ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

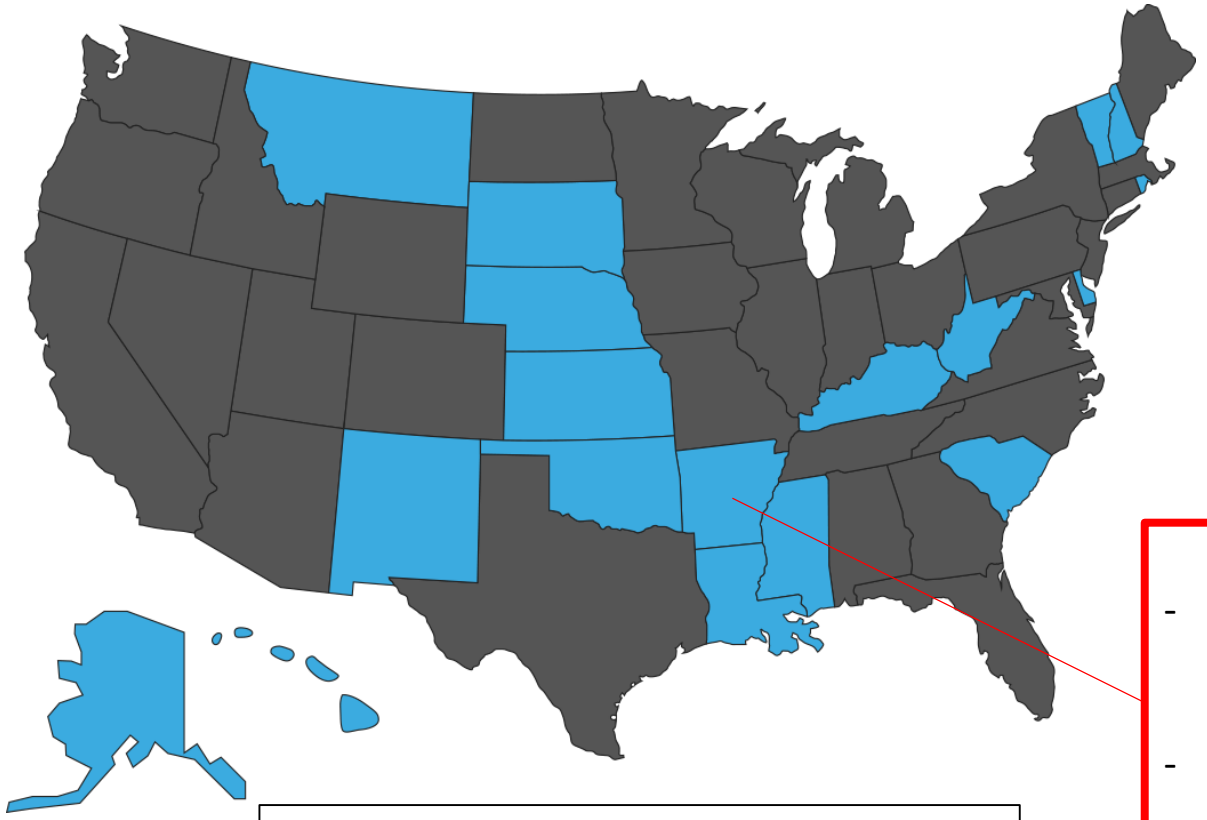
IDeA States Pediatric Clinical Trials Network

Junior Investigator Pilot Workshop

IDeA States Pediatric Clinical Trials Network

- To provide medically underserved and rural populations with access to state-of-the-art clinical trials
- To build pediatric research capacity at a national level
  - support professional development of faculty-level pediatricians to conduct clinical trials
  - support infrastructure and teams in the conduct of clinical trials research

ISPCTN Composition



Blue states = 18 ECHO ISPCTN Awardee sites that perform the multisite clinical trials and join the DCOC and NIH to form the Steering Committee for the Network

UAMS DCOC

- Coordinate design, implementation, data management, and analysis of multisite clinical trials
- Coordinate Network programmatic functions
- Lead multisite professional development

Pilot Project Duration

- Duration: 3 years to complete the following activities:
  - 1st year study development and approvals.
  - – Protocol development
  - – Review by PRC and DSMB
  - 2-year study conduct:
  - – Implementation (enrollment and follow-up)
  - – Project closeout

Application format for Initial Concept Proposal

- Description of full-scale trial, excluding references (1 page maximum)
- Description of pilot study, excluding references (2 pages maximum)

- APPLICATIONS THAT DO NOT ADHERE TO THESE PAGE LIMITS WILL NOT BE REVIEWED.

Budget

- Year 1 (October 1, 2021 – August 31, 2022):
  - Up to 30% FTE salary support for PI(s) and no less than 15% FTE for a single PI (Maximum of 2 MPIs)
- Years 2-3: Maximum of $300,000 direct costs across entire period, NOT per year (September 1, 2022 – August 31, 2024)
  - Salary support for junior investigator effort per year; no more than 1 PI per awardee institution and maximum of 2 MPIs at 2 institutions (minimum: 15% for each MPI or maximum 30% for one PI)
  - May not include salary support for senior faculty development person
  - Does not include DCOC activities (summarized on the next slide)

Timeline for Initial Concept Submission

Expect that not all initial concept proposals will be selected for further development

December 2020

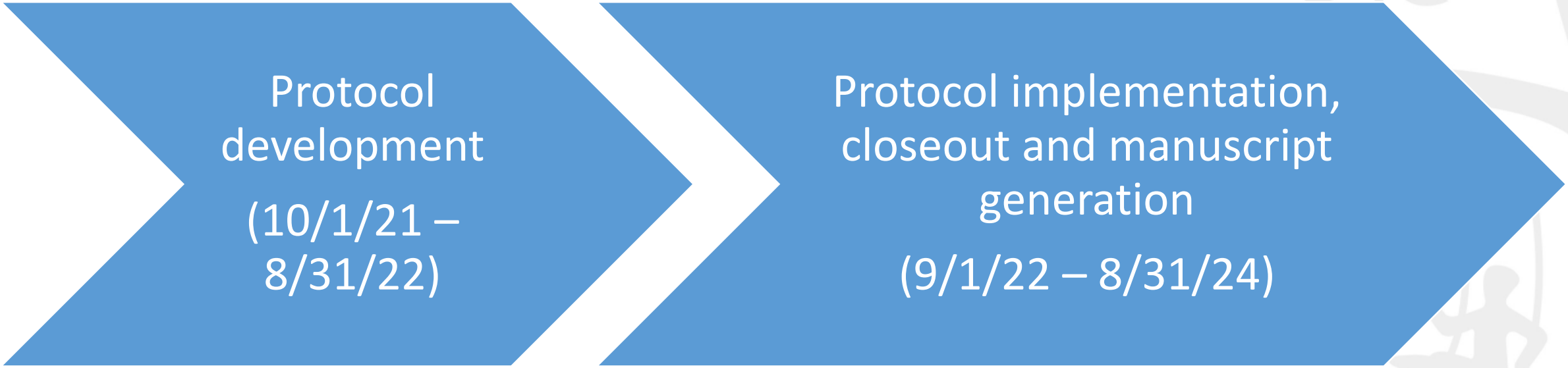
Jan-Feb 2021

April 2021

September 2021

Note: review criteria for initial and expanded concept proposals are under development

Protocol development and implementation timeline (for expanded concepts selected for full development)



Pilot resources

- Small-scale test of methods & procedures to be used on the larger scale
  - Feasibility concerns, refining procedures, etc
  - May also give some information about effect size or side effects, but not always powered for this
  - Not “does this work” but rather “**Can I do this**?”
- Resources
  - Pilot Studies: Common Uses and Misuses | NCCIH (nih.gov)
  - Recommendations for Planning Pilot Studies in Clinical and Translational Research (osu.edu)
  - A Guide on Organizing a Multicenter Clinical Trial: The WRIST Study Group
  - Consort - Pilot and Feasibility Trials (consort-statement.org)
  - Guidance for conducting feasibility and pilot studies for implementation trials | Pilot and Feasibility Studies | Full Text (biomedcentral.com)
  - A tutorial on pilot studies: the what, why and how | BMC Medical Research Methodology | Full Text (biomedcentral.com)

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WRITING IN RESPONSE TO A REQUEST FOR APPLICATION (RFA)

Janice E. Sullivan, MD
Professor & VCR
Department of Pediatrics
University of Louisville
Louisville, KY

February 18, 2021

Purpose

- **Identify an effective approach to responding to an RFA**

Where to begin?

- **Systematic approach**
  - Identify the specific RFA
    - Jr faculty proposal
  - Identify your grant team
    - Expertise
    - Mentorship
    - Collaboration
    - Thought leaders
  - Start early-want time to be on your side
  - WRITE!

