Optimizing Inclusion and Exclusion Criteria in Clinical Research

Mary H. Samuels, M.D.
Program Director, CTRC

DATE: April 18, 2019

Inclusion/Exclusion Criteria

- **Inclusion/Exclusion Criteria should have clear scientific or clinical rationale, and may differ depending on the study design (ex. observational vs. interventional):**
  - Balance of scientific ideals and the real world
  - Balance of essential and trivial details
  - Balance of structure and flexibility

OHSU OREGON CLINICAL & TRANSLATIONAL *Research Institute*

Inclusion/Exclusion Criteria

- **Gender**
  - Need compelling reason to only include one gender (ex. prostate cancer, menopause)
  - May need increased sample size if gender differences expected
- **Age range**
  - Consider pubertal and developmental changes (ex. brain development)
  - Don’t exclude older subjects just on age
  - For pediatric studies, tailor criteria to disease biology, scientific objective, existing data regarding safety

OHSU

Inclusion/Exclusion Criteria

- **Weight and Diet**
  - Does the study design require a certain BMI range?
  - Do the subjects need to be consuming a stable diet?
  - Do you need to exclude certain diets or foods?
- **Smoking etc**
  - Do the subjects need to be nonsmokers?
  - What about marijuana, other recreational drugs?
- **Physical activity**
  - Do the subjects need to be sedentary, or avoid extremes in physical activity?

OHSU

Inclusion/Exclusion Criteria

- **Medical conditions**
  - Are there medical conditions that would compromise patient safety or data fidelity?
- **Medications**
  - Are there medications that would interfere with or increase the risk of the experimental therapy?
  - Are there medications that would compromise data fidelity?
  - Are contraceptives OK?
  - What about any OTC products?

OHSU

Inclusion/Exclusion Criteria

- **Laboratory abnormalities**
  - Are there laboratory abnormalities that need to be excluded due to safety issues (ex. GFR for reduced renal function, ECG for underlying cardiac disease)?
  - Are there laboratory abnormalities that need to be excluded due to interference with your study aims, aside from safety issues?

Inclusion/Exclusion Criteria

- **Practical/logistical issues**
  - Do the subjects need to reside within a certain distance of Portland due to transportation issues?
  - Are there exclusions due to language barriers (ex. surveys only validated in English)?
  - Are there cognitive or cultural barriers to consent?

Inclusion/Exclusion Criteria

- **Consider broad exclusion statements**
  - like “other medical conditions/medications that would interfere with subject safety or data collection in the opinion of the PI,” rather than trying to think of everything.
- **Consider broad statements** like “clinically relevant laboratory abnormalities” or cut-off levels, rather than any laboratory abnormalities, to avoid excluding subjects for trivial laboratory findings.
- **Consider dosing adjustments for mild renal insufficiency** rather than outright exclusion.
- **Consider dose adjustments for BMI ranges**, if BMI extremes are a problem, rather than excluding BMIs at upper or lower extremes.

OHSU

Example: Enrollment Criteria too Broad

Study: Blood samples for new lab assay

- **Inclusion Criteria**
  - Healthy Subjects
- **Exclusion Criteria**
  - Evidence of infection
  - On medication
  - Medical conditions that may compromise the quality of cells
  - Disorders that may cause problems for the subject

OHSU OREGON CLINICAL & TRANSLATIONAL *Research Institute*

Example: Enrollment Criteria Too Narrow

Study: The relationship between hormone levels and PMS symptoms

- **Inclusion Criteria**
  - Women between 18 and 30
  - PMS symptoms every cycle for at least 1 year
  - Normal pap smear within last year
  - Regular Menstrual cycles >26 and <32 days
- **Exclusion Criteria**
  - Hysterectomy
  - Hormonal contraceptives in last 3 months
  - History of smoking
  - History of psychiatric disorder
  - History of alcohol/drug abuse
  - Use of medications that could affect mood or sleeping
  - Abnormal screening blood tests (TSH, LFT, HGB)
  - Pregnancy within last year or plan to get pregnant during study
  - Use of medications/alternative treatments for PMS within last 60 days
  - History of insomnia
  - History of migraines

