed the treatment
  - all patients were followed up for a year, until they completed their treatment, died, were classified as "incompletely treated," or were lost to follow-up
  - very pragmatic
- Participant compliance
  - compliance was an element of the outcomes, and so was measured for this purpose, but not used to improve patient compliance
  - this was pragmatic, but not at the most extreme end

Examples

...DOT

- Practitioner adherence
  - there were no measurements of protocol adherence, and no adherence-improving strategies were employed
  - this was the most pragmatic approach possible
- Analysis of primary outcome
  - all randomized patients were included in the primary analysis
  - patients who failed to meet the criteria for "successful treatment" (including those who died, were lost to follow-up, or transferred to another clinic) were classified "failures."
  - extremely pragmatic

DOT


Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
Flexibility of the Experimental Intervention
Follow-up Intensity
E
Eligibility Criteria
Outcomes
Primary Analysis
Participant Compliance
Practitioner Adherence

Examples

NASCET . . .

- The second example uses the North American Symptomatic Carotid Endarterectomy Trial (NASCET).
- Its question was, "Among patients with symptomatic 70–99% stenosis of a carotid artery (and therefore at high risk of stroke), can the addition of carotid endarterectomy (performed by an expert vascular or neurosurgeon with an excellent track record) to best medical therapy, compared with best medical therapy alone, reduce the outcomes of major stroke or death over the next two years?"
- Here, the experimental intervention was carotid endarterectomy.

Examples

...NASCET...

- Participant eligibility criteria
  - symptomatic patients stratified for carotid stenosis severity, with primary interest in a severe carotid stenosis (high-risk) group who were thought to be most likely to respond to endarterectomy, if it was efficacious
  - no prior compliance testing and many exclusion criteria
  - very near the extreme explanatory end of the scale
- Experimental intervention flexibility
  - endarterectomy had to be carried out (rather than stenting or some other operation), but the surgeon was given leeway in how it was performed
  - simultaneous coronary-artery bypass grafting was proscribed and bilateral carotid endarterectomy could be performed provided the symptomatic side was operated on first
  - same co-interventions (best medical care) as medical group
  - very explanatory, but could be more so

Examples

...NASCET...

- Practitioner expertise (experimental)
  - surgeons had to be approved by an expert panel, and were restricted to those who had performed at least 50 carotid endarterectomies in the last 24 months, with a post-operative complication rate (stroke or death within 30 days) of less than 6%
  - extremely explanatory
  - follow-up assessments were carried out by board-certified neurologists or their senior sub-specialty trainees (a slightly less explanatory approach)
- Comparison intervention
  - anti-platelet therapy (usually 1300 mg of ASA per day) was prescribed
  - co-interventions applied to surgical patients were also applied to control patients (anti-hypertensive therapy with blood pressure targets and feedback, anti-lipid and anti-diabetic therapy) as indicated
  - strongly explanatory

Examples

...NASCET...

- Practitioner expertise (comparison)
  - patients in the medical arm were managed and followed by board-certified neurologists or their senior sub-specialty trainees, just like the surgical patients
  - very explanatory in approach
- Follow-up intensity
  - patients had pre-scheduled appointments at 1, 3, 6, 9, 12, 16, 20, and 24 months (and every 4 months thereafter) consisting of medical, neurologic, and functional-status assessment
  - all blood pressure records were reviewed centrally, and elevated readings triggered reminder letters
  - a highly explanatory approach is evident

Examples

...NASCET...