Step 1

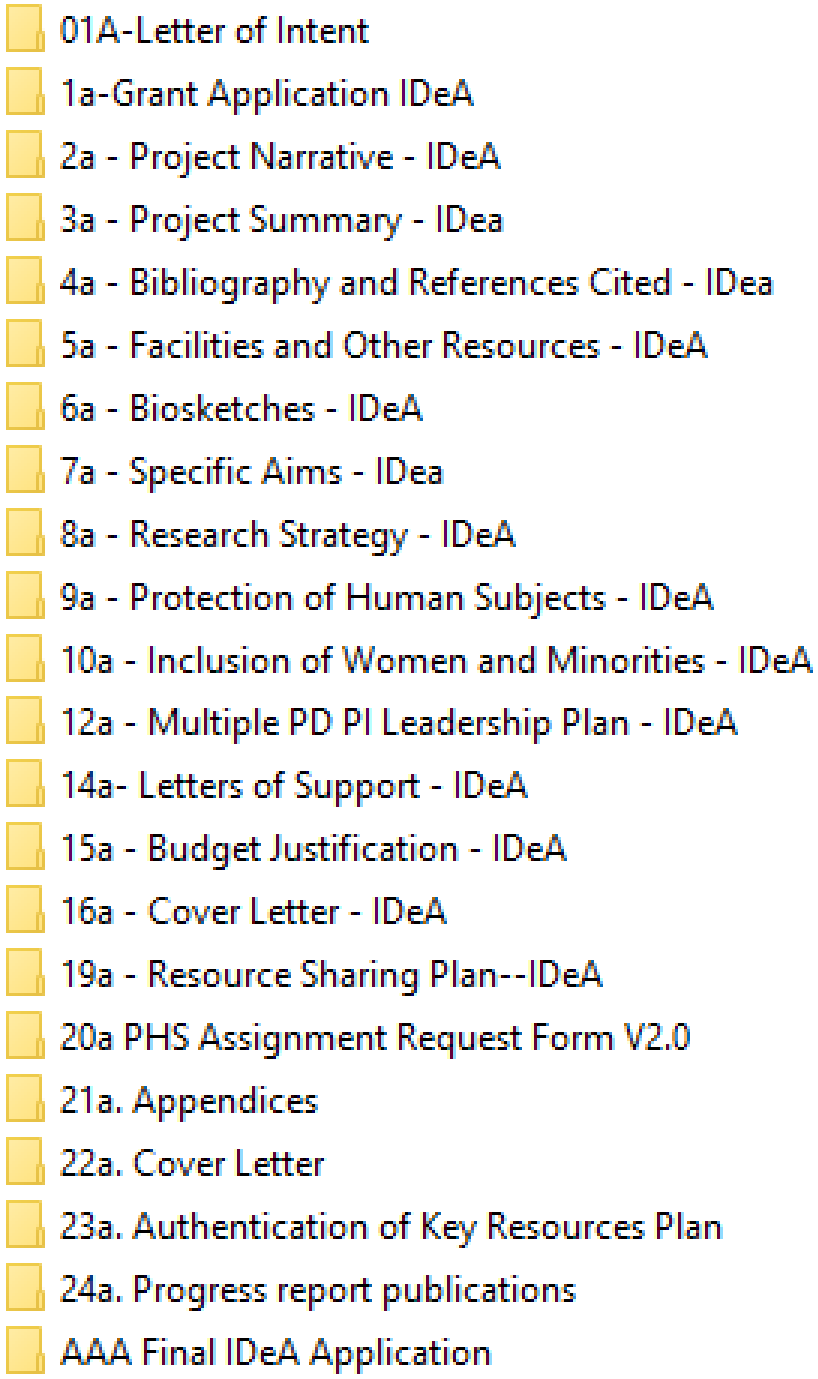
- **Read the RFA**
  - What am I looking for?
    - Overview of:
      - Specific Aims of RFA
      - Expectations for submission
        - Including page limits, font, margins, etc.
      - Timelines
        - Grant application
        - Project timelines if funded
  - Does this RFA fit with my goals?

Step 2

- **Establish a Timeline**
  - Work backwards—Due DATES:
    - Funding agency
    - University Grants office
    - Final internal review (before grants office)
    - Different components (internal)
    - Letter of Intent
  - Schedule yourself to WRITE!
    - Block time on your calendar
    - Delegate tasks to others
    - Writing is how you communicate to your reviewers!
      - Use active voice

Step 3

- **Create component folders**



•Create a table or checklist

Step 4

M-PI's UG1 submission	Specific Guidance/Due Dates	Status	Writer	Comments
Letter of Intent (Page 10)	**DUE xx/xx/xx**	Done xx/xx/xx	JES/SEW/LAD	
eraCommons #'s				
Attachment	**Page Limit, if specified**			
Project Narrative	No more than 3 sentences	Done xx/xx/xx	JES/SEW/LAD	
Project Summary/Abstract	No more than 30 lines of text	Done xx/xx/xx	JES/SEW/LAD	
Bibliography/References			JES/SEW/LAD	
Facilities and Other Resources		To SEW-LPD xx/xx/xx	JES	
Equipment		Done xx/xx/xx	JES	
Biosketches	See Tab 2	Done xx/xx/xx	JES	
Specific Aims	1 page	Draft Done xx/xx/xx; FINAL xx/xx/xx	JES/SEW/LAD	Sent to leadership team xx/xx/xx
Research Strategy	12 pages		JES/SEW/LAD	SS1:ALL; SS2 SEW; SS3 JES; SS4 LAD; SS5 PND
Protection of Human Subjects		Done xx/xx/xx	SEW	
Inclusion of Women and Minorities		Done xx/xx/xx	SEW	
Inclusion of Children		Done xx/xx/xx	SEW	
Multiple PI Leadership Plan		Done xx/xx/xx	JES	
Letters of Support	See Tab 3		SEW/JES/KBB	
Budget		Done xx/xx/xx	KMB/JES	Sent request to KMB to work on draft xx/xx/xx
Budget Justification		Done xx/xx/xx	JES	
Resource Sharing Plan		Done xx/xx/xx	JES	
Cover Letter (PHS Assignment Request Form V2.0)		Done xx/xx/xx	JES/SEW/LAD	
Authentication of Key Resources Plan:	1 page	Done xx/xx/xx		
Optional:				
Appendixces				
Timelines				
Meeting with Grants Office	**xx/xx/xx**	Done xx/xx/xx		
Internal deadline (To Grants Office)	**xx/xx/xx**			
External deadline	**xx/xx/xx**			

Step 5

- **Grant Team meeting**
  - Discuss RFA and proposed submission
    - Provide RFA overview
    - Ideas for your response—Refine
    - Optimize the science
  - Timelines
  - Division of responsibilities (delegate)
    - Writing
    - Specific components
    - If grant funded, what will roles be?
  - Communication plan

Step 6

- **Write Specific Aims**
  - Start with this section
  - Be sure you are responding to the Specific Aims of the RFA
    - Well-vetted ideas (compelling, novel, etc.)
  - Share draft with grant team; use constructive feedback
  - Revise and share again
  - When have vetted Final Draft, move to Research Plan
  - Stay on target with timeline
  - Remember, this is you communicating to your reviewers!
    - **Tell your story!**

Step 7

- **Write Research Plan**
  - Follow the specific guidance in the RFA
    - Be sure your proposal meets the proposed timelines if funded
    - **Set the stage!**
  - Use your Specific Aims as your guide
    - Write your approach to address each of your Specific Aims
  - Review the criteria for review of your application
    - Make sure you have addressed these in your proposal
      - Significance, Investigators, Innovation, Approach, Environment
      - ECHO ISPCTN: has specific criteria for review
  - Share your draft with grant team; utilize feedback
  - Revise and share with grant team

Step 8

- **Once your Research Plan is complete:**
  - Finalize your Specific Aims
  - Write Project Narrative
  - Write Project Summary/Abstract
  - Finalize Bibliography/references

Step 9

- **Simultaneous to writing your Research Plan, delegate the following:**
  - Budget
    - Include only what is allowed
    - Be sure to use the appropriate indirect rate for your institution
  - Budget justification
    - Provide justification for personnel (include their role) and other expenses included in the proposal
      - Specify percent effort or calendar months for personnel

Step 10

- **Simultaneous to writing your Research Plan, delegate the following:**
  - Facilities and Resources/Equipment
    - Provide only what is asked for
    - Provide information showing you can support your proposal if funded
  - Letters of support
    - Obtain those from persons identified in RFA and others you think are essential
    - Write letters for them
  - Resource sharing plan: make sure it fits with expected dissemination of results per funding agency

Step 10

- **Simultaneous to writing your Research Plan, delegate the following:**
  - Biosketches
    - Follow the NIH instructions for biosketches
      - Make sure each person has their specified role on the project in their initial paragraph of the biosketch (good to have that be the opening sentence)
      - Include their expertise and why it is essential to this proposal
      - Science paragraphs—only 4 publications allowed for each one
    - Use the current form

Step 11

- **Once all sections are complete:**
  - Spellcheck
  - Share with grant team for their final review
  - Submit
    - Try to do at least 1 day before the deadline

Step 12

- **Relax & Wait**

RECAP

- **RFA Jr Investigators ISPCTN**
  - **Objective of RFA**
    - The ***purpose*** of this funding opportunity is to support pilot studies whose results are critical to the design and/or implementation of a full-scale multicenter clinical trial.

