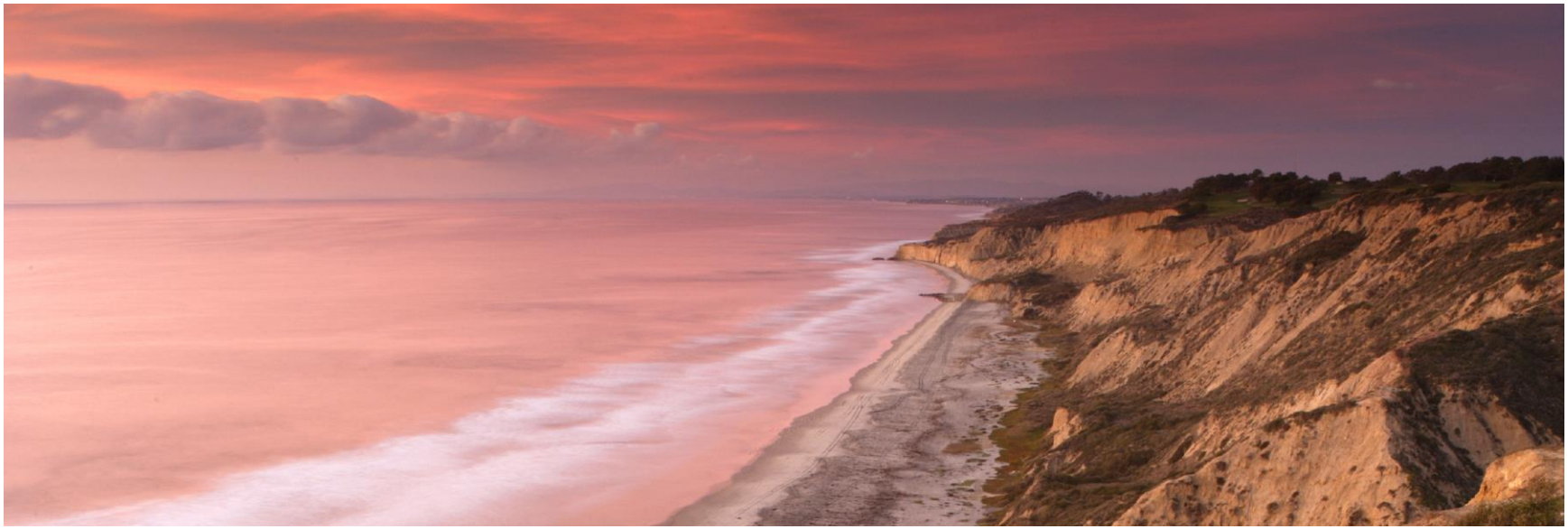

PRECIS Guidance and Pragmatic Clinical Trials

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PRECIS

- **PR**agmatic-**E**xplanatory **C**ontinuum **I**ndicator **S**ummary (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?