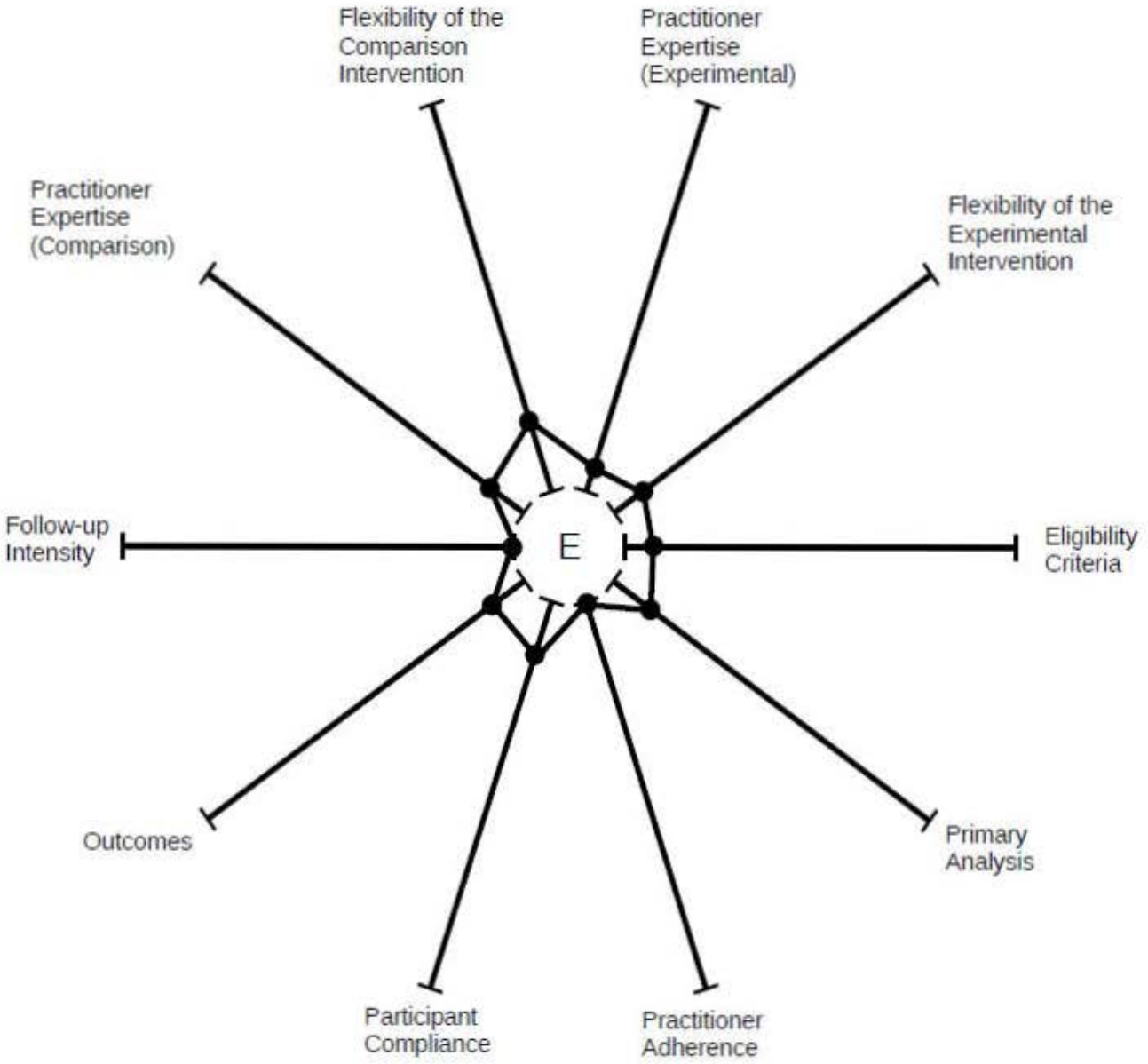
- Primary trial outcome
  - primary outcome was time to ipsilateral stroke, the clinically relevant, explanatory outcome most likely to be affected by carotid endarterectomy
  - other outcomes were more pragmatic: all strokes, major strokes and mortality were secondary outcomes
  - very explanatory
- Participant compliance
  - experimental intervention was a one-time operation
  - because the 50% probability of operation was clearly stated in the original consent documents, patients who didn't want surgery were unlikely to enter the trial (only 0.3% of admitted patients randomized to the operation refused it)
  - this is a prophylactic strategy for achieving compliance and is thus, an explanatory approach

Examples

...NASCET...

- Practitioner adherence
  - the completeness, timeliness, and accuracy of clinical data forms generated at admission, follow-up, and for events were monitored centrally and deficiency would result in more frequent visits from the trial PI
  - blood pressure reports from each visit were scrutinized centrally, with letters pestering clinical collaborators when they were elevated
  - extremely explanatory

NASCET


Flexibility of the Comparison Intervention
Practitioner Expertise (Experimental)
Practitioner Expertise (Comparison)
Flexibility of the Experimental Intervention
Follow-up Intensity
E
Eligibility Criteria
Outcomes
Primary Analysis
Participant Compliance
Practitioner Adherence

Outline

1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

Discussion

- This is a work in progress and we welcome suggestions for its continued development.
- If applied by a design team during the planning stages of a trial, we believe this is a useful tool to ensure the trial is fit for its intended purpose.
- The graphical representations are helpful for readily identifying domains that are not as pragmatic or explanatory as the trial designers desired.

