Pitfalls in Clinical Trials of Yoga Interventions

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Potential Pitfalls and Threats to Validity in Clinical Trials
Sources of Error in Clinical Trials

- **Inadequate sample size**
- Sampling and Selection bias
- Poor or differential compliance
- Unintended cross-over
- High or differential drop-out (attrition bias)
- Placebo/Nocebo effects
- Inadequate blinding
- Performance bias
- Detection bias
- Low power
- Confounding
Sample Size (N)

Inadequate sample size - Why an issue?

- Potential problems with small sample sizes:
  - Reduced **power** (ability to reliably detect true differences in outcomes over time or between groups) ->
    - Can lead to non-significant results even with an apparently large effect!
  - Less representative => Generalizability of findings reduced
  - Lead to more tentative conclusions
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Sampling Bias

Sampling bias:

- Some members of population more likely to be selected => Skewed/non-representative study sample => *Can limit generalizability*

E.g., Trial of yoga for improving sleep in a Punjabi population
Sampling Bias

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- Some members of population more likely to be selected => Skewed/non-representative study sample => Can limit generalizability

E.g., Trial of yoga for improving sleep in a Punjabi population
Selection Bias

Systematic differences between groups at baseline and/or preferential enrollment of specific participants into one tx group

Due to:
- Chance (esp smaller studies)
- Non-random assignment
- Treatment allocation not concealed

Can confound/bias study results
Randomization: Hallmark of contemporary trials

• **Why randomize?**
  - Help ensure tx groups comparable in factors, *both known and unknown*, that could influence study outcome(s)
  - Reduce bias and confounding
  - *But no guarantee, especially in small trials!*

• **Is randomization procedure appropriate?**
  - Specific procedures for randomization
  - *Random allocation does not equal haphazard assignment*
Selection bias. *Non-random assignment*

*Treatment allocation by:*
Selection bias. Non-random assignment

Treatment allocation by:

Participant Preference

Yoga

Stretching

Strength training

Usual care
Selection bias. *Non-random assignment*

*Treatment allocation by:*

- School
- Participant Preference
  - Yoga
  - Stretching
  - Strength training
  - Usual care

#1

#2
**Concealment of treatment allocation**

- Critical feature of RCTs
- Participant tx assignment should be concealed before entering the study (e.g., via numbered, opaque, sealed envelopes; central randomization system, etc)
- *I.e., neither participants nor investigators/clinicians should be aware of (or be able to influence) next tx assignment*

- **Why important?**
Concealment of treatment allocation

**Why important?** Advance knowledge of (and control over) tx assignment by investigators/assessors can seriously compromise study =>
- ↑ Likelihood of bias, confounding, ↓ power

**Tales of woe** (non-random allocation in RCT’s)
- Many cases in which investigators, providers, or patients were able to identify the impending treatment allocation and influence pt enrollment/assignment =>
  
  *Skewing of tx groups so no longer comparable*
Potential Problems with Failure to Conceal Group Allocation

Effects of Teasing on Aggression: Study Participants
Failure to Conceal Group Allocation, cont

Effects of Teasing on Aggression: Potential motivation for tampering with group assignment
Failure to Conceal Group Allocation

Study Participants

‘Randomized’ (Evaluator controls group allocation)

Intervention Group

Control Group
Sources of Error in Clinical Trials

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Potential Pitfalls, cont.

- **Poor/differential adherence**
  
  *E.g.*, participants may
  - Miss a large % of study classes, home practice
  - Not adhere to prescribed lifestyle changes
  - Not complete all assessments

- **Unplanned cross-over**: Participants are exposed to a different intervention than assigned.
  
  *E.g.: Yoga vs. usual care for type 2 diabetes*
  - Spouses randomized to different groups
  - Husband (usual care) decides to try yoga, practices with his wife during final 6 weeks of study

*Can compromise power, validity of study*
Sources of Error, cont.

High Drop-out, Differential drop-out: (Attrition bias)

Can ↓ power, compromise validity

- E.g., Yoga vs. conventional exercise for hypertension=>
Sources of Error, cont.

