Randomized Controlled Trials

Today’s Outline

- Class logistic questions
- Brief review of week 6 material
- CHARM Lake County: A cluster RCT in action!
- Q & A

Study Designs

- Generally, two major categories of epidemiologic study designs
  - Experimental
    - Randomized Controlled Trial (RCT)
  - Non-Experimental
    - Cohort studies
    - Case-Control studies
    - Cross-Sectional studies
    - Ecologic studies

Randomized Controlled Trials

- Types of Trials: Related to aspects of interventions tested
  - Efficacy (under *ideal* circumstances) and Effectiveness (“real-world” circumstances)
  - Phase I, phase II, phase III trials
- Types of trials: Related to how participants are exposed
  - Parallel trials: Participants are exposed to one intervention or one control
  - Crossover trials: Participants receive all treatments at different times (remember - carryover effects and period effects matter!)
  - Trials with factorial design: Participants receive combinations of interventions & single interventions
- Specific types of trial common in drug trials
  - Equivalence Trials
  - Superiority Trials
  - Non-inferiority Trials
  - Know WHEN to use each, the null/alternative hypotheses for each, and how to interpret the equivalence margin based on confidence intervals
- Types of Randomization
  - Cluster Sampling
  - Simple Random Sampling
  - Stratified Sampling
  - Block Sampling
- Analysis
  - Intention-to-treat vs Per-Protocol
    - Related to Effectiveness vs Efficacy trials
- Reporting
  - Consort!

Example: Testing the Effectiveness of CHARM: A Community-Based Climate Resilience Intervention in Lake County

Abstract

Objective:
To test the effectiveness of CHARM: a community-based climate resilience intervention designed to improve heat safety knowledge, preparedness behaviors, and community connectedness among vulnerable populations in Lake County, California.

Method:
A cluster randomized controlled trial will be conducted with eight community resilience hub sites in Lake County, including senior centers, Tribal organizations, and peer support centers. After a pilot phase at 3 centers in Year 1, the 8 sites will be randomly allocated to receive the intervention in either the first or second year. The intervention includes staff training, 1-on-1 resource navigation with participants, delivery of community-based resilience activities, and provision of a heat resilience kit. Participants will be surveyed at baseline and 12 months of follow-up to assess outcomes related to self-reported heat stress, heat safety knowledge, preparedness behaviors, and social connectedness. Analyses will follow an intention-to-treat framework, with mixed-effects regression models used to account for clustering at the site level (anticipated $N \approx 520$).

