Lecture 6
RCTs for Nonpharmaceutical Settings

In 2000, RCTs of nonpharmacologic therapies accounted for 1 in 4 RCT publications.

- *Your examples?*

Example of nonpharmaceutical interventions (Lecture 5):

Goal: Reduce 7-day mortality rate among sepsis patients in resource-poor settings

Hypothesis: Monitoring and charting of vital signs by family/friend will occur more frequently and thus decrease patient's 7-day mortality rate

Interventions:

- *Arm C*: "Vitals" monitoring is handled only by (busy) nursing staff, when available (NSI)
  - *A fair amount of missing data is expected*
- *Arm E+C*: Supplemental monitoring is handled by trained family/friend (FFI)
  - *Fairly complete data is expected but subject to inaccuracy*

Outcomes:

- Intermediate:
  - Variables that capture (i)Completeness and (ii)Accuracy of the interventions
  - In this trial, patient's role is passive; adherence is a nonissue.
- Ultimate (primary): Death within 7 days of randomization

Intervention features:

- Cannot *blind* interventionists or patients to study arm; Difficult to standardize interventions among *care providers*; Below the surface, *intervention looks more complex*

    - *Arm C*: Same NSI across patients throughout study period; may behave competitively and inconsistently over study period; care provider effect may occur
        - Training of NSI to achieve study goals is required
        - Monitoring and retraining may be needed
        - Some NSIs may dropout and new NSIs may join during the study period
        - Can a patient-level measure of NSI adherence be devised and implemented?

    - *Arm E+C*: Different FFI per patient; Intensity of intervention can vary among interventionists
        - Training of FFI to achieve study goals is required
        - New FFI will join throughout the study period
        - Can a measure of FFI adherence be devised and implemented?

    - Potential crossover between arms in both directions

    - Analysis can account for clustering of outcomes within NSI (there will be multiple patients per NSI) but not FFI (there will be one patient per FFI; FFI+patient comprise an experimental unit)

- **Q:** Does this intervention reduce staff workload, or simply shift workload from clinic staff to research staff?
    - Requires research personnel time to train NSI and FFI throughout the study period
    - [Aside: A longer follow-up period (than 7 days) also would require monitoring of interventionists and booster sessions]

Outcome feature:

- FFI potentially generates value at the population level in addition to study level: More educated population. Will this create better *Arm E* outcomes, and larger treatment effect, later in the trial?

Q: How do RCTs of nonpharmacologic therapies differ from RCTs for pharmacologic therapies?

A: CONSORT[†] guidance [see REF] highlights contrasts between Ph and NonPh RCTs, with emphasis on three *intervention features:*

1. Blinding is more difficult to achieve. When feasible, relies on complex methods and specific design
   - Intervention delivery: Neither Participants nor Providers of interventions can be blinded
   - Outcome collection: Assessors can possibly be blinded. (e.g., different clinicians deliver and assess)
     → May affect internal validity (Lecture 1)

2. Interventions are complex and involve several components →
   - difficult to standardize, administer consistently to all patients (experimental units),
   - difficult to describe,
   - difficult to reproduce.

3. Care providers' expertise and centers' volume of care affect outcomes → are potential confounders of the treatment effect estimate

→ All of these variations could have important impacts on the <u>estimate</u> of the treatment effect.

[†] CONSORT – Consolidated Standards of Reporting Trials

Review of CONSORT / Nonpharmaceutical, Table 1 ideas ... within these three topics

A. *Blinding: Interventionists, Patients*

Section	*Item*	*Standard*	*Extension*
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the experimental treatment, comparator, care providers, centers, and *blinding status*
Methods			
Blinding (masking)	11A		Whether or not *those administering co-interventions* were blinded to group assignment
	11B		If blinded, *method of blinding* and *description of the similarity of interventions*
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	In addition, take into account the choice of comparator, *partial lack of blinding*, and unequal expertise of care providers or centers in each group.

Tracing through the study write-up, blinding should be presented . . .

- in Methods of abstract and manuscript
    - Need to address those often blinded: participants and interventionists.
- in Discussion of manuscript, addressing potential bias raised and its effect on interpretation of results.

During conduct of the trial, study arms might be revealed to participants for the first time in the Consent document.

Q: How specific must this info be?

A: Setting dependent.