Example: Enrollment Criteria Just Right

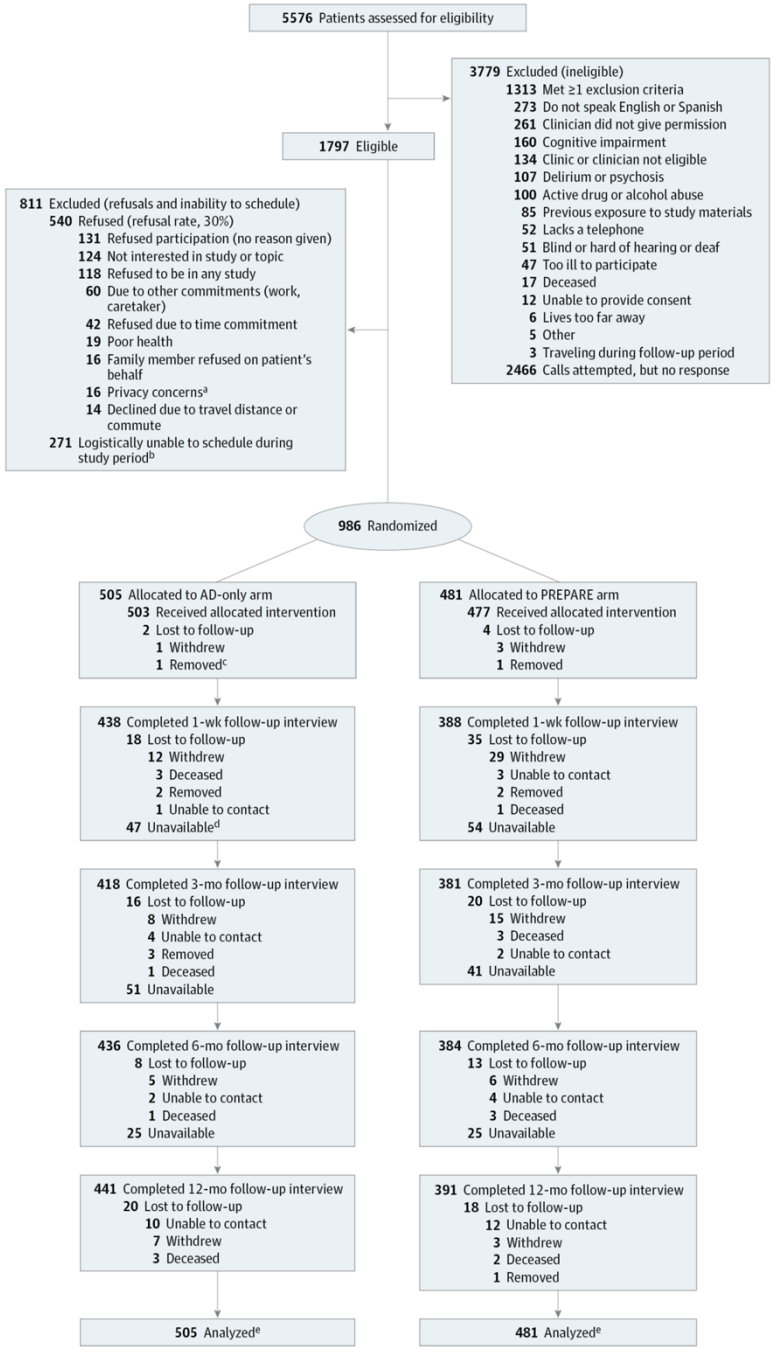
Study: Any Clinical Research Study

- **Inclusion Criteria**
  - Characteristics that are relevant to the research question
  - Demographic characteristics (e.g. age)
  - Clinical characteristics (e.g. diagnosis)
  - Geographic characteristics (e.g. Clinic Patients)
  - Vulnerable Populations (if applicable)
- **Exclusion Criteria**
  - Describe subset of population that won't be studied
  - Characteristics that make it unethical to withhold treatment
  - Subjects at high risk of side effects
  - High likelihood of lost to follow-up
  - Characteristics that might interfere with the quality of the data

Pragmatic Vs. Explanatory Trials

Cynthia Morris, PhD, MPH
Senior Associate Director and PI, OCTRI Workforce Development