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TRACKING CALIFORNIA
INFORMING ACTION FOR HEALTHIER COMMUNITIES

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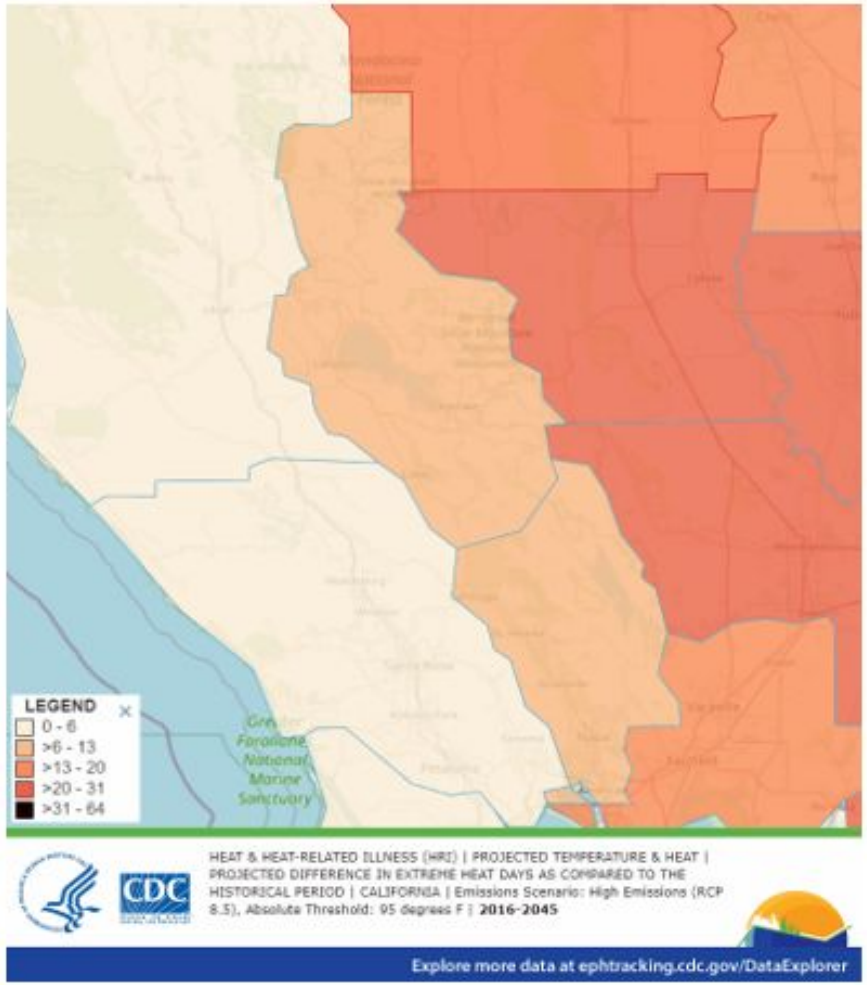
Heat waves are projected to increase in frequency



High Emissions Scenario, 2016 - 2099

Additional days above 95 F*:

- 2016-2045: 12 days
- 2046-2065: 23 days
- 2070-2099: 44 days

* Compared to historical period from 1950-2005

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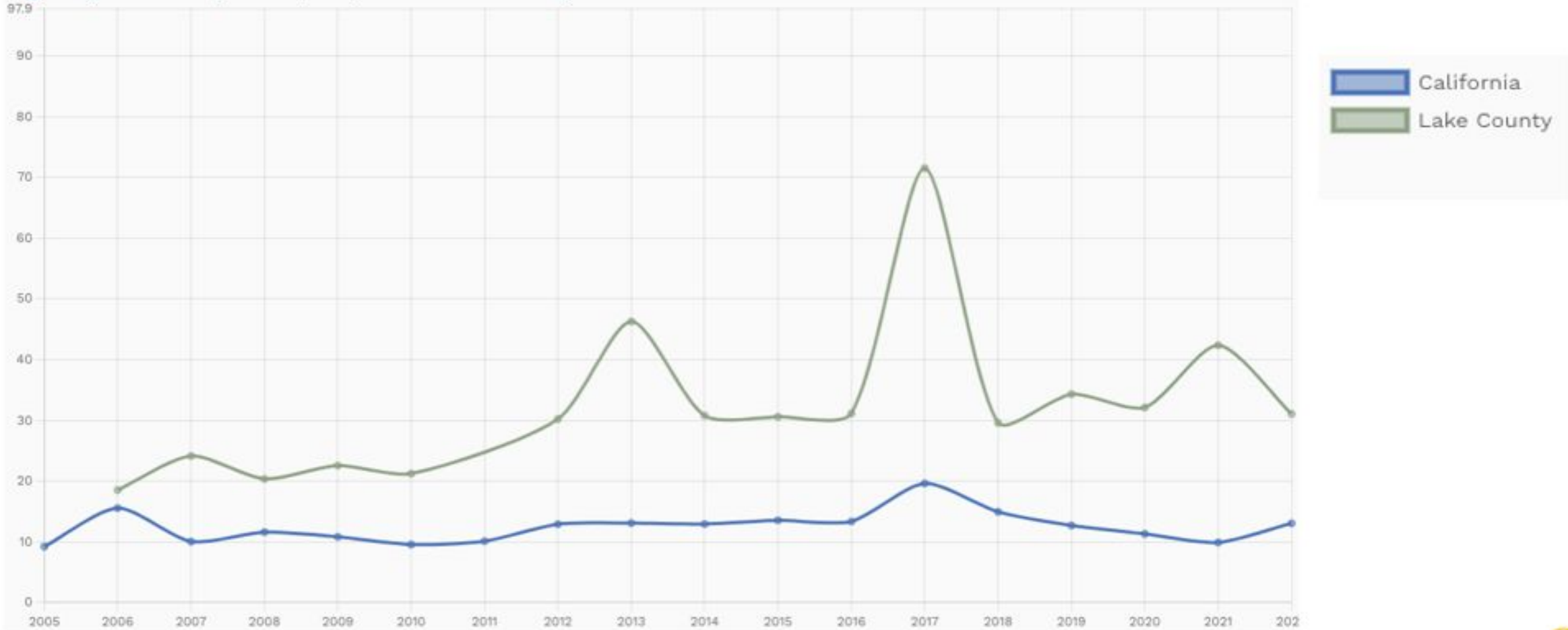
Heat-related illness in Lake County is more than double the state average