RECAP

- **RFA Jr Investigators ISPCTN**
  - **Timelines**
    - 3 page concept proposal
    - Expanded concept proposal
  - **Funding Information**
  - **Applicant Eligibility**
  - **Application Format (both attached)**
    - Initial concept proposal template
    - Expanded concept proposal template

RECAP

- **RFA Jr Investigators ISPCTN**
  - **Evaluation of applications**
    - …will also consider the ***potential public health impact and overall design*** of the full-scale multicenter clinical trial that would follow the pilot project.
    - the application should provide a ***concise description of the larger, full-scale clinical trial***, and an ***explanation of how the results of the pilot study*** proposed by the junior faculty member ***will be used to facilitate the development of the full-scale clinical trial***.
    - Both the pilot study and planned full-scale trial ***should address topics within the mission and scope*** of ISPCTN.
  - The Steering Committee will evaluate the expanded concept proposals using the **review criteria for expanded protocol concepts.**

RECAP

- **RFA Jr Investigators ISPCTN**
  - Reviewers will score each of the four areas based on the information provided in the *concept proposal*
    - Clinical or public health impact
    - Relatedness to ECHO ISPCTN
    - Scientific merit
    - Feasibility
    - Impact scale:
      - 1-5 with 1=exceptional, 2=excellent, 3=good, 4=fair, and 5=low

RECAP

- **RFA Jr Investigators ISPCTN**
  - Reviewers will score each of the four areas based on the information provided in the *expanded concept proposal*
    - Clinical or public health impact and significance
    - Relatedness to ECHO ISPCTN
    - Scientific merit including approach and protection of human subjects
    - Feasibility (not scored but considered)
    - Impact scale:
      - 1-9 with 1=exceptional, 2=outstanding, 3=excellent, 4=very good, 5=good, 6=satisfactory, 7=fair, 8=marginal, and 9=poor

Wishing you success!

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Generating Research Questions: Finding Your “Big Win” Sweet Spot

Jessica Snowden MD

Conflicts

- I have no relevant conflicts of interest.

What makes a good question?

SMART, FINER

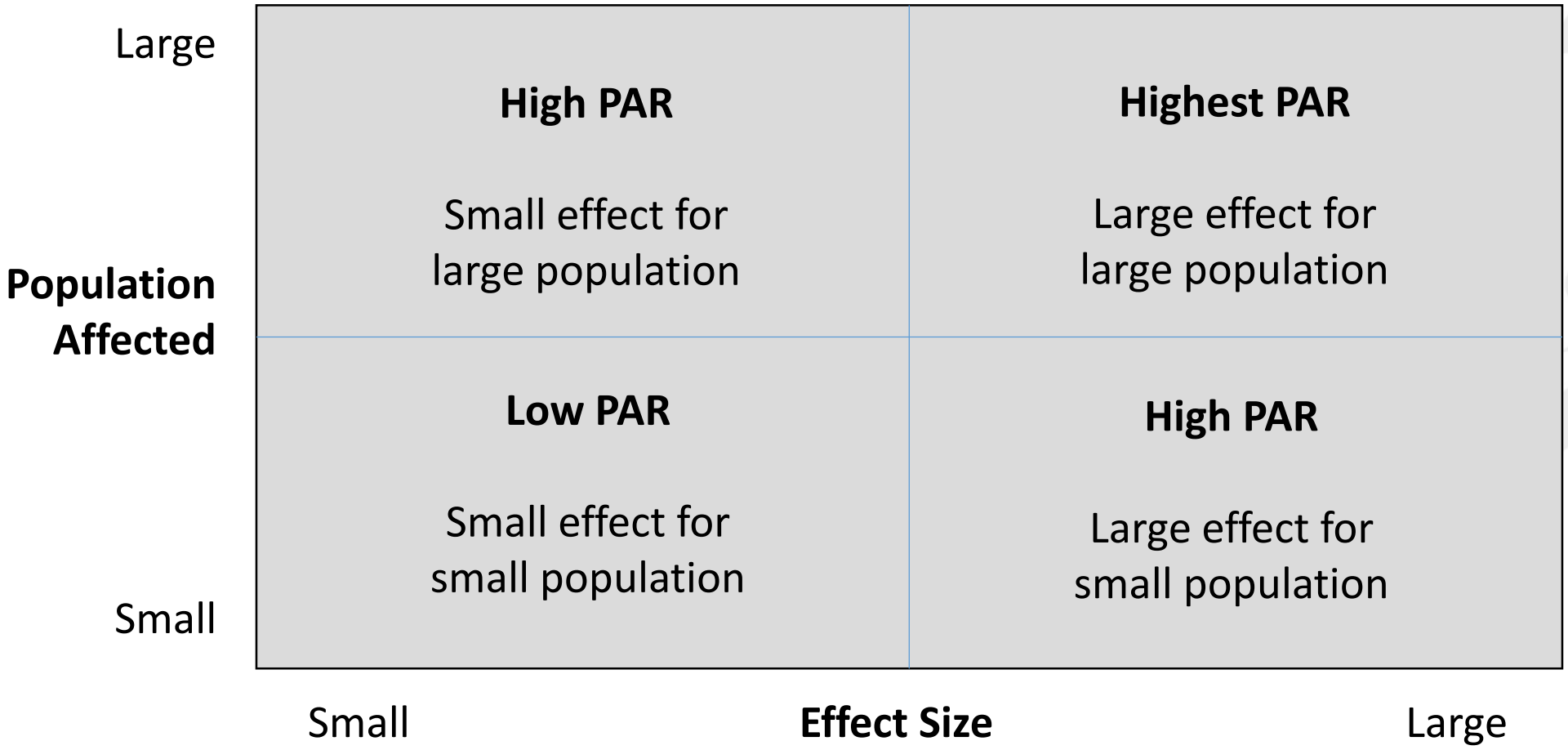
- Specific (simple to understand)
- Measurable (able to assess pertinent variables and outcomes)
- Achievable (within a reasonable timeframe)
- Relevant (adds to existing knowledge)
- Timely (provides relevant answers within a specified period)

Criteria for a Good Research Question: *FINER*

***F* EASIBLE**
Adequate number of subjects
Adequate technical expertise
Affordable in time and money
Manageable in scope
***I* NTERESTING**
To the investigator
***N* OVEL**
Confirms or refutes previous findings
Extends previous findings
Provides new findings
***E* THICAL**
***R* ELEVANT**
To scientific knowledge
To clinical and health policy
To future research directions

Adapted from REF [13].

You want your question to matter!



PAR = Population Attributabl

Steps	Questions
1 Research question	1 What topic (idea) of study are you interested in?
	2 What has already been done in this area? The literature.
	3 What major outcome(s) (dependent variable) you are interested in?
	4 What intervention (independent variable) are you interested in?
	5 Are you looking for differences or a relationship (association)?
	6 To what group (population) do you wish to apply your results?
	7 What is your specific research question?
	8 What answer do you expect to find to your question? The research hypotheses.
	9 Why is this question important today? Relevance.
2 Instrumentation	10 Will you use an existing instrument, modify one, or develop a new one?
	11 What are the psychometric qualities of the scores?
3 Research design	12 Do you want to intervene or simply observe?
	13 Do you need a control group?
	14 How will you control for confounding variables?
	15 What is the 'best' research design to answer your question?
4 Statistics	16 Which statistical method is optimal?
5 Sample	17 What are your criteria for inclusion and exclusion of subjects?
	18 How are you going to obtain your subjects?
	19 If an experiment, how will you assign the subjects?
	20 How many subjects do you need? Power.
6 Data collection and quality	21 How are you going to collect data and monitor the quality?
7 Timetable and budget	22 What is the timetable? Schedule.
	23 Who will be doing what? Personnel.
	24 What equipment and materials will you need?
	25 How much will it cost? Budget.
8 Protocol and grant proposal	26 How will you keep track of the study? Research protocol.
	27 What is the granting agency interested in funding? Grant proposal.
	28 What forms and application process will you follow?