High Drop-out, Differential drop-out: (Attrition bias)

*Can ↓ power, compromise validity*

- E.g., Yoga vs. conventional exercise for hypertension =>
  - High, differential attrition

=> *Important to monitor compliance and retention carefully, devise strategies to encourage retention and adherence!*

[Image of people exercising, labeled 'Exercise' and 'Yoga']
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Placebo/Nocebo Effects

Placebo ("I will please") effect: Health improvement in response to perceived/expected benefit (e.g., of an intervention)/conditioning

- Can account for large % of tx effects
- Affects both physiological and psychological outcomes: E.g.:
  - Motor function:
  - Pain
  - Mood, cognition, sleep
  - Blood pressure, heart rate
  - Metabolic and immune function
  - Other
    - Edema, blood counts, electrolyte balance
    - GI symptoms, gastric acid, etc
Nocebo Effect

Nocebo Response: ‘Voodoo effect’

Health deterioration due to negative expectations/conditioning (‘I will harm’) E.g.:

- **Side effects**: Occur in 20-30% of healthy adults on sham tx, account for up to 90% of observed side effects in medication trials
- Edema, pain, diarrhea, CVD sx
- Allergic/immune response/Asthma sx
- ‘Placebo OD’
- ↑ Risk of death

*Why randomization, measurement of treatment expectancy, and blinding so important!*
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- Performance bias
- Detection bias
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- Confounding
Blinding

Why is blinding important?

- ↓ influence of placebo/nocebo effects
- ↓ likelihood of detection, attrition, etc bias

• Single blind:
  - Outcome assessors (data collectors, clinicians) do not know (are blinded to) participant tx assignment (or baseline status if uncontrolled trial)

• Double blind:
  - Participants as well as outcome assessors blinded
  - Problem: not feasible in most yoga studies

However, pts can be blinded to direction of study hypotheses, tx options made comparably attractive
Performance and Detection Bias

- **Performance Bias:** Groups may differ in care provided, or in exposure to factors other than the interventions of interest. *E.g.: Study of yoga and obesity*
  - Instructor gives (off protocol) dietary and exercise recommendations (or free coupons) to control group

- **Detection bias:** Systematic between group differences in assessment of outcomes. *E.g.,*
  - Unblinded therapist evaluates symptoms of pts receiving yoga differently from those receiving Prozac

Why blinding of outcome assessors (and monitoring of tx fidelity) is important!
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- Inadequate Blinding
- Performance bias
- Detection bias
- **Low power**
- **Confounding**
Sources of Error, cont.

- **Low power:** ↓ Ability to detect true differences
  
  *Esp. problematic in case of null results*
  
  *Low power can result from, e.g.:*
  - Small sample size
  - Poor retention
  - Smaller effects than anticipated - *e.g.:
    - Pts healthier than anticipated
    - Pts include those unlikely to benefit
    - Competing risk
    - Placebo effects
    - Poor compliance, unintended cross-over
    - Confounding, effect modification*
Confounding in Clinical Trials

• Confounding is an apparent effect of an intervention on an outcome that is caused by a third factor associated with both the outcome and intervention but not part of the causal pathway.

• E.g., Trial to test the effects of yoga vs. usual care on respiratory symptoms in adults with mild asthma.
Confounding In Clinical Trials

Trial to test the effects of yoga vs. usual care on respiratory symptoms in adults with mild asthma.

**Conclusion:**

Yoga leads to increased risk for respiratory symptoms. *Valid?*
Confounding In Clinical Trials

Trial to test the effects of yoga vs. usual care on respiratory symptoms in adults with mild asthma.

**Conclusion:**
Yoga leads to increased risk for respiratory symptoms. *Findings are confounded by smoky yoga class room*
Eligible Patients

Randomization/Tx allocation

Intervention group

Intervention

Follow-up

Outcomes

Sampling bias

Control group

Control

Follow-up

Outcomes

Selection bias

Performance bias

Unintended cross-over

Placebo/Nocebo effects

Differential/Poor Compliance

Differential/poor retention

Confounding

Detection bias; Low power

Pitfalls in Clinical Trials
Planning, evaluation, and conduct of clinical trials.

Always a good idea to remain alert, aware, and prepared.
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Potential Pitfalls, cont.

**Effect modification:** Effects of treatment vary according to a third variable (e.g., age, sex, BMI, symptoms, etc.). E.g.