Discussion

- There is clearly some subjectivity involved in placing each domain within the continuum.
- Extreme positions are easiest to identify while less extreme positions are more challenging.
- We don't see this as a problem, especially when the entire team is involved, since those domains where agreement is hard to achieve are exactly the domains that need attention.

Outline

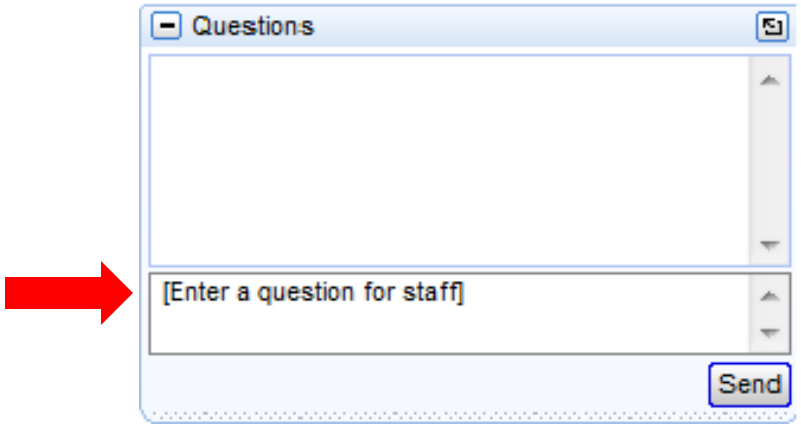
1. Introduction
2. PRECIS in detail
3. Examples
4. Discussion
5. References

References

- Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic—explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal Clin Epidemiol* 2009; 62: 464–475, *Can Med Assoc J* 2009; 180(10)
- Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chron Dis* 1967; 20: 637–48
- Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet* 1998; 352: 1340–3
- North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991; 325: 445–53

How to Submit a Question

- At any time during the presentation, type your question into the “Questions” section of your GoToWebinar control panel.
- Select “Send” to submit your question to the moderator.
- Questions will be read aloud by the moderator.



Obtaining CME Credit

This Live series activity, AHRQ Practice-Based Research Network Resource Center National Webinars, from 09/10/2014 - 09/10/2015, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This webinar has been approved for **1.25 elective CME credit(s).**

To obtain CME Credit for your participation in this webinar, please:

1.) Complete the online evaluation. You will be prompted to complete this online evaluation when you exit the webinar.

2.) E-mail PBRN@abtassoc.com to request a copy of your CME Certificate of Participation

Upcoming Events

- Upcoming AHRQ PBRN RC Webinar: Practical Insights on Meeting Objectives of Meaningful Use III **January 28th, 12:30pm – 2:00pm ET**
- Upcoming PBRN Pragmatic Research and Translation Learning Group Call **January 5th, 1pm – 2pm ET**
  - Paul Meissner, Rowena Dolor, and Jonathan Tobin invite you to join the "renewed" learning group for PBRNs engaged in pragmatic trials and practical strategies for translation into practice.
  - If you are interested in participating in this learning group, e-mail PBRN@abtassoc.com with the subject line PBRN PRT LG Call.

Visit http://pbrn.ahrq.gov/events for webinar registration information and details on other upcoming PBRN-relevant events

If you have a suggestion for a webinar topic or would like to be a webinar presenter, send your feedback to: PBRN@abtassoc.com

PBRN Listserv:
Join the Conversation among PBRNs!

PBRN Listserv:

Are you interested in learning about:

- ✓ free, CME-earning National Webinars,
- ✓ research publications,
- ✓ practical guidance for administering or conducting research,
- ✓ funding opportunities, and
- ✓ employment opportunities that are relevant to PBRNs, especially around primary care?

PBRN Listserv members receive a **bi-weekly digest** and **other announcements of interest**, and are able to reach out directly to the PBRN community by posting to the PBRN Listserv (PBRNLIST@list.ahrq.gov). **To join**, simply send an e-mail to the AHRQ PBRN Resource Center (PBRN@abtassoc.com) with the subject "Please add me to the PBRN Listserv."

Thank you for attending today's PBRN webinar!