Experimental study design and grant writing in eight steps and 28 questions; G Bordage & B Dawson

Literature Review

- **Why is the problem important?**
  - **What are the applications for your solution?**
  - **Who are the key stakeholders interested in the problem?**
- **What is currently known about the problem?**
- **What are the gaps in knowledge?**
  - **Questions raised in other papers**
  - **Approaches used in other studies and how yours is different**
- **What more do you need to know about the disease/problem/process to define your question?**

- A good mentor (and librarian!) can help you design your literature review.

Why do you need to spend so much time on a literature review?

- Justify your question (Be sure it hasn't already been answered!)
- Refine your question
- Demonstrate your knowledge of the field
  - Analyze, but be careful how you criticize
  - Primary sources

- Be sure you summarize all of this in your proposal!
  - Dinner party analogy
    - Role of the Literature Review - Library Guide to Capstone Literature Reviews - Academic Guides at Walden University

Refine your question

- What exactly do you want to know?
  - Base this on your original question and the gaps you've identified in the literature
- Things to consider
  - What are the risk factors in your area of interest? Are they modifiable?
  - What interventions do we use to treat this condition?
  - What factors affect how the intervention works?
  - How many people are affected by the condition? How many people would it take to answer your question (sample size)?
  - Is the answer useful whether your hypothesis is correct or not?

The answer to your question should matter – no matter what the answer is

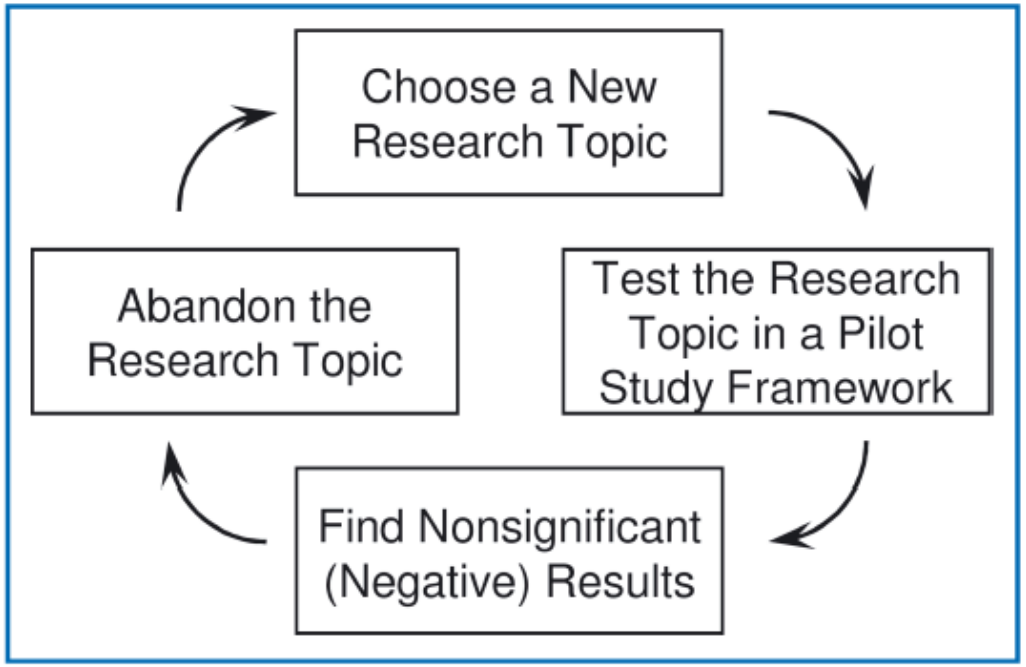


Figure 1. Nonproductive scientific strategy involving the use of pilot studies.

Moore, et al, Planning Pilot Studies; 2011

Elements of a Good Question

- Who (population of interest)
- Where (what setting are you specifically interested in)
- When (what time in the disease course; are you looking forward or backward)
- What (outcome of interest; relationship or difference?)
- How (specific measures, intervention)

What outcome are you interested in (dependent variable)?

What intervention are you applying (independent variable)?

Are you considering differences or a relationship?

To what group do you wish to apply your results (population)?

How are you going to answer the question?

One of the most common errors in question design! All of these elements MUST

How are you going to answer it?

- Retrospective vs Prospective?
- Groups to compare?
  - Control vs intervention? Two different interventions? Two different disease processes? What defines your groups and do their differences answer your question?
- Is your outcome measure validated? What do you know about the use of the outcome measure in your population?
- What variables do you need to consider?
  - Define up front any variables that may be of interest so that you collect the appropriate information.
    - IRB wants to know exactly what you'll collect
    - You only want to go through charts once (if retrospective) or only get one shot to collect data from your patient (if prospective)
    - Don't go overboard – look back to your question and focus on ESSENTIALS

Common Pitfalls

- Inadequate literature review
  - This can take weeks & is essential to framing your question
- Imprecise question
  - With a SMART question, everything else falls in line much easier
- Question, approach, and outcomes don’t align
  - Outcomes won’t actually answer your question
  - Approach won’t actually yield the outcomes you’re looking for

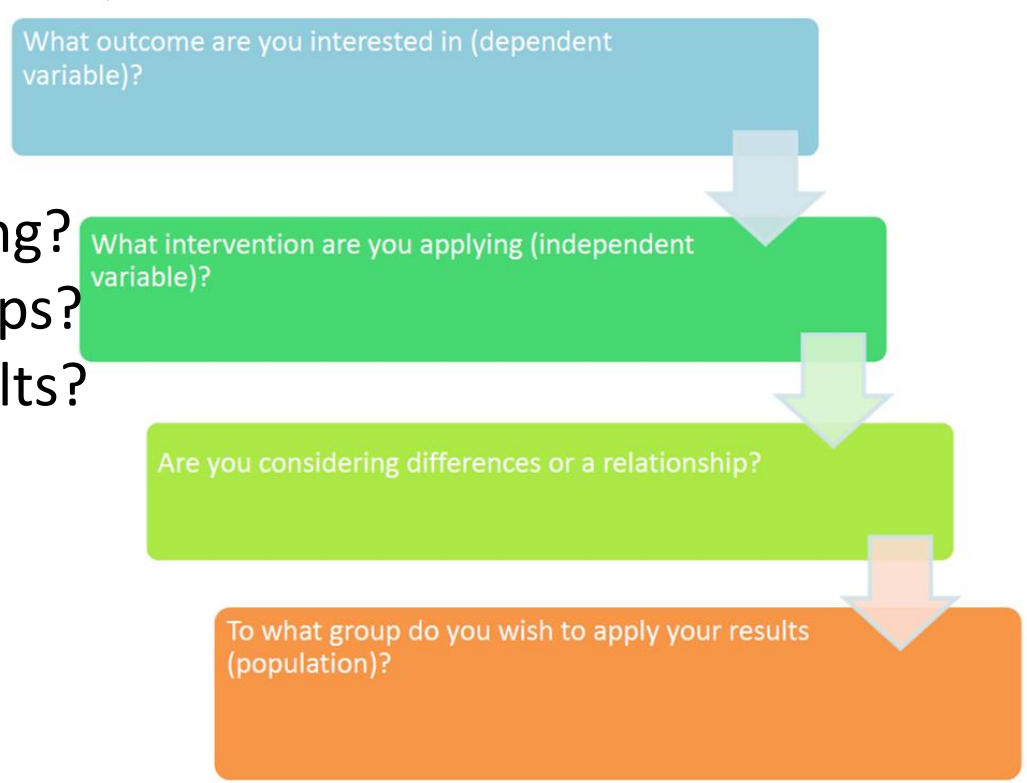
Examples

- Do asymptomatic people have lower COVID-19 viral loads in their nose?

- Can an app increase vaccine uptake?

Let's Practice . . .

- What outcome are you interested in?
- What intervention are you applying or studying?
- Are you considering differences or relationships?
- To what group do you wish to apply your results?