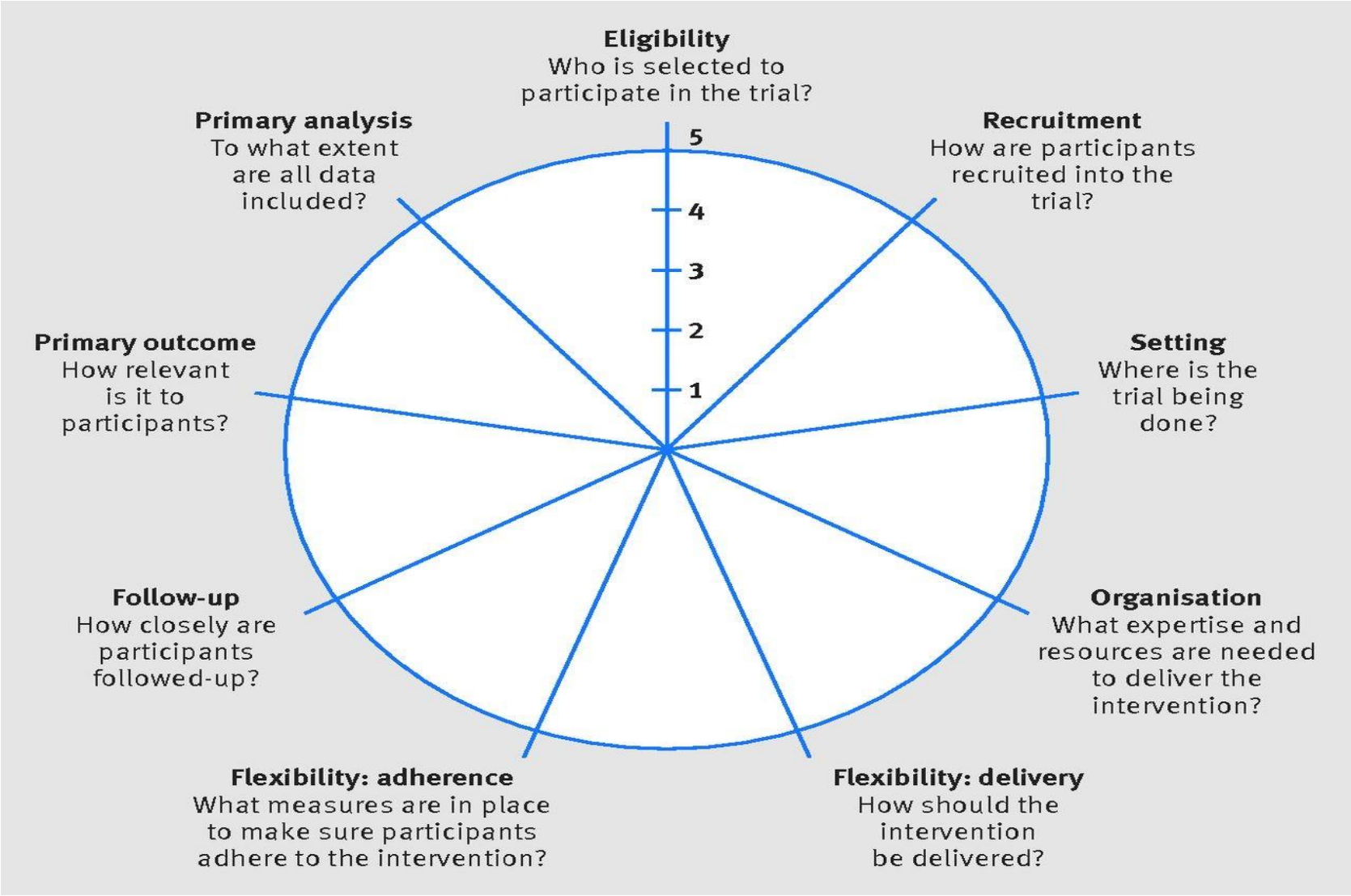
The PRECIS Structure

- 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)

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

The PRECIS-2 Wheel



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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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

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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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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.

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

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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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

Loudon K, Treweek S, Sullivan F, et al. BMJ. 2015; 350:h2147.

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

Traub ML, Finnell JS, Bhandiwad A, Oberg E, Suhaila L, and **Bradley R**. Impact of Vitamin D3 Dietary Supplement Matrix on Clinical Response. **Journal of Clinical Endocrinology & Metabolism**. 99(8):2720-8.

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):

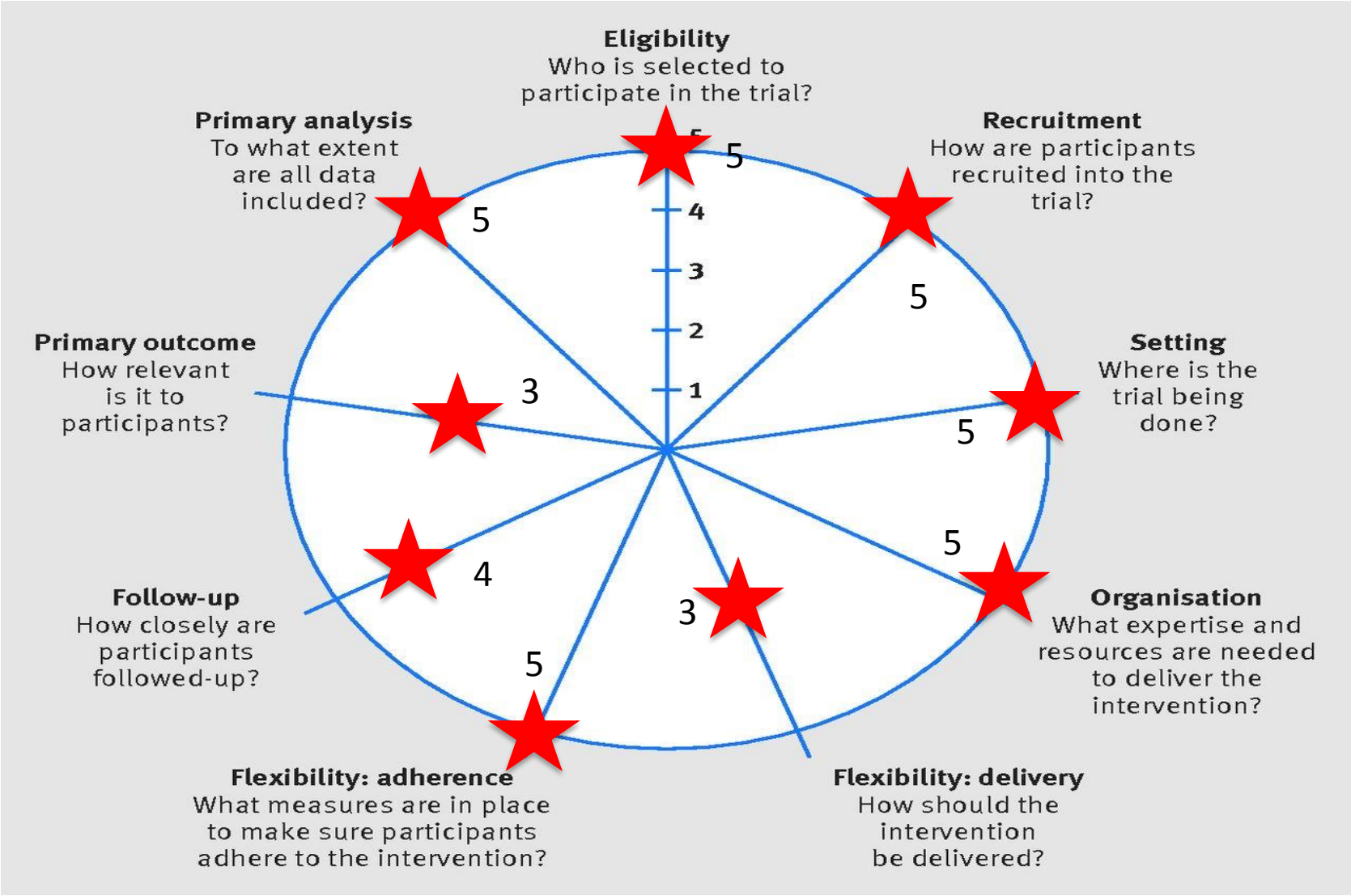
Primary: Change in serum 25OHD concentration (ANOVA; intention to treat (ITT))