DATE: April 18, 2019


5576 Patients assessed for eligibility
3779 Excluded (ineligible)
1313 Met ≥1 exclusion criteria
273 Do not speak English or Spanish
261 Clinician did not give permission
160 Cognitive impairment
134 Clinic or clinician not eligible
107 Delirium or psychosis
100 Active drug or alcohol abuse
85 Previous exposure to study materials
52 Lacks a telephone
51 Blind or hard of hearing or deaf
47 Too ill to participate
17 Deceased
12 Unable to provide consent
6 Lives too far away
5 Other
3 Traveling during follow-up period
2466 Calls attempted, but no response
1797 Eligible
811 Excluded (refusals and inability to schedule)
540 Refused (refusal rate, 30%)
131 Refused participation (no reason given)
124 Not interested in study or topic
118 Refused to be in any study
60 Due to other commitments (work, caretaker)
42 Refused due to time commitment
19 Poor health
16 Family member refused on patient's behalf
16 Privacy concerns[a]
14 Declined due to travel distance or commute
271 Logistically unable to schedule during study period[b]
986 Randomized
505 Allocated to AD-only arm
503 Received allocated intervention
2 Lost to follow-up
1 Withdrew
1 Removed[c]
481 Allocated to PREPARE arm
477 Received allocated intervention
4 Lost to follow-up
3 Withdrew
1 Removed
438 Completed 1-wk follow-up interview
18 Lost to follow-up
12 Withdrew
3 Deceased
2 Removed
1 Unable to contact
47 Unavailable[d]
388 Completed 1-wk follow-up interview
35 Lost to follow-up
29 Withdrew
3 Unable to contact
2 Removed
1 Deceased
54 Unavailable
418 Completed 3-mo follow-up interview
16 Lost to follow-up
8 Withdrew
4 Unable to contact
3 Removed
1 Deceased
51 Unavailable
381 Completed 3-mo follow-up interview
20 Lost to follow-up
15 Withdrew
3 Deceased
2 Unable to contact
41 Unavailable
436 Completed 6-mo follow-up interview
8 Lost to follow-up
5 Withdrew
2 Unable to contact
1 Deceased
25 Unavailable
384 Completed 6-mo follow-up interview
13 Lost to follow-up
6 Withdrew
4 Unable to contact
3 Deceased
25 Unavailable
441 Completed 12-mo follow-up interview
20 Lost to follow-up
10 Unable to contact
7 Withdrew
3 Deceased
391 Completed 12-mo follow-up interview
18 Lost to follow-up
12 Unable to contact
3 Withdrew
2 Deceased
1 Removed
505 Analyzed[e]
481 Analyzed[e]

OHSU

Pragmatic vs. Explanatory Trials

- **Pragmatic trials**
  - seek to answer the question “Does an intervention work under usual conditions?”
- **Explanatory trials**
  - seek to answer the question “Can an intervention work under ideal conditions?” Can help to explain the mechanism…the why.

OHSU

Pragmatic trials determine…

- Does it work?
- For whom does it work?
- How much does it cost?
- Is the new treatment better than existing care?
  - Does not determine if the new treatment is better than no treatment or placebo.
- Pragmatic trials sacrifice internal validity for generalizability

OHSU

Why are pragmatic trials important?