Resources

- https://www.youtube.com/watch?v=tOj9TimZU7k
  - NIH lecture on identifying questions for clinical research
- https://ocr.od.nih.gov/courses/ippcr_info.html
  - NIH Course on Clinical Research
- Literature review resources
  - Home - Conducting a Literature Review - LibGuides at University of North Florida (unf.edu)
  - How To Write A Literature Review For A Research Paper - PapersOwl.com
  - Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed | JAMAevidence | McGraw-Hill Medical (mhmedical.com)
  - The Literature Review | A Complete Step-by-Step Guide (scribbr.com)

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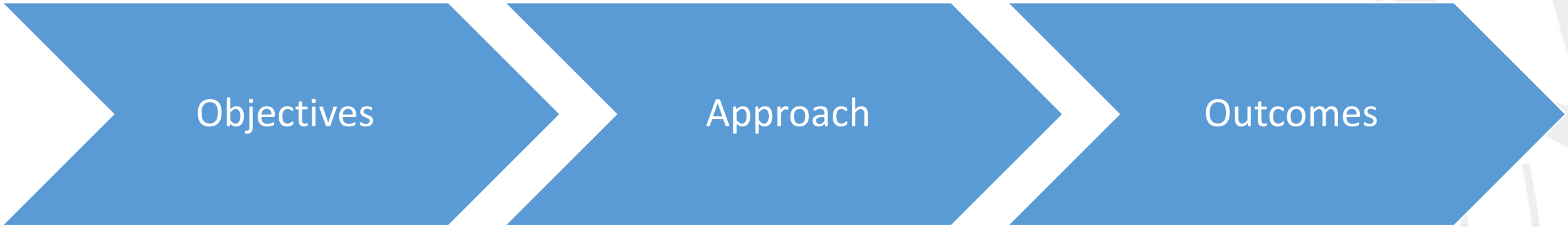
Aligning Specific Aims, Objectives, Approaches & Outcomes

Jeannette Lee, Ph.D.
UAMS, Department of Biostatistics
DCOC
February 18, 2021

Objectives, Approaches and Outcomes



Objectives

- Is the objective to establish an estimate of efficacy, acceptability, safety or feasibility or other measure with respect to an intervention?
- Is the objective to compare one or more interventions with respect to an outcome measure (e.g. efficacy)

Estimation


Objectives
Estimate
Approach
Single/multi arm
Outcomes
Measures

Comparison

Establish a preliminary estimate of efficacy, acceptability or feasibility

- Define the outcome measure
- Set a target for the outcome measure or range for the outcome measure
- Select design for study

Smoking Cessation

- Outcome measure: Stopped smoking at end of intervention (Y/N)
- Target: 20%
- Single arm study – all participants undergo smoking cessation intervention

Design option #1 – early signal

- Enroll 14 study participants
- Determine how many participants have stopped smoking at the end of the intervention period
- If none have stopped smoking, then conclude that the cessation rate is < 20%
- If at least one participant has stopped smoking, then conclude that the cessation rate is >=20%
- Advantage: few participants
- Disadvantage: no precision

Design option #2 – estimation/precision

- Estimate the proportion of smokers who stop with the intervention with a 95% confidence interval of +/- Y

Y	N
5%	245
10%	62
15%	28

This approach can also be used to get a precision estimate for a continuous measure

Single arm Studies

- One-stage design
- Two-stage design

Binary Endpoint – Headache Relief (Y/N)

- Objective: to obtain preliminary estimate that demonstrates that experimental (new) therapy is better than standard therapy
- Example: headache relief (Y/N)
- Standard therapy: relief occurs in 40% of patients
- Goal for experimental therapy: relief in 60% of patients

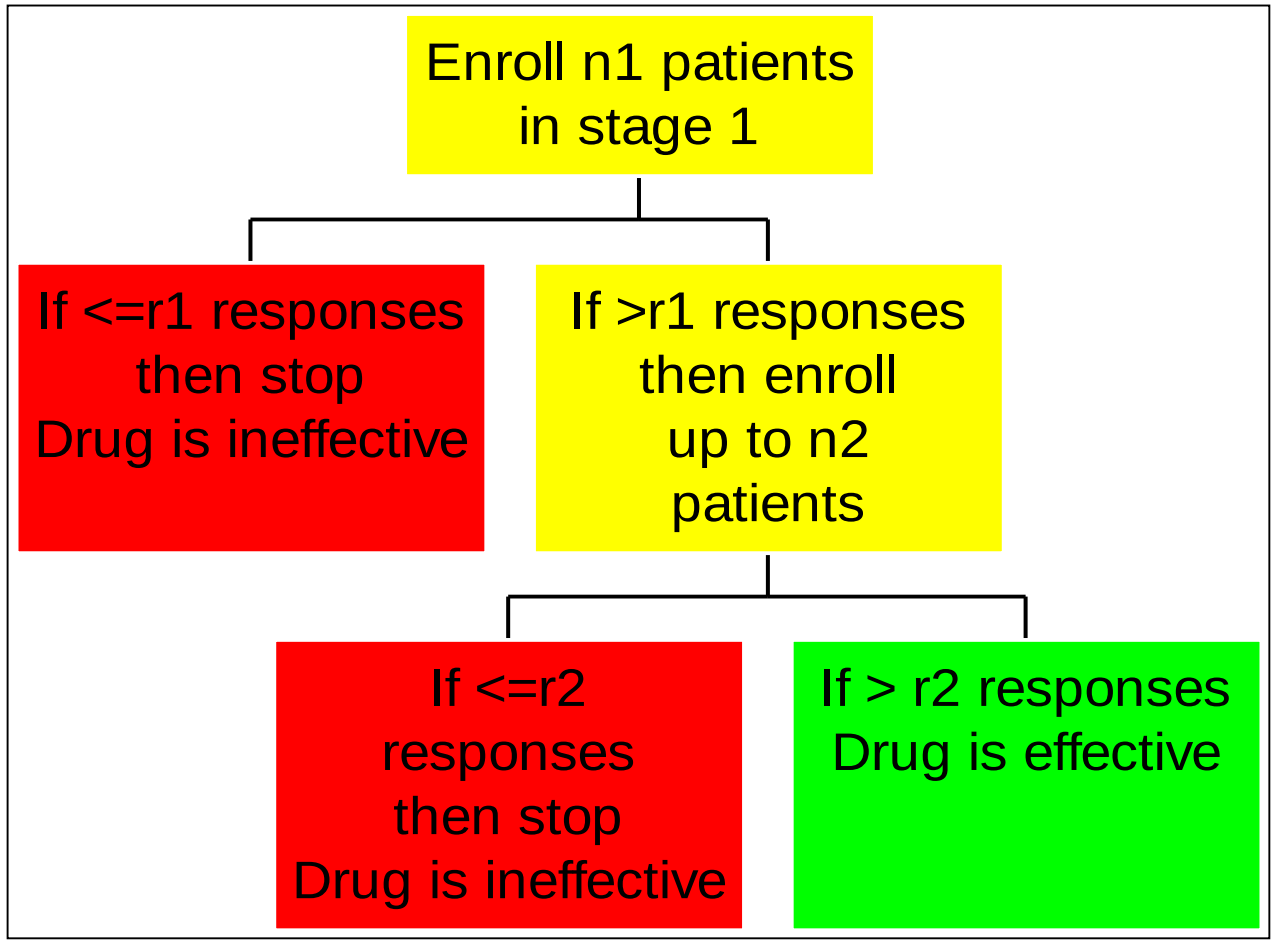
(Simon R (1989): Controlled Clinical Trials 10: 1-10.

One-stage design

- Enroll 40 study participants
- Assess the proportion who experience headache relief

Power = 90%, one-sided 10% significance level

Two-stage Design with Stopping



Headache example

- Stage 1: enroll 28 participants
- If no more than 11 participants experience headache relief, stop
- If > 11 participants experience headache relief, then enroll up to another 13 study participants in stage 2
- If there no more than 20 participants experience headache relief of the 41 (28 + 13), then conclude that the new agent's headache relief rate is < 60%.
- If > 21 participants experience headache relief, then conclude that relief occurs in >=60% treated with new agent.

Power = 90%, one-sided 10% significance level

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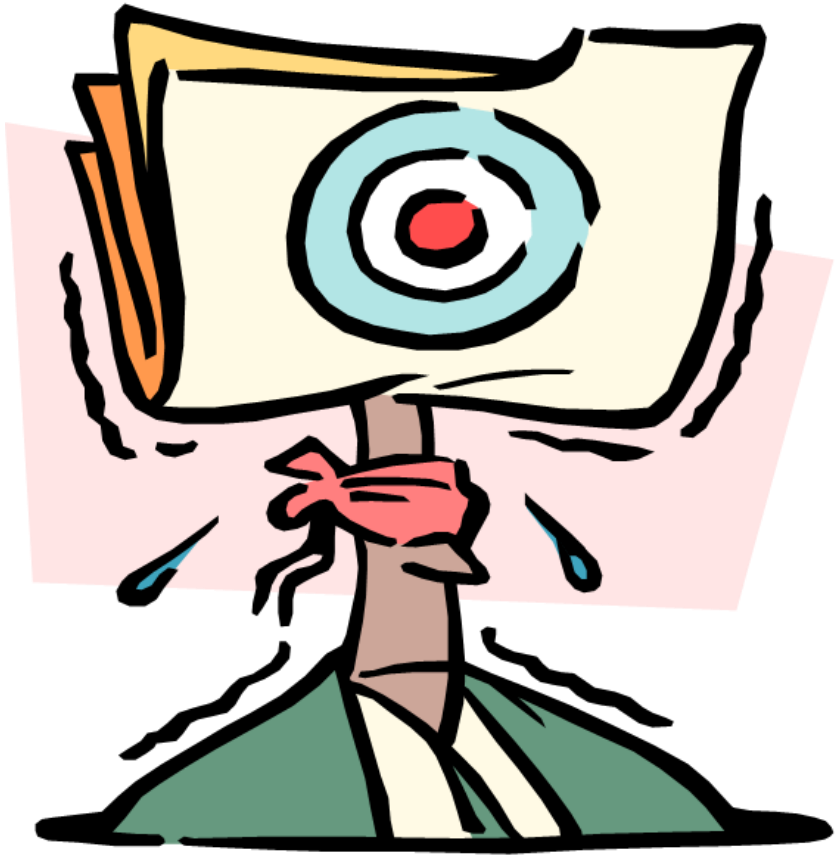
Comparative Clinical Trials

Selecting Outcome Measures to Compare Interventions

Is masking required in a comparative clinical trial?