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



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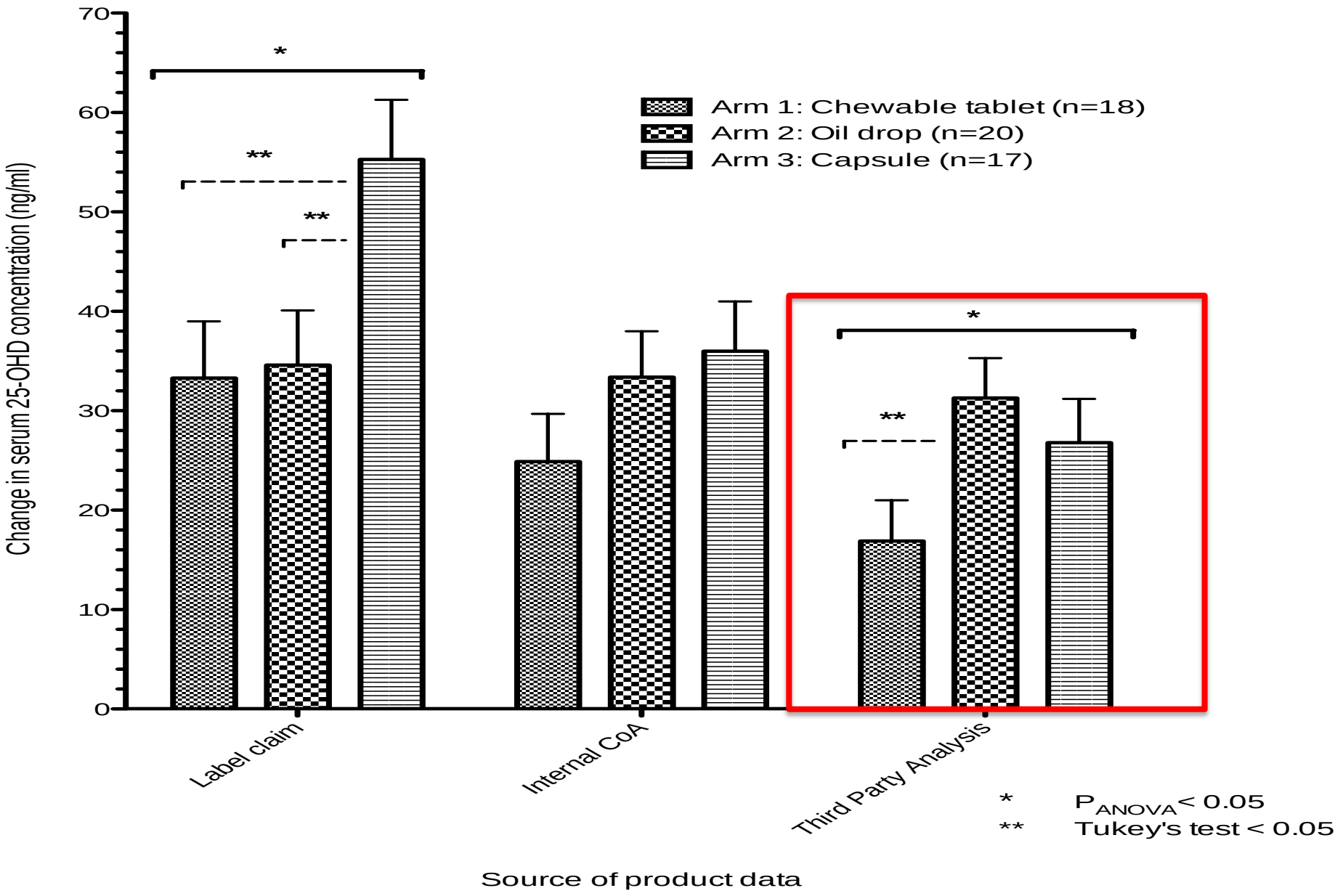

