PRECIS Guidance and Pragmatic Clinical Trials

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PRECIS

• **PRagmatic-Explanatory Continuum Indicator Summary (PRECIS)**

• PRECIS = a summary

• Why? Structure for defining explanatory vs. pragmatic trials
  – Explanatory (efficacy) trials conducted under tight conditions with exclusions on participation and lots of structure on procedures, follow-up, etc.
    • Influences clinical decision making, but may not completely represent the priority clinical question
  – Pragmatic (effectiveness) trials designed to increase generalizability and maximize clinical decision making
    • Can directly affect “real-world” clinical decision making
Advantages vs. Disadvantages

• Explanatory trial:
  – If negative, can disregard potential treatment
  – If positive, will it work in the real world?

• Pragmatic trial:
  – If positive, can be scaled for maximum benefit
  – If negative, need to differentiate why intervention failed, i.e., was it the intervention, or the setting, or does it matter?
The PRECIS Structure

- 9 domains ("spokes"): scored as restrictions, i.e., higher score = more restrictions and thus less generalizable
  - Eligibility
  - Recruitment
  - Setting
  - Organization
  - Flexibility: delivery
  - Flexibility: adherence
  - Follow-up
  - Primary outcome
  - Primary analysis

- All criteria "scored":
  - 1= very explanatory (ideal conditions),
  - 2= rather explanatory,
  - 3= equally explanatory and pragmatic,
  - 4= rather pragmatic,
  - 5= very pragmatic (usual care conditions)

The PRECIS-2 Wheel

- **Eligibility**: Who is selected to participate in the trial?
- **Recruitment**: How are participants recruited into the trial?
- **Setting**: Where is the trial being done?
- **Organisation**: What expertise and resources are needed to deliver the intervention?
- **Primary analysis**: To what extent are all data included?
- **Primary outcome**: How relevant is it to participants?
- **Follow-up**: How closely are participants followed-up?
- **Flexibility: adherence**: What measures are in place to make sure participants adhere to the intervention?
- **Flexibility: delivery**: How should the intervention be delivered?

Eligibility

• To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?

• Highly pragmatic: include anyone with condition of interest who would be a candidate for the intervention provided in usual care

• Reduced scores:
  – Limiting gender, ethnicity, sex
  – Limiting participation based on co-treatments
  – Exclude those not known to be highly adherent
  – Using tests or measures to determine eligibility (unless typical of usual care)
  – Excluding children, adults over 65 and/or PG women
  – Excluding those whose f/u may be challenged

Recruitment

• How much extra effort is made to recruit over and above what would be used in usual care?

• Highly pragmatic: Recruit patients who present to the clinic (or multiple clinics) on their own behalf

• Reduced scores:
  – Searching EHRs
  – Media advertising
  – Offering participation incentives

Setting

• How different are the settings of the trial from usual care settings?

• Highly pragmatic: Trial conducted in an identical setting to which one intends to apply the results

• Reduced scores:
  – Setting limited to specialty centers or clinical research center
  – Running trial in a single center

Organization

• How different are the resources, provider expertise, and organization of care delivery in the intervention arm of the trial, compared to usual care?
• Highly pragmatic: Intervention articulated in the usual flow of care, making use of no more than existing staff and resources
• Reduced scores:
  – Increase staffing to deliver the intervention or follow-up
  – Providing significant additional training
  – Requiring providers to have some minimal level of experience in working with the intervention
  – Requiring trial staff to have a specialty certification

Flexibility: Delivery

• How different is the flexibility in how the intervention is delivered (compared to usual care)?

• Highly pragmatic: Delivery left up to the individual provider, not dictating what other interventions were permitted or how to deliver them.

• Reduced scores:
  – Highly specified, protocol driven intervention
  – Including measures to assess provider/staff adherence to protocol
  – Timing of delivery carefully controlled
  – Restrictions placed on number and type of co-interventions and/or co-interventions are protocolized
  – Specific directions for managing complications/AEs

Flexibility: Adherence

• How different is the flexibility in how the participants are monitored and encouraged to adhere, than encountered in usual care?

• Highly pragmatic: Allows for full flexibility in how end user participants engage with the intervention.

• Reduced scores:
  – Including a pre-screening “wash in” stage
  – Withdrawing participants if their adherence drops below a set limit
  – Having measures/procedures in place to monitor adherence, i.e., pill counts, diaries, phone calls, etc.

Follow-up

• How different is the intensity of follow-up measurement in the trial compared to in usual care?

• Highly pragmatic: No more follow-up than what would occur in usual care; minimal additional data collection from administrative or clinical record systems.