- No, if outcome measures can be obtained objectively without masking

How ?



- Use of a central laboratory
- Blinded review of case report forms to determine if a participant has met a study endpoint

Central Lab

- Vitamin D oral replacement therapy for asthma – vitamin D levels are assessed at a central lab (results from central lab go to the coordinating center, not back to the clinical site)

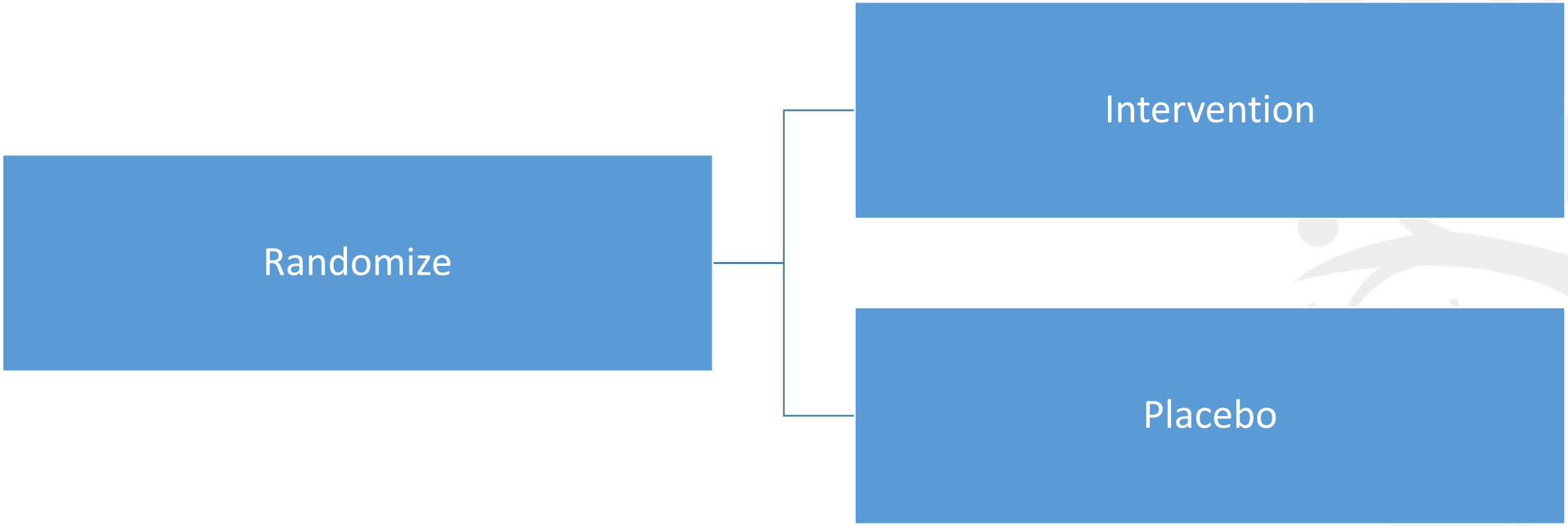
Blinded Review

- Moderna/Pfizer Covid-19 vaccine studies
- Blinded review committee (adjudication committee) reviews all reports of COVID-19 illness (mild and severe).

Baden et al, NEJM 384(5): 403-416, Feb 4, 2021.

Polack et al, NEJM 383(27): 2603-2615, Dec 31, 2020.

Comparing intervention against placebo



Saw palmetto vs placebo for benign prostatic hyperplasia

Randomize

Saw Palmetto

Placebo

Outcome measure

- Symptom score developed by the American Urological Association
- Participant responses to 7 questions scored on a Likert scale regarding urinary urgency, frequency and burning were summed
- Higher scores reflected greater symptomology

JAMA Network™

From: **Effect of Increasing Doses of Saw Palmetto Extract on Lower Urinary Tract Symptoms: A Randomized Trial**

JAMA. 2011;306(12):1344-1351. doi:10.1001/jama.2011.1364

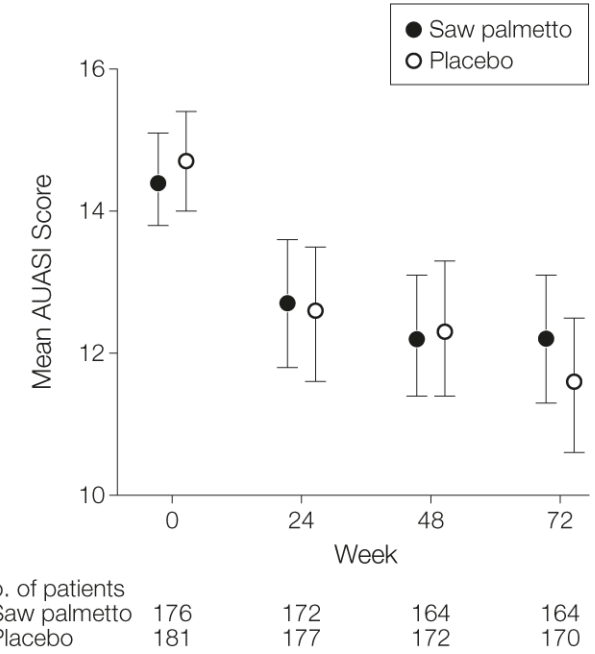


Figure Legend:

AUASI indicates American Urological Association Symptom Index. Error bars indicate 95% CI.

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Vaccine Studies

Key Target: Vaccine efficacy (VE)

- $I_{control}$ = Incidence of disease on control
- $I_{vaccine}$ = Incidence of disease on vaccine
- VE = $(I_{control} - I_{vaccine}) / I_{control}$
- VE = the proportion of disease prevented by the vaccine

Primary EFficacy endpoints – COVID-19 vaccine Recommendations

- Virologically confirmed SARS-CoV-2 infection WITH one or more of the following symptoms:

Fever or chills	New loss of taste or smell
Cough	Sore throat
Shortness of breath or difficulty breathing	Congestion or runny nose
Fatigue	Nausea or vomiting
Muscle or body aches	Diarrhea
Headache	

Efficacy secondary endpoint - recommendation

- Severe COVID-19 defined as virologically confirmed SARS-CoV-2 with any of the following:
  - Clinical signs indicate of severe systemic illness
  - Respiratory failure
  - Evidence of shock
  - Significant renal, hepatic or neurologic dysfunction
  - Admission to ICU
  - Death

Vaccine efficacy target (FDA guidance)

- For a placebo-controlled trial, the primary vaccine efficacy point estimate should be at least 50% AND
- Lower bound of an alpha-adjusted confidence interval around the primary efficacy endpoint be at least 30%