B. *Experimental and Comparator Interventions*

Section	*Item*	*Standard*	*Extension*
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the *experimental treatment, comparator*, care providers, centers, and blinding status
Methods			
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	*Precise details* of both the experimental treatment and comparator
	4A		Description of the *different components* of the interventions and, when applicable, descriptions of the *procedure for tailoring the interventions to individual participants*
	4B		Details of how the interventions were *standardized*
Results			
Implementation of intervention	NEW		Details of the experimental treatment and comparator as they were *implemented*
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	In addition, take into account the *choice of comparator*, lack of partial blinding, and unequal expertise of care providers or centers in each group.
Generalizability	21	Generalizability (external validity) of the trial findings	Generalizability (external validity) of the trial findings according to the *intervention, comparators*, patients, and care providers and centers involved in the trial

Tracing through the study write-up, study arms …

- Intervention arms are fleshed out with as much detail as is needed to ensure trial could be replicated
    - Methods deals with planned arms
    - Results deals with achieved arms
        - Did crossover occur? Did protocol violations occur?
        - If intervention training was required, how complete was attendance / follow-through?

C. *Care Providers & Centers*

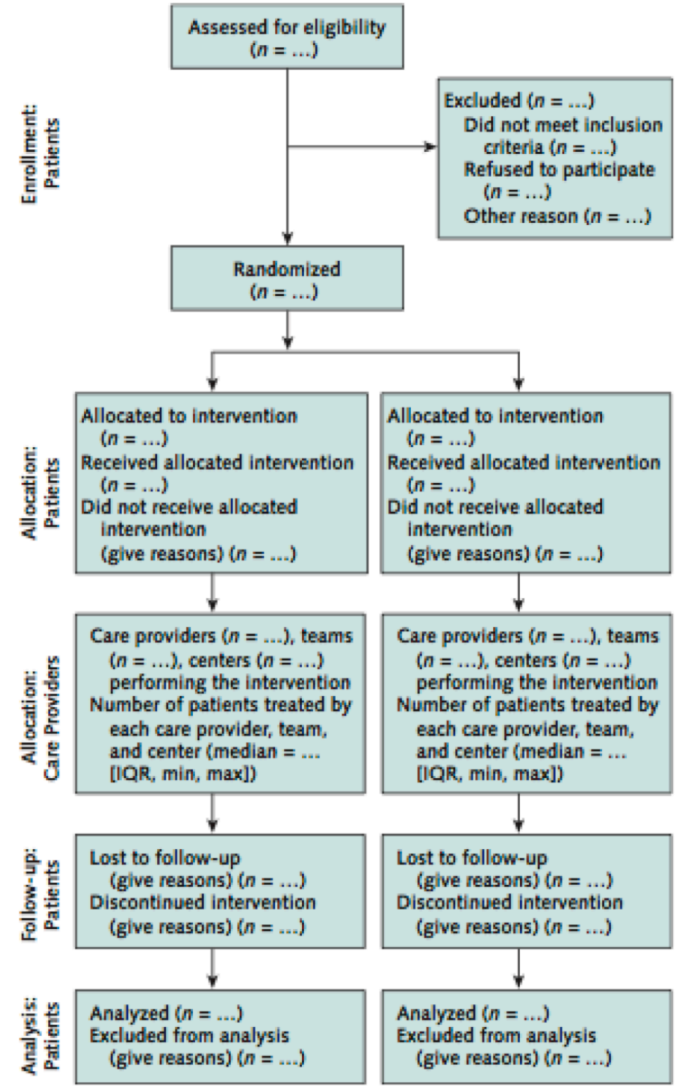
Section	*Item*	*Standard*	*Extension*
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the experimental treatment, comparator, *care providers, centers*, and blinding status
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	When applicable, *eligibility* criteria for centers and those performing the interventions
	4C		Details of how *adherence* of care providers with the protocol was assessed or enhanced
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	When applicable, details of whether and how the *clustering* by care providers or centers was addressed
Randomization / sequence generation	8	Method used to generate the random allocation sequence, including When applicable, how care providers were allocated to each sequence generation details of any restriction (e.g., blocking, stratification) trial group	When applicable, how care providers were *allocated* to each group
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	When applicable, details of whether and how the *clustering* by care providers or centers was addressed
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended) — specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe protocol deviations from study as planned, together with reasons	The *number* of care providers or centers performing the intervention in each group *and the number* of patients treated by each care provider or in each center.
Baseline data	15	Baseline demographic and clinical characteristics of each group	When applicable, a *description* of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group

Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	In addition, take into account the choice of comparator, lack of partial blinding, and *unequal expertise* of care providers or centers in each group.
Generalizability	21	Generalizability (external validity) of the trial findings	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial

Tracing through the study write-up, study arms …

- Methods:
  - This aspect of the trial receives a great deal of attention in the NP version of the CONSORT guidance
  - Item 3: Recruit (*care providers* and) *centers* consciously, aware of trade-offs in expertise:
    - to achieve generalizability (heterogeneous) or
    - to know if intervention works (homogeneous) or
    - to complete the trial as quickly as possible ?
  - Item 4C: What provider errors and missing data can be anticipated and avoided via strong protocol, procedures, and training? Pilot study could be helpful. [See Ref]
  - Items 7, 8, & 12 → *I highly recommend that PIs collaborate with faculty statisticians on these issues*
    - The sample-size calculation and analysis must reflect the design.
    - Do interventionists deliver both arms (treat as a random effect in the analysis) or only one (treat as a fixed effect)? Sometimes no choice (e.g., surgical expertise dictates).
- Results:
  - Item 13: From example:
    - Both arms: Multiple patients per NSI
    - Arm E: One patient with multiple FFIs? → How successful was this intervention scheme?
  - Item 15: In parallel to typical baseline comparison of arms by participant characteristics ("Table 1" from homework), it may be helpful to provide comparison of arms by intervention(ist) characteristics
- Discussion:
  - Item 20: What are consequences of unequal intervention delivery for interpretation of "treatment effect"?

Figure 1. Modified CONSORT flow diagram for individual randomized, controlled trials of nonpharmacologic treatment.



An extra box per intervention group relating to care providers has been added. For cluster randomized, controlled trials, authors should refer to the appropriate extension. IQR = interquartile range; max = maximum; min = minimum.

← Note addition of boxes that quantify
- number of care providers per arm, and
- number of participants per care provider

← Note that CONSORT has also published guidelines for cluster-randomized trials

Return to example

- Every patient will require monitoring of vital signs at least once a day
    - If the vital signs signal clinically relevant decline, the interventionist (NSI or FFI) should ensure that the patient receives the needed care.

Cross-sectional view:

- Both arms are exposed to the NSI interventionists (nursing staff).
- Arm E patients are also exposed to FFI interventionists (family/friend).

Longitudinal view:

- If there are multiple NSI in the clinic, each patient will most likely be exposed to every NSI on multiple occasions: This would average out the NSI effect across arms and patients.
- If there are few (e.g., 2) NSI in the clinic, design steps might be needed to avoid having one NSI monitor Arm-C patients only and the other monitor Arm-E patients only.

- Arm E patients may be exposed to multiple FFI interventionists. This information should be captured and reported.

More generally

Centers

It's well known that expertise varies by center, and this may affect outcomes.

In multi-site RCTs (including pharmaceutical),

- we typically conduct stratified randomization within center
- we conduct a stratified analysis: this compares E to C within strata and then averages the treatment effect across strata

In cluster-randomized trials (e.g., school is a cluster), there could be contamination of the intervention effects if both arms were present in the same school: this might wash out any treatment effect. If there are few schools to allocate, paired-cluster designs might be used to match them as well as possible. (From Lecture 1, this is an example of a stratified blocked design with blocks of size 2.)

Care providers

The intervention exposure can be affected by the expertise of the care provider. If feasible, we would like to have each care provider influence both arms, so that this effect can be adjusted away.

In some settings, it's not feasible to have every care provider influence both arms.

- Due to different levels of expertise to provide arm-specific interventions
- Due to importance of "blinding" (i.e., avoiding contamination of the intervention effects)

Often clustered responses within care provider are handled by random effects in hierarchical models.

These influences may also be handled via "instrumental variables."

Summary

Center and *Care provider* influences are potential confounders that should be anticipated and handled via appropriate design considerations. Design choices will affect the analysis plan. *Collaborating with a statistician is high recommended to avoid an unworkable plan.*

Reference for today's lecture

Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P; CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med. 2008 Feb 19;148(4):295-309.

Suggested Reading

Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011 May;45(5):626-9.