Relevance…..We are

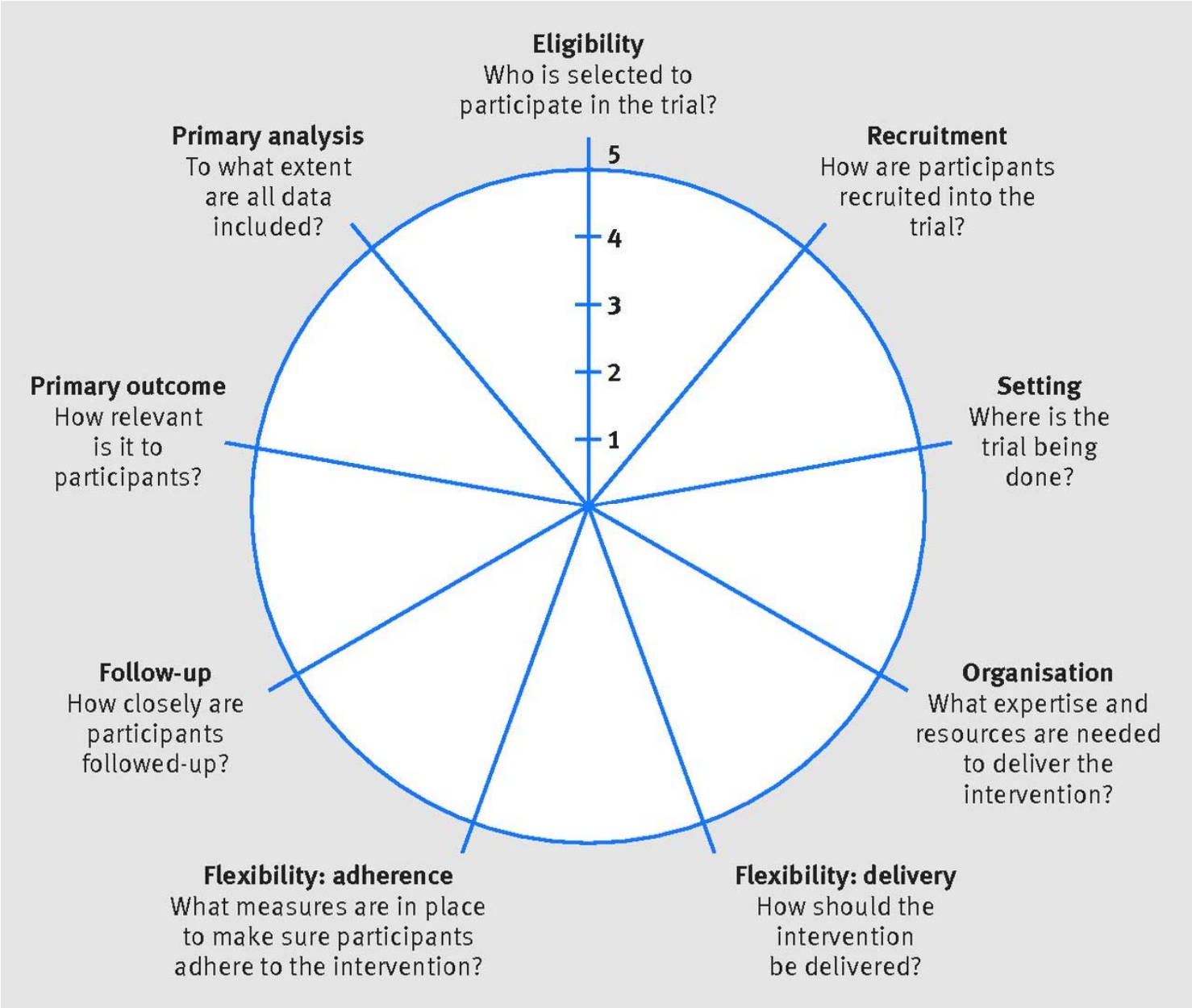
- Not reaching patients with complex, comorbid conditions
- Not testing in conditions and with staff most similar to clinical situations
- Not addressing issues most important to clinicians, policy makers, patients
- Some evidence-based interventions are not feasible in real world