Heat-related Illness Emergency Department Visits, 2005 - 2022

Age-adjusted rate per 100,000, CA vs Lake County



Source: Tracking California, California, Department of Healthcare Access & Information

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CHARM Working Group

- **Quarterly in-person and virtual meetings**
- **Guide and contribute to project activities**
- **Conduct outreach and facilitate connections**

Tribes

Big Valley Band of Pomo Indians
Habematolel Pomo of Upper Lake
Middletown Rancheria of Pomo Indians
Robinson Rancheria of Pomo Indians
Scotts Valley Band of Pomo Indians

CBOs/NGOs

The Essential Public Information Center
Latinos United
North Coast Opportunities
Red Cross of America, Community Adaptation Program

Lake County Agencies

Adult Services
Area Agency of Aging
Community Development
Health and Human Services
Office of Climate Resiliency
Office of Emergency Services
Public Health Department
Social Services
Tribal Health
Water Resources Dept

Municipalities

City of Clearlake
City of Lakeport

State Agencies

CDPH, Office of Health Equity

What is the CHARM Phase 2 project?

- **4-year research project** led by Big Valley and Tracking California (June 2025-May 2029)
- 1 of 3 projects funded by **National Institutes of Health**
- Purpose: **Test the effectiveness of a "community adaptation and resilience intervention" (CARI)** that aims to build community resilience to extreme heat and other natural emergencies
- Proposed intervention is **guided by CHARM Phase 1 findings**, including:
  - Trusted spaces play a critical role in emergency preparedness and response
  - Overall need to strengthen individual preparedness and access to communications, support, and resources

Project team

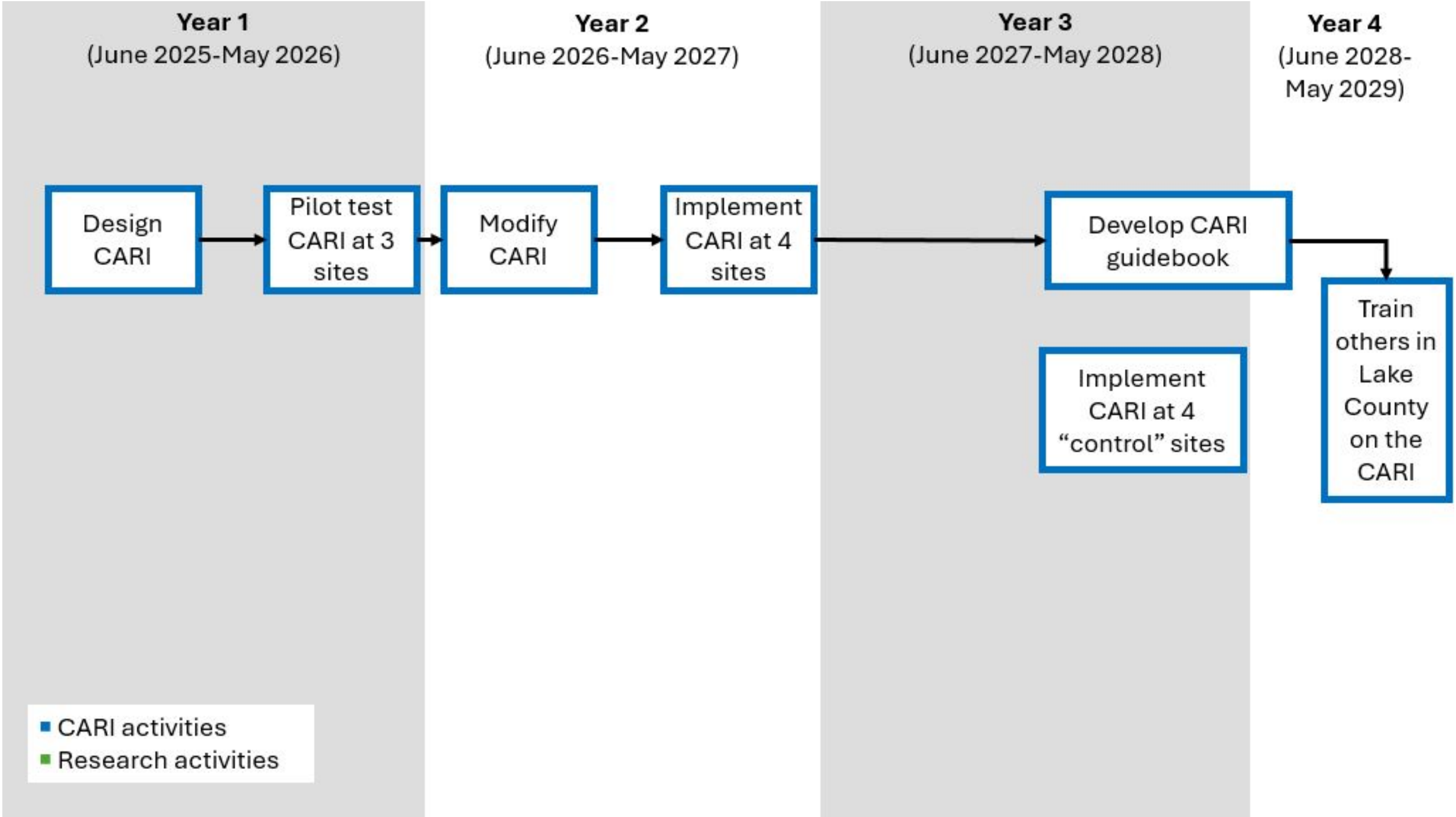
- Big Valley
- Tracking California
- Terre Logsdon (Lake County)
- Carmela Lomonaco (PHI)

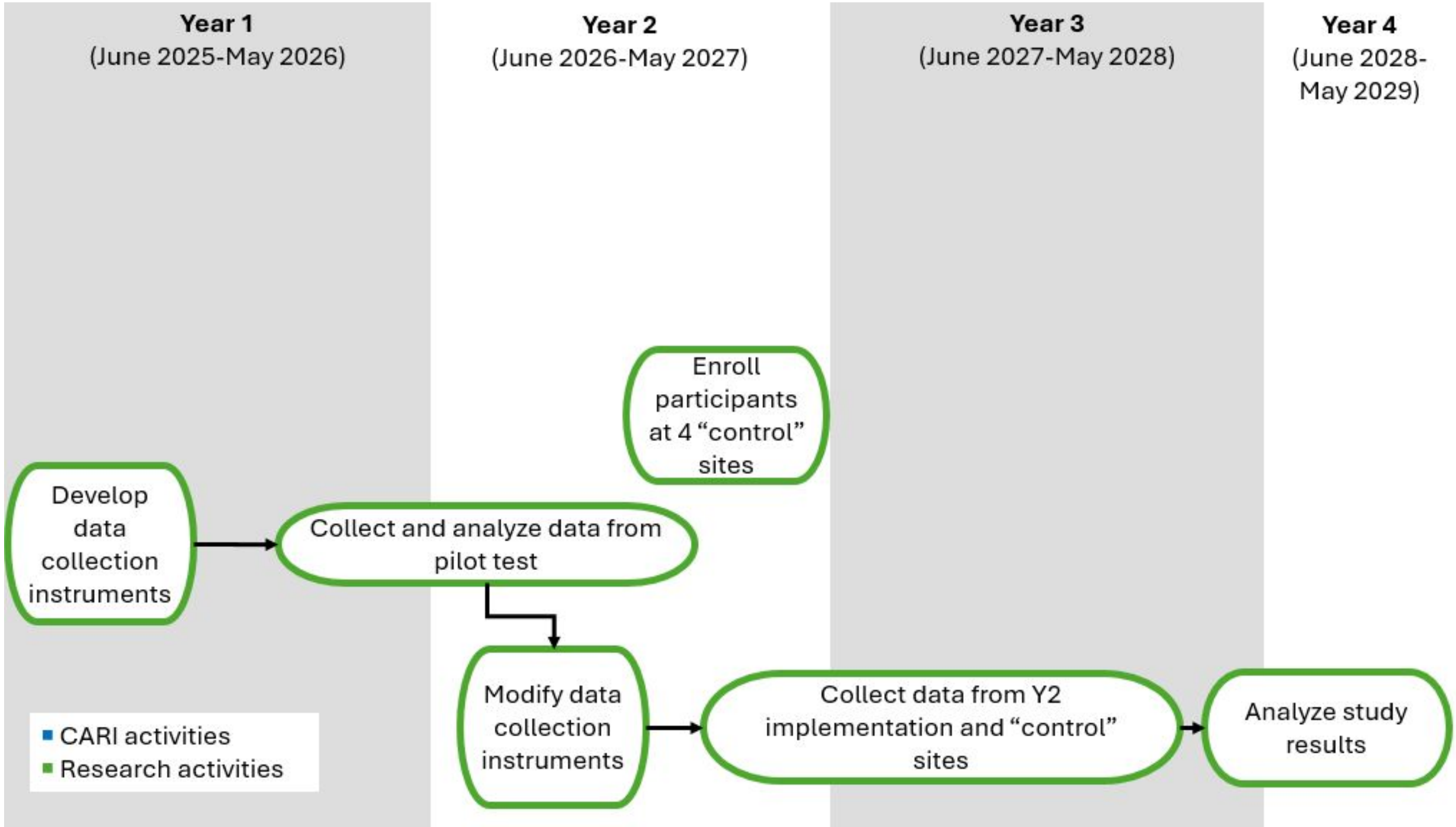
- Project team
- Training partners
  - CAL TERRA
  - North Coast Opportunities
  - Red Cross
- Study sites

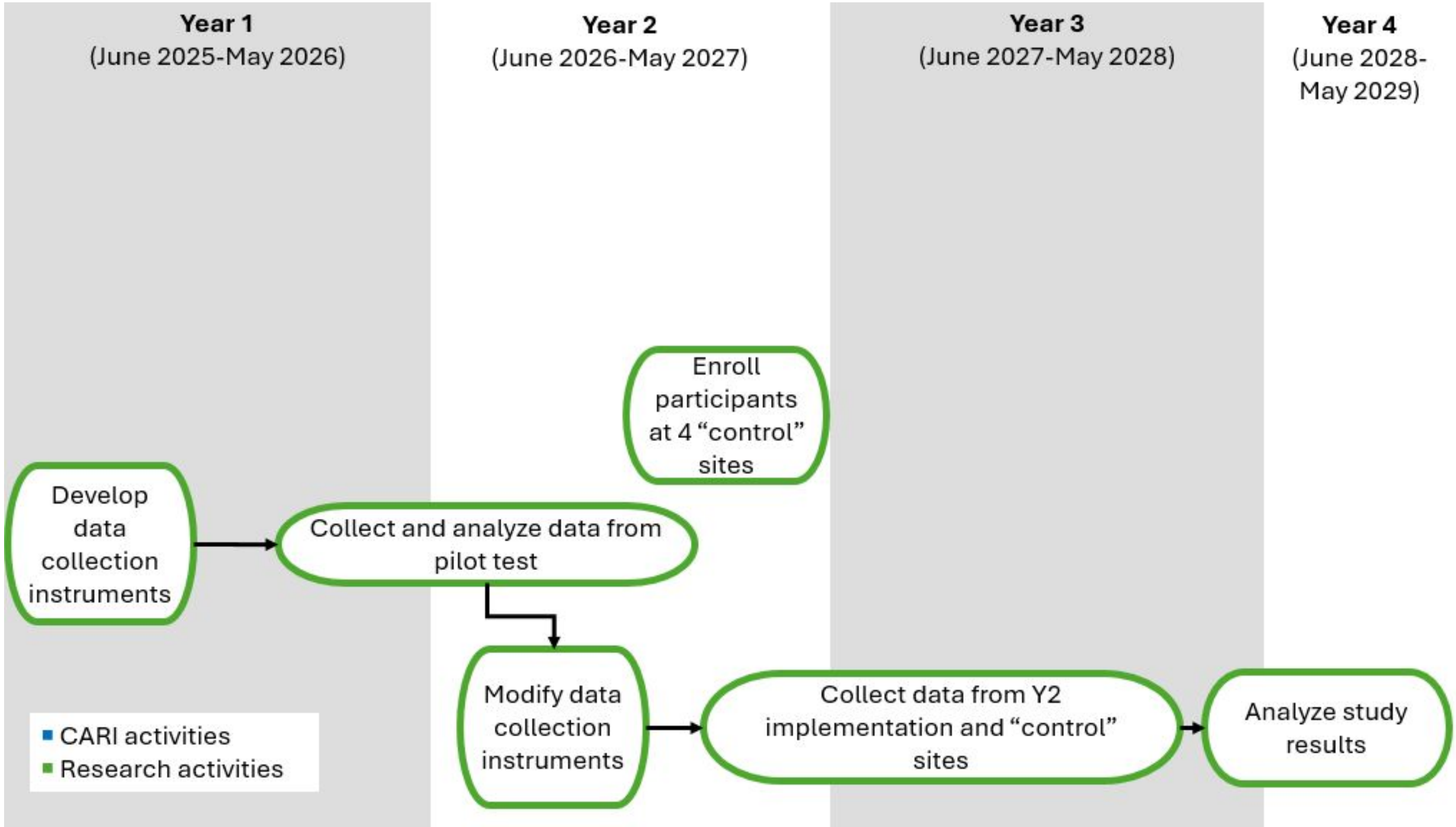
- Project team
- David Gonzalez (UC Berkeley)

- Big Valley
- Habematolel
- Clearlake Senior Center
- Big Oaks Peer Support Center
- Circle of Native Minds
- TBD
  - Lakeport Senior Center
  - Kelseyville Family Apartments
  - Lakeport Family Apartments

CHARM Advisory Group


Year 1
(June 2025-May 2026)
Year 2
(June 2026-May 2027)
Year 3
(June 2027-May 2028)
Year 4
(June 2028-May 2029)
Design CARI
Pilot test CARI at 3 sites
Modify CARI
Implement CARI at 4 sites
Develop CARI guidebook
Train others in Lake County on the CARI
Implement CARI at 4 "control" sites
CARI activities
Research activities


Year 1
(June 2025-May 2026)
Year 2
(June 2026-May 2027)
Year 3
(June 2027-May 2028)
Year 4
(June 2028-May 2029)
Enroll participants at 4 "control" sites
Develop data collection instruments
Collect and analyze data from pilot test
Modify data collection instruments
Collect data from Y2 implementation and "control" sites
Analyze study results
CARI activities
Research activities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