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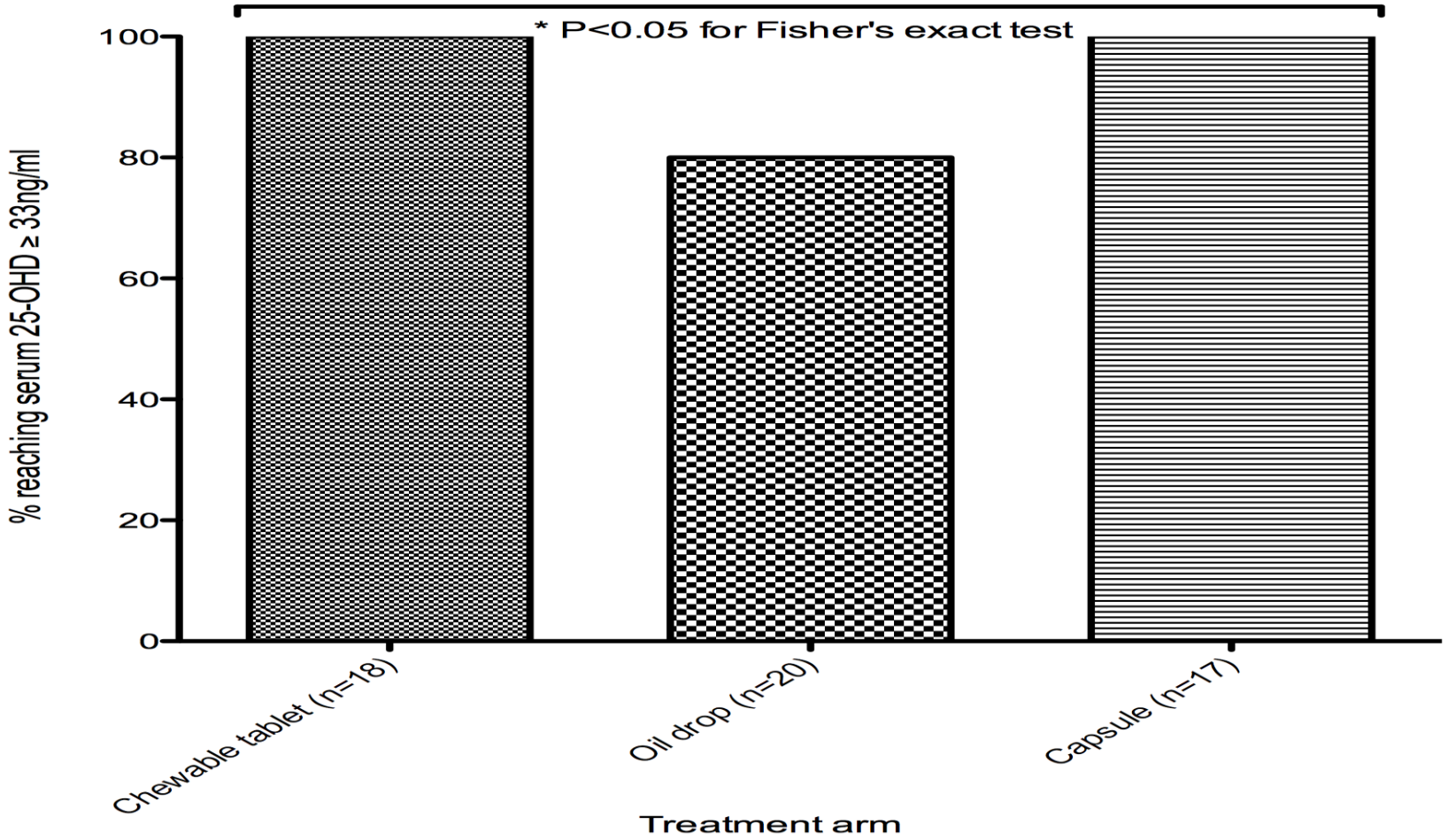
Secondary Aim: % Reaching Sufficiency



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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

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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