OHSU

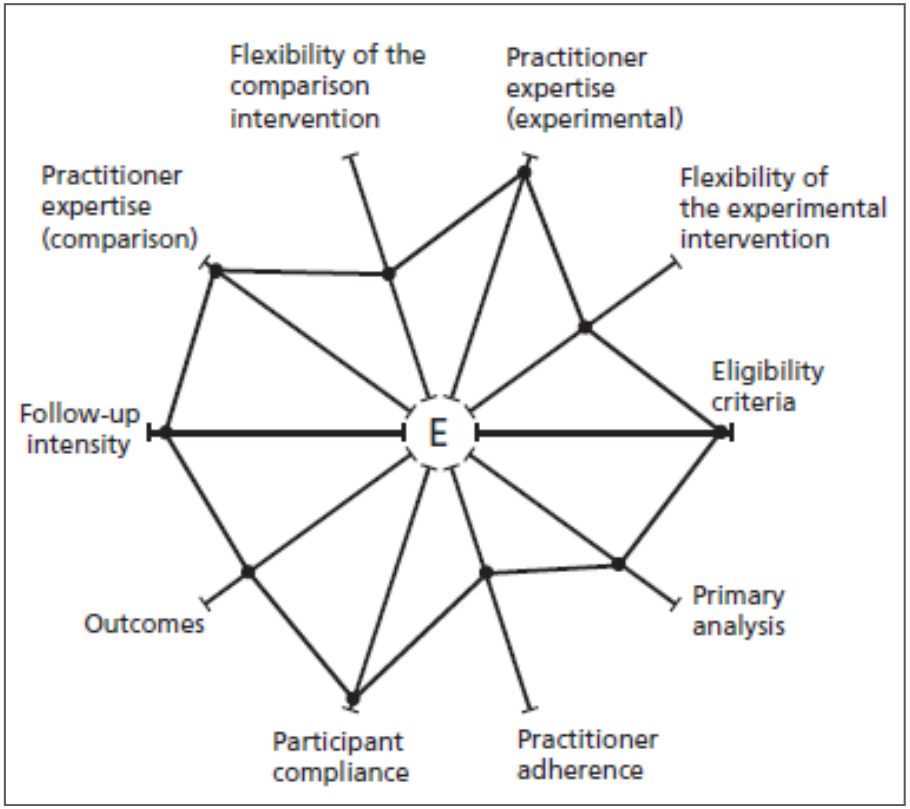
Key features of pragmatic trials

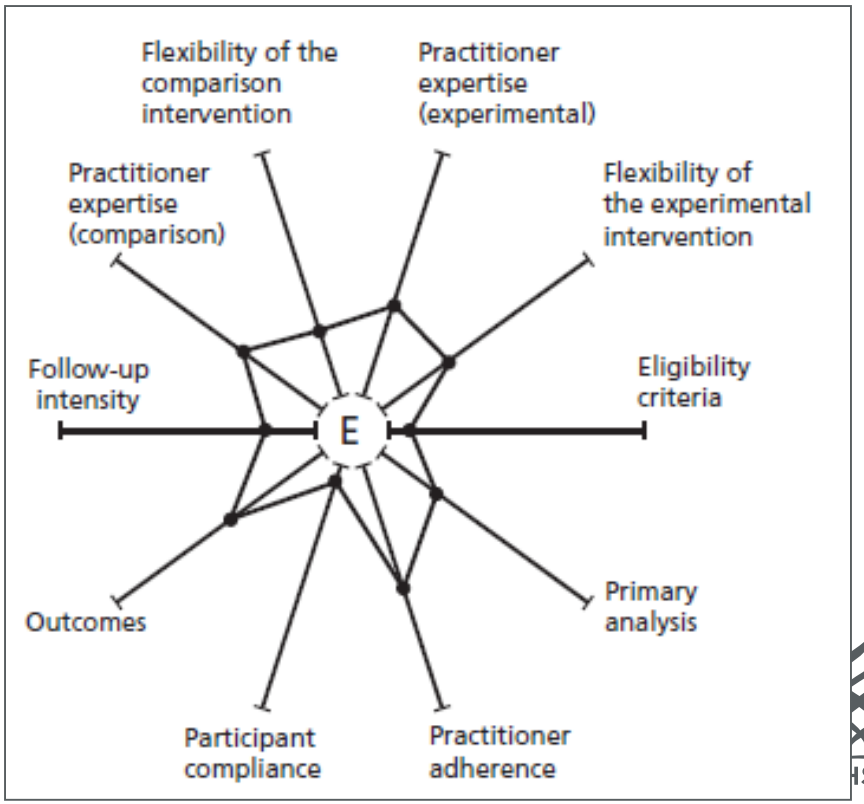
- Broad eligibility
- Recruit from a variety of settings to increase generalizability
- Usually head-to-head comparison of two active drugs
- Medical management consistent with clinical care
- Often omits study procedures that alter ecology of care
- Outcomes of importance to the patient
- Duration to examine benefits, risk
- Large enough sample size to examine benefits, risks
- Objective and subjective measures

OHSU


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?
5
4
3
2
1

OHSU


Flexibility of the comparison intervention
Practitioner expertise (experimental)
Practitioner expertise (comparison)
Flexibility of the experimental intervention
Eligibility criteria
Follow-up intensity
E
Outcomes
Primary analysis
Participant compliance
Practitioner adherence


Flexibility of the comparison intervention
Practitioner expertise (experimental)
Practitioner expertise (comparison)
Flexibility of the experimental intervention
Follow-up intensity
Eligibility criteria
E
Outcomes
Primary analysis
Participant compliance
Practitioner adherence

Thank You