- **Interpretive (insight) vs. supportive therapy**
  - 89 male and female adult psych pts randomized to 20 week insight or supportive therapy program
  - Measure depressive symptoms, anxiety, distress

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Women may respond differently to treatment than men

Findings: Women showed significantly larger gains with supportive than insight therapy; men improved significantly more with insight than supportive therapy. (Gender a significant modifying factor)
Pitfalls in Clinical Trials

Eligible Patients

Randomization

Selection bias

Intervention group

Intervention

Follow-up

Outcomes

Report

Sampling bias

Control group

Control

Follow-up

Outcomes

Performance bias

Unintended cross-over

Placebo/Nocebo effects

Differential/Poor Compliance

Differential/poor retention

Confounding, Effect modification

Detection bias; low power
Publication Bias: ↑ likelihood that certain trials will be published/appear in name journals, depending on:
- Direction of findings (Positive vs. negative, except CAM)
- Congruence of findings with mainstream thought/dogma (those which are vs. are not)
- Study size (Larger vs. smaller)

Funding bias: Bias in design, outcome, and reporting to favor goals of sponsor (e.g., industry, DOE): E.g.:
- Failure to report side effects
- Selective reporting of positive results
- Omission of negative findings
- Data fraud
Pitfalls in Clinical Trials

Eligible Patients

Randomization

Selection bias

Intervention group

Performance bias

Unintended cross-over

Placebo/Nocebo effects

Differential/Poor Compliance

Differential/poor retention

Sampling bias

Control group

Outcomes

Con founding, Effect modification

Detection bias; low power

Funding bias/Reporting bias

Report

Outcomes

Follow-up

Detection bias; low power

Publication bias

Follow-up

Control

Intervention

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Con founding, Effect modification

Detection bias; low power

Publication bias
What is a clinical trial?

• A planned experiment in humans
• Designed to test the effects of a specific intervention on pre-specified outcomes.
• Exposure (intervention) is manipulated (mode, timing, delivery, intensity, etc.);
• Eligibility criteria often restrictive
• All participants enrolled, treated, followed over same time period
• Outcomes monitored in same way, at same time points/ intervals
• Compare outcome(s) in experimental group to outcome in control group(s) upon completion (controlled trials)
Randomized Controlled Trial

**Baseline:** Assess outcome(s)

- Define and Screen Study Sample
  - Randomized
  - Non-participants

**Receive intervention**

- Yes
  - Loss to follow-up

- No (Control)
  - Randomized

**Follow-up:** Reassess Outcome(s)

- Improved
- Not Improved

**Time**
Relative merits of RCTs

**Advantages**
- Strong claims for causality
- Control of confounding, many biases
- Tight control on exposure/treatment
- High internal validity
- Possible to examine multiple outcomes
- Basis for & clinical practice and public health policy change

**Disadvantages**
- Time, cost, and resource intensive
- Logistically complex
- Limited by sometimes severe ethical constraints
- Pt recruitment, adherence, drop-out can be issues
- Generalizability may be limited
- Assessing long term outcomes can be problematic
- *Not appropriate for many research questions*
Blinding, *cont.*

**Single blind: Possible Cons**

*Participants but not investigators blinded*

- Investigators may provide additional advice/care/treatment (tx) to controls => ↓ ability to detect difference between groups
- Investigator/clinician may assess outcomes more favorably in patients receiving ‘active tx’ (subconsciously or consciously)

*Investigators but not participants blinded*

- Participants in experimental (exptl) group may have ↑ expectation of benefit => report/experience ↑ improvement, ↓ side effects, ↑ satisfaction with ‘active’ tx; opposite with ‘control’
- Pt compliance, retention may be better in ‘active’ tx

*Why important to blind participants to direction of study hypotheses and to blind outcome assessors!*
Potential Pitfalls, cont.: Placebo/Nocebo Effects

Placebo ("I will please") effect: Health improvement in response to perceived/expected benefit (e.g., of a sham intervention)/conditioning

- Can account for large % of tx effects
- Affects both physiological and psychological outcomes: E.g.:
  - **Motor function**: E.g.,
    - Placebo controlled trials of gene therapy, brain stimulation for Parkinson’s Disease
  - **Pain**: E.g.:
    - Study of >1000 pain pts¹: 35%, incl those w/ postop pain, experience relief w/placebo
    - Arthroscopy vs. sham surgery for OA

¹Beecher, 1955, *JAMA* 17: 1602-6
Potential Pitfalls: Placebo Effect, cont.