• Reduced scores:
  – Follow-up visits more frequent than in usual care
  – Unscheduled visits triggered by outcome events
  – Patients are contacted if they fail to meet trial appointments
  – Visits are longer than in usual care

Primary outcome

- To what extent is the trial’s primary outcome directly relevant to patients’/participants’ priorities?
- Highly pragmatic: Outcomes of obvious importance to patients, measured in a manner typical to usual care
- Reduced scores:
  - Surrogate biomarkers
  - Composite primary outcome measures
  - Central adjudication
  - Outcome mainly important to providers
  - Modifying the time horizon for the trial

Primary analysis

• To what extent are all data included in the analysis of the primary outcome?
• Highly pragmatic: Intention to treat with all available data
• Reduced scores:
  – Per protocol analyses
  – Excluding non-adherent participants
  – Analyze treatment received, not treatment randomized
  – Excluding data on non-adherent providers
  – Excluding data from providers who recruited below expected numbers

Example: Comparative Effectiveness of Vitamin D: A Randomized Trial

- Eligibility: 25-OH D< 33ng/ml upon routine screening
- Recruitment: By patients’ typical providers
- Setting: 3 primary care settings (Seattle, WA and Kona, HI)
- Organization:
  - Interventions dispensed by pharmacy (routine practice), f/u visits by providers, baseline questionnaires provided upon Rx pick-up
- Flexibility: delivery:
  - Dosing recommendations given: 10,000 IU/day (5 dosing units per day); 6-week standardized interview for AEs; Ca2+ measurement for any symptoms of hypercalcemia; Dose reduction protocol for AEs
- Flexibility: adherence: Not assessed (participant or provider)
- Follow-up: 3 months at the laboratory
- Primary outcome: Change in 25-OHD
- Primary analysis: ITT

Pragmatic Trial to Compare the Effectiveness of Vitamin D3 Delivery Matrix

Design:
3-arm randomized, active comparative effectiveness, pragmatic clinical trial

Participants:
n=66 with 25OHD <33 ng/mL upon routine testing

Recruitment sites:
Seattle, WA & Kailua-Kona, HI

Intervention:
Random allocation (by pharmacy) to one of three VitD3 dietary supplements: capsules, oil drops, or chewable tablets - all 2,000 IU/unit
- Dosage: 10,000 IU per day (i.e., 5 dosage units/day)
- Duration: 12-weeks
- Sunscreen use required and sunscreen dispensed

Safety:
6-week standardized interview for adverse events (AEs)
Ca2+ measurement for any symptoms of hypercalcemia
Dose reduction protocol for AEs

Outcome Measures (analysis):
Primary: Change in serum 25OHD concentration (ANOVA; intention to treat (ITT))
Secondary: % reaching sufficiency (Fisher’s Exact; ITT)
Tertiary: Change in serum 1,25 dihydroxycholecalciferol (1,25OH2D) concentration (ANOVA, ITT)
Exploratory: Change in 25-OHD/IU administered based on label claim, internal certificate of analysis, and third party analysis (per protocol analysis)
The PRECIS-2 Wheel

Eligibility
Who is selected to participate in the trial?

Recruitment
How are participants recruited into the trial?

Setting
Where is the trial being done?

Organisation
What expertise and resources are needed to deliver the intervention?

Flexibility: delivery
How should the intervention be delivered?

Flexibility: adherence
What measures are in place to make sure participants adhere to the intervention?

Follow-up
How closely are participants followed-up?

Primary outcome
How relevant is it to participants?

Primary analysis
To what extent are all data included?

Change in serum 25-hydroxycholecalciferol (25-OHD) concentration per standardized dosing unit by treatment arm

Source of product data

Secondary Aim: % Reaching Sufficiency

Recommended sequence

• Step 1: What design approach are you taking?
• Step 2: Consider trial design choices for each of the 9 PRECIS domains
• Step 3: Score each domain from 1-5
• Step 4: Review the PRECIS wheel and re-evaluate your design choices as needed to meet your objective

Words of Caution

• Although a useful structure and thought exercise, not all factions (reviewers) are aware of PRECIS, and thus of the differentiation between “explanatory” and “pragmatic”

• Many reviewers stuck on explanatory designs

• Some funding agencies, e.g., PICORI, may have targeted FOA for pragmatic trials, and thus the PRECIS structure is key to include

• Focus on the correct design for the state of the science and practice for the research question, not necessarily increasing the PRECIS score

• Will need to justify/substantiate design choices no matter the audience