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Pfizer BioNTech

December 10, 2020

Figure 1. Safety Evaluation Follow-Up Periods in Study C4591001

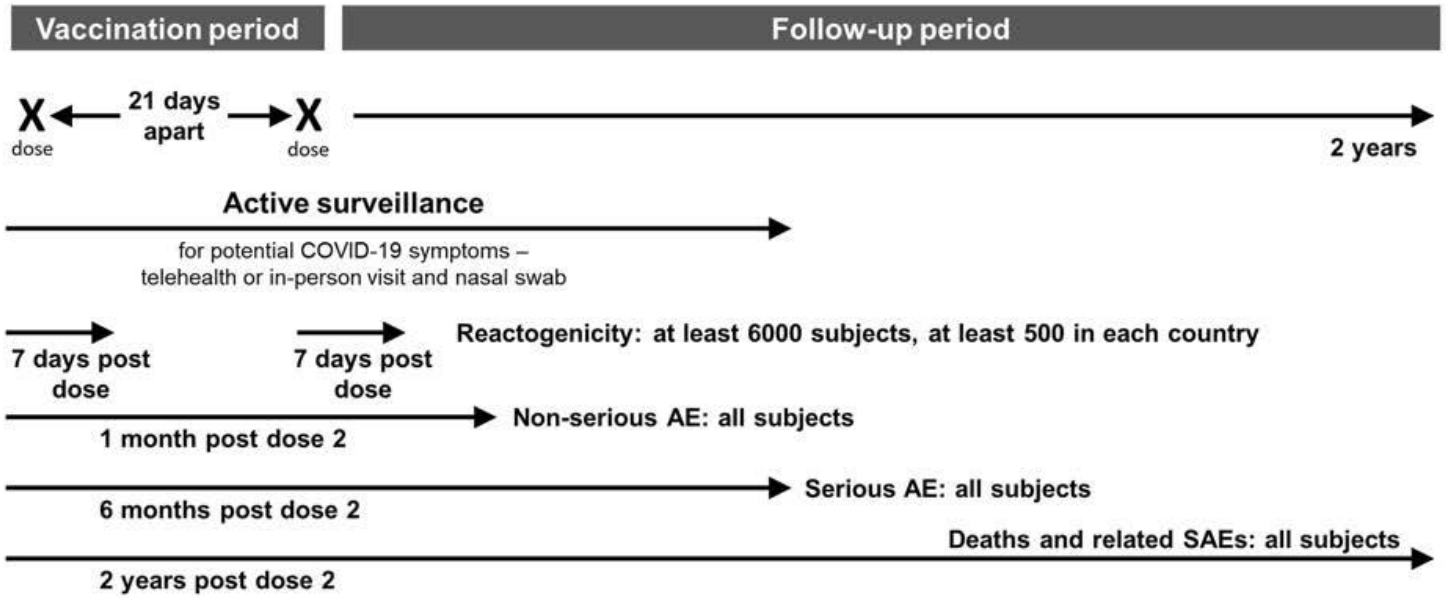
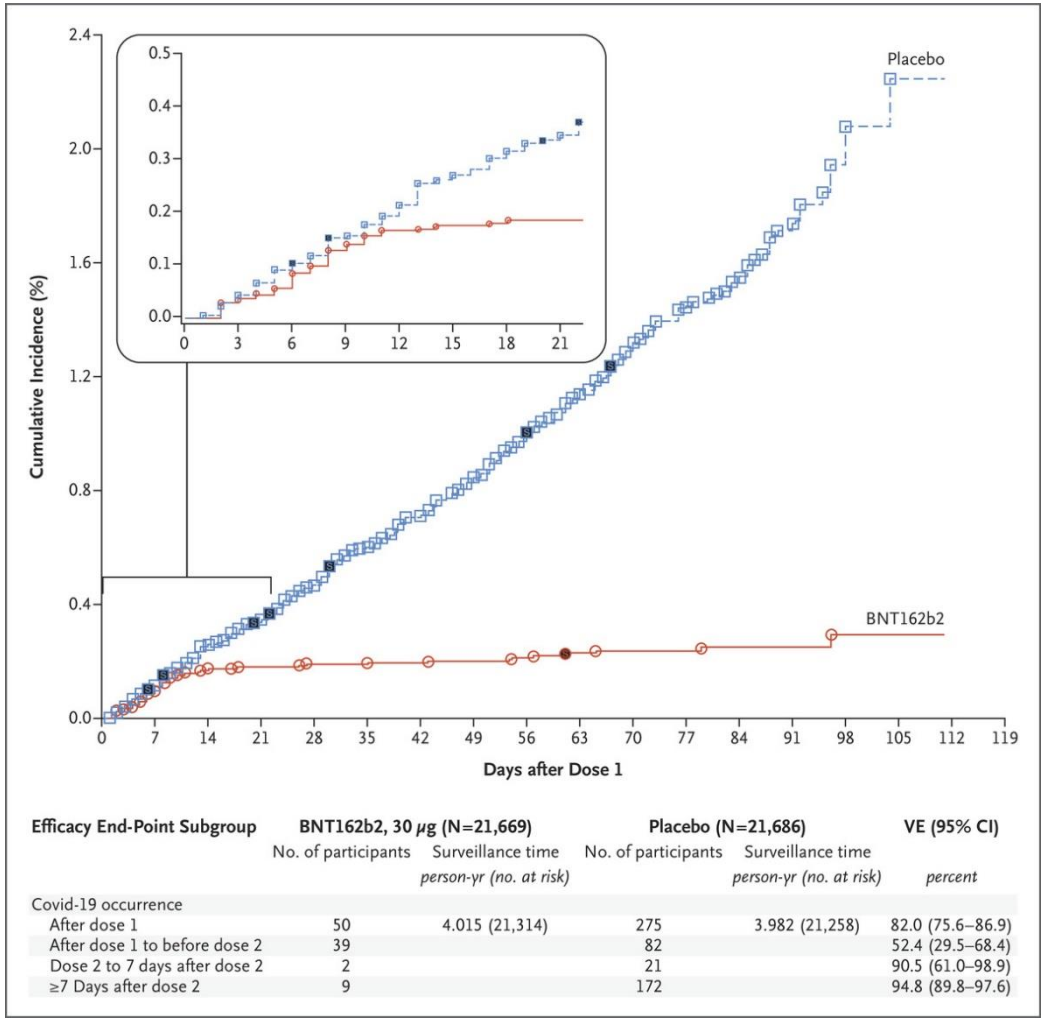


Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

FP Polack et al. N Engl J Med 2020;383:2603-2615.



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

FP Polack et al. N Engl J Med 2020;383:2603-2615.

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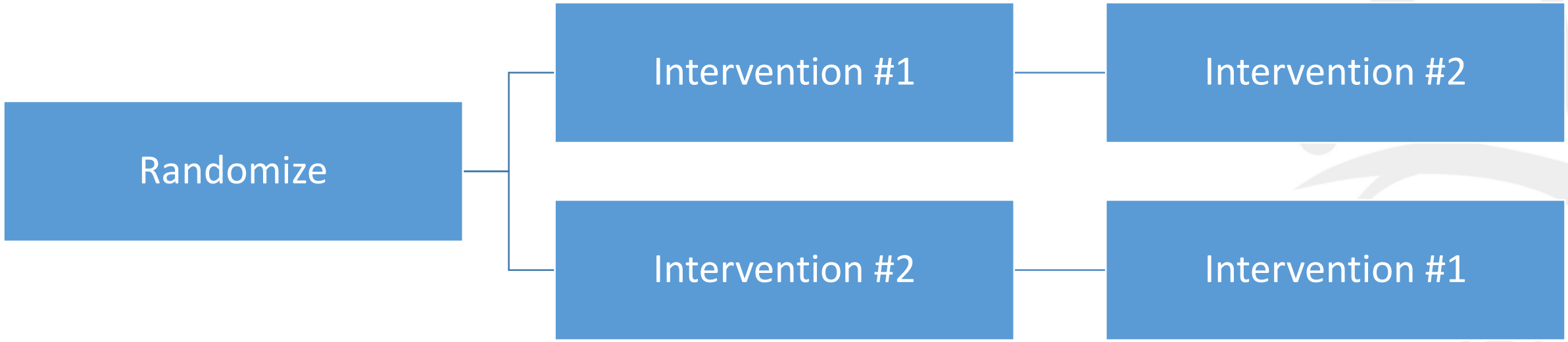
Crossover Designs

Two-Period Crossover Design



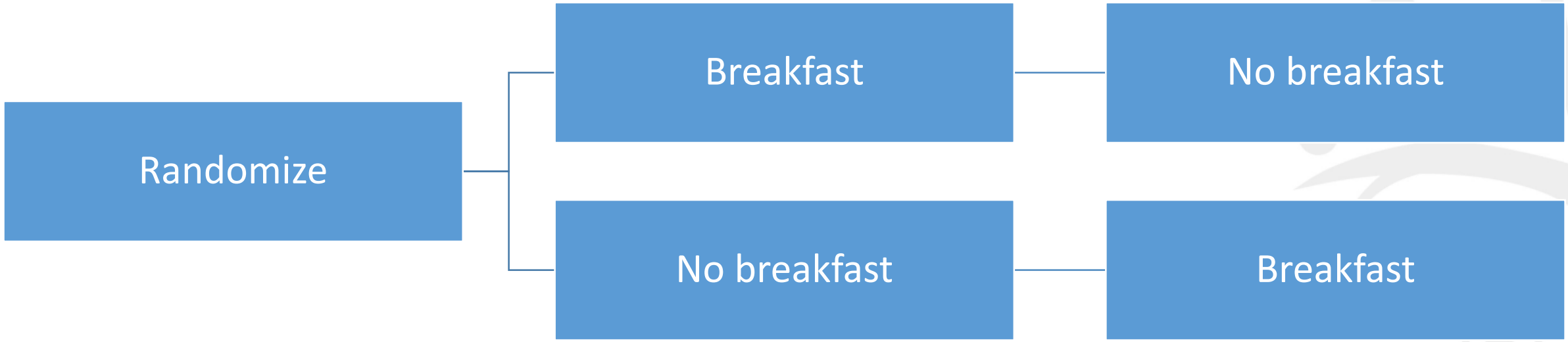
Pros and Cons of Cross-over Designs

- Pros
  - Each participant acts as his/her own control which reduces the number of required participants and, often, the number of assessments needed to achieve a specific level of power
- Cons
  - Potential residual influence of interventions in subsequent treatment periods which may bias direct treatment comparisons
  - Complications for analysis and interpretation arising from loss of participants
  - Potential for carryover effects leads to challenges in determining causality of adverse events that occur in later periods