- Placebo effects on physiological and psychological outcomes: E.g.:
  - Mood, cognition, sleep: *E.g.*
    - Trials of SSRI’s vs. placebo for depression
    - Trials of valerian for insomnia
  - Blood pressure, heart rate: *E.g.*,
    - Can reduce DBP up to 9 mmHg, SBP up to 28 mmHg
  - Metabolic and immune function
    - Glucose tolerance, cholesterol
    - Allergic response, other immune response
  - Other
    - Edema, blood counts, electrolyte balance
    - GI symptoms, gastric acid, etc
Placebo Effect, cont

- **Influenced by multiple factors**
  - Shape, color, dosing, branding, delivery of ‘medication’
  - Behavior, expectations of provider
  - National and cultural factors: E.g.
    - Placebo resp low in Brazil, high in Germany
      B:7% vs. G: 59% vs. avg: 36% ulcer healing
  - Health condition: *E.g.*
    - Germans: High placebo response to ulcer meds, low placebo response to BP meds

- **Increased over past 10-12 years**
  - Effective ad campaigns by drug co.s?
    - Rise steadily following FDA OK of direct marketing to consumers in 1997
Nocebo Response: ‘Voodoo effect’

Health deterioration due to negative expectations/conditioning (“I will harm”) E.g.:

- **Side effects**: Occur in 20-30% of healthy adults; account for up to 90% of observed side effects
  - Prostate drug and sexual dysfunction
  - Chemo placebo => nausea, vomiting, etc
  - Sham current to scalp => 70% report headache
  - Edema, pain, diarrhea, palpitations, rashes

- **Allergic/immune response/Asthma sx**
  - Bronchoconstrictors vs. bronchodilators
  - Saline injections => allergic response
  - Harmless leaves => Rash, welts
Nocebo Effect

Nocebo Response: ‘Voodoo effect’

- ‘Placebo OD’
  - Sham Antidepressants => Hypotension
- ↑ Risk of death (AIDS, cancer, CVD, etc + healthy individuals)
  - Voodoo death
  - Effect of poor prognosis on cancer pt outcome
  - Framingham: Women who expect to die from MI: 4x ↑ risk

Why measurement of treatment expectancy, randomization, assessment of blinding important!

Potential Pitfalls, cont.

**Effect modification:** Effects of tx vary according to a third variable (e.g., age, sex, BMI, neuropsych sx)

E.g. Certain baseline characteristics

- Demographics, lifestyle factors, health status/hx, etc
- EX1: Neuropsychiatric sx in AD and Ginkgo biloba trial¹
  - Those w/out sx => no improvement in cognitive function
  - Those with sx => significant improvement
- EX2: Interpretive (insight) vs. supportive therapy²
  - 89 psych pts randomized to 20 wk insight or supportive ther
  - Measure depressive sx, anxiety, distress

Learning Objectives

• To understand:
  ▪ Major pitfalls and threats to validity in clinical trials
  ▪ Key issues in conducting and interpreting systematic reviews, including meta-analyses
  ▪ Major applications of systematic reviews
Evaluating Research Findings:  
Is the Effect Real?  
Is the Effect Meaningful?

• Examine the methods for statistical procedures, results for statistical significance and clinical meaning

• Examine the methods and analysis for possible sources of error (e.g., bias, confounding)

• Consider other potential explanatory factors
Evaluating Results: Statistical (and Clinical) Significance

• Possible to have changes that are statistically significant but not clinically meaningful.
  ▪ Especially a problem in large studies
  ▪ E.g., a drop in systolic blood pressure of 1 mmHg in a large trial of gentle exercise and prehypertension (N=300; p<0.001)

• Possible to have changes that are clinically meaningful but not statistically significant
  ▪ Especially an issue in small studies
  ▪ E.g., a drop in systolic blood pressure of 20 mmHg in a small study of yoga and restless legs syndrome (N=20, p=0.08)

• Important to examine the findings in the context of both statistical significance and clinical meaning
Sources of Error in Clinical Trials

- Sampling/Selection bias
- Low power
- High or differential drop-out (attrition bias)
- Poor or differential compliance
- Unintended cross-over
- Placebo/Nocebo effects
- Performance bias
- Detection/Ascertainment bias
- Funding/reporting bias
- Publication bias
- Confounding
- Effect Modification
Sources of Error: Selection Bias

Selection Bias

- Systematic differences between groups at baseline and/or preferential enrollment of specific participants into one tx group

  - **Due to:**
    - Chance (esp smaller studies)
    - **Treatment allocation not concealed**
      - Effects of teasing on aggression
      - Obesity intervention trial
      - Likely responders vs non-responders
    - Non-random assignment

  - **Can confound/bias study results**
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- Effect Modification
Is sample size adequate?

• Potential problems with small sample sizes:
  - Reduced *power* (ability to reliably detect true differences over time or between groups) ->
    - Can lead to non-significant results even with an apparently large effect!
  - Less representative; Generalizability of findings reduced
  - Lead to more tentative conclusions

Is sample size based on power analysis?
Sources of Error, cont.

- **Low power:** ↓ Ability to detect true differences
  - *E.g., due to:* Small sample size
    - Smaller effects than anticipated- *e.g.:
      - Pts healthier than anticipated
      - Pts include those unlikely to benefit
      - Competing risk
  - Esp. problematic in case of null results

- **High Drop-out, Differential drop-out:** (Attrition bias)
  - *E.g.,* Yoga vs. exercise for hypertension=>
    - High, differential attrition
  
  *Can ↓ power, compromise validity*
Conducting and Evaluating Clinical Trials: Recap

**METHODS:**

*Ethical and data quality issues?*
- **Study design?** Strength? Appropriate?
- **Study population**
  - Well-defined and appropriate? Clear eligibility criteria?
  - Recruitment procedures? Representative?
- **Sample size adequate?**
- **If controlled, were participants randomized?** If so,
  - Procedures appropriate? Effective (no baseline differences)?
  - Treatment allocation concealed?
- **Blinding?**
  - Outcome assessors/investigators?
  - Participants (treatment and/or study Ho)?
  - Matching issues addressed? Blinding successful?
Issues to consider, cont.

METHODS, cont.

- **Intervention and comparison conditions?**
  - Clearly described, including duration, frequency, intensity, etc?
  - Appropriate, well thought out?
  - Delivery uniform?
  - Comparison condition appropriate?

- **Outcomes of interest?**
  - Appropriate and well-defined (including assessment procedures)?

- **Participant retention and compliance**
  - Reported? Adequate?
  - Different between groups?
Issues to Consider, cont.

ANALYSIS/RESULTS, DISCUSSION, CONCLUSIONS

- **Power/Statistical analysis/Significance**
  - Statistical procedures appropriate? Between group comparisons? ITT analyses?
  - Findings statistically significant? Clinically meaningful?

- **Limitations/Threats to Validity? Other factors that may influence outcomes?**
  - Sampling/selection bias, low power?
  - Evidence of bias or confounding?
  - Poor/differential retention or compliance; cross-over?
  - Detection/performance bias?
  - Publication/funding/reporting bias?
  - Confounding or effect modification?

- **Conclusions justified & limitations addressed?**
Define and screen study population

Eligible and willing (N= )

Ineligible/decline participation (N= )

Randomization described and appropriate?

Tx allocation concealed?

Participants randomized?

Intervention/control well-described, appropriate?

Sample size adequate?

Study design? (e.g., RCT)

Study population well-defined, representative? Selection bias?

Assess Outcome(s)

Drop-out

Attrition and compliance Reported? High/differential?

Intervention

Control

Statistical analysis well-described, appropriate?

Blinding of participants, evaluators?

Outcomes well-defined, appropriate?

Statistical analysis

Sources of error? (bias, confounding, other?)

Conclusions justified?

Presentation, Discussion of Findings

Publication/Funding/Reporting bias?

Findings: significant?
Conducting and Evaluating Clinical Trials: Recap

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Ethical and data quality issues?

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- Conclusions justified & limitations addressed?
Confounding in Clinical Trials

- **Confounding** is an apparent effect of an intervention on an outcome and that is caused by a third factor not taken into consideration (and not part of causal pathway).
- *E.g.*, Trial to test the effects of yoga vs. usual care on respiratory symptoms in adults with mild asthma.

**Conclusion:**
Yoga leads to increased risk for respiratory symptoms. *Valid?*
Selection bias. Non-random assignment

Treatment allocation by:

School

Participant Preference

Yoga

Stretching

Strength training

Usual care

#1

#2
Failure to Conceal Group Allocation, *cont*

**Effects of Teasing on Aggression:** Potential motivation for tampering with group assignment
Sources of Error, *cont.*

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- E.g., Yoga vs. conventional exercise for hypertension=>
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*Can ↓ power, compromise validity*

=> *Important to monitor compliance and retention carefully, devise strategies encourage retention and adherence!*
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What is a clinical trial?