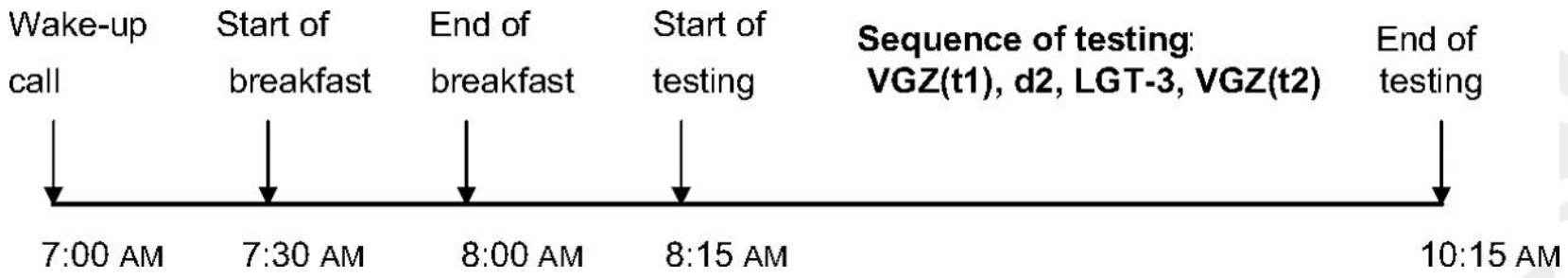
Influence of Breakfast on Cognitive Function and Mood in High School Students

- Two periods separated by 7 days
- Outcome measures
  - Cognition
  - Mood

Two-Period Crossover Design



Time bar. t1 indicates the first measurement (15 minutes after breakfast); t2 indicates the second measurement (2 hours after breakfast).



Katharina Widenhorn-Müller et al. Pediatrics 2008;122:279-284

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Concentration Results

TABLE 2 **Effect of Breakfast on Concentration Performance (d2 Test) and Results of Multifactorial Analysis of Variance With Repeated Measures**

	n	Score, Mean ± SD			Breakfast		Group		Breakfast According to Group	
		No Breakfast	Breakfast	Difference	*F*	*P*	*F*	*P*	*F*	*P*
Male										
Total no. of items processed	43	372.30 ± 58.13	371.00 ± 62.48	−1.30 ± 59.76	1.52	.224	0.80	.376	82.25	<.001
Concentration performance	43	137.91 ± 25.72	138.05 ± 28.59	0.14 ± 26.89	1.76	.192	3.18	.082	61.35	<.001
No. of errors	43	19.86 ± 21.45	19.02 ± 18.45	−0.84 ± 15.69	0.18	.676	1.70	.200	0.24	.629
Female										
Total no. of items processed	25	371.96 ± 61.70	390.56 ± 74.51	18.60 ± 69.18	0.05	.819	0.25	.620	59.91	<.001
Concentration performance	25	141.16 ± 23.17	150.40 ± 27.87	9.24 ± 28.78	0.47	.498	0.00	.970	100.03	<.001
No. of errors	25	16.92 ± 12.72	14.28 ± 10.49	−2.64 ± 13.09	0.50	.485	2.56	.123	0.83	0.371

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Factorial Designs

2 X 2 Factorial Design

	Intervention A (+)	Intervention A (-)
Intervention B (+)	A+/B+	A-/B+
Intervention B (-)	A+/B-	A-/B-

School Inner-City Asthma Intervention Study

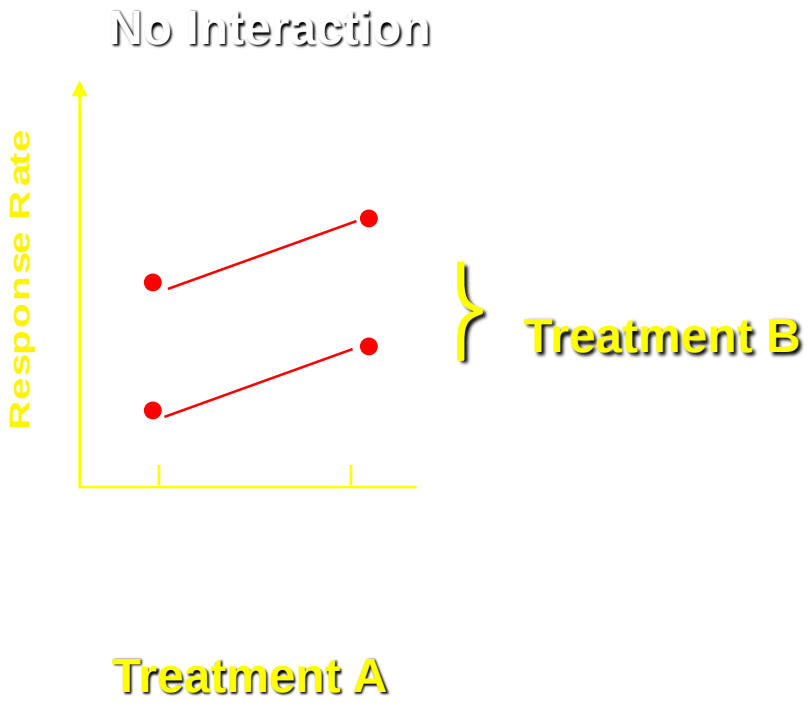
- Cluster design with two levels: school and classroom
- 300 students with asthma
- 40 northeastern inner-city schools
- Grades K-8
- School wide intervention – Integrated Pest Management (IPM)
- Classroom wide intervention – HEPA air filters
- Primary outcome – maximal days of asthma symptoms in 2 weeks prior to clinical interview (taken at 2 time points)

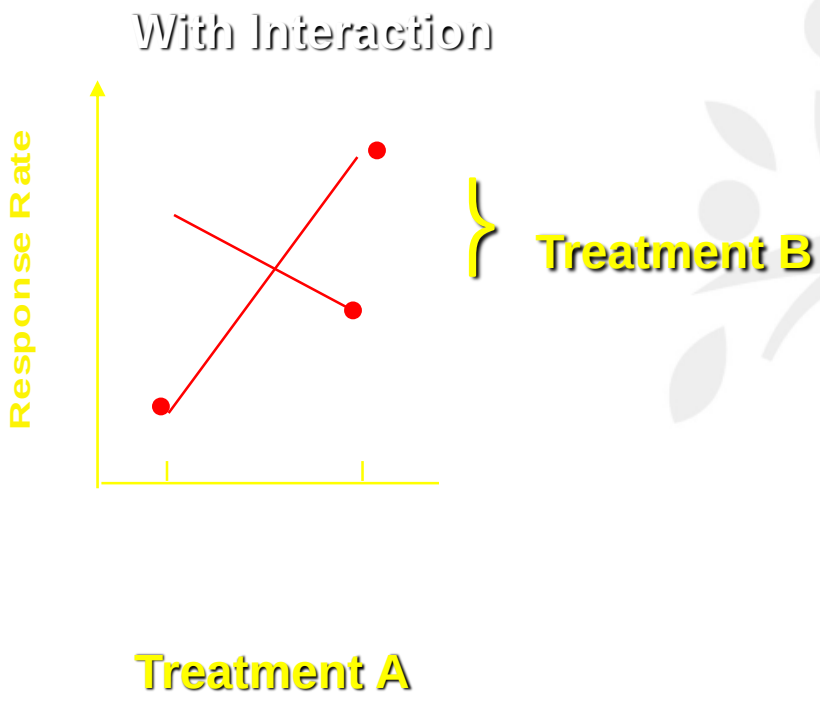
Phipatanakul W et al. Contemp Clin Trials 60:14-23, September 2017

School Inner-City Asthma Intervention Study

	IPM (+)	IPM (-)
HEPA filter (+)	IPM+/HEPA+	IPM-/HEPA+
HEPA filter (-)	IPM+/HEPA-	IPM-/HEPA-

2 x 2 FACTORIAL DESIGN





Interaction

- Plan for interaction (based on estimates from other studies)
- Factor potential interaction into sample size estimation
- Project the anticipated main effects (integrated pest control, HEPA filters)

Types of Measures

Type of Measure	Example
Binary	Response: Yes, No
Categorical	Size: Small, Medium, Large
Continuous	Body weight; body mass index
Time to event	Time from start of marathon to finish line (Censored fo those who don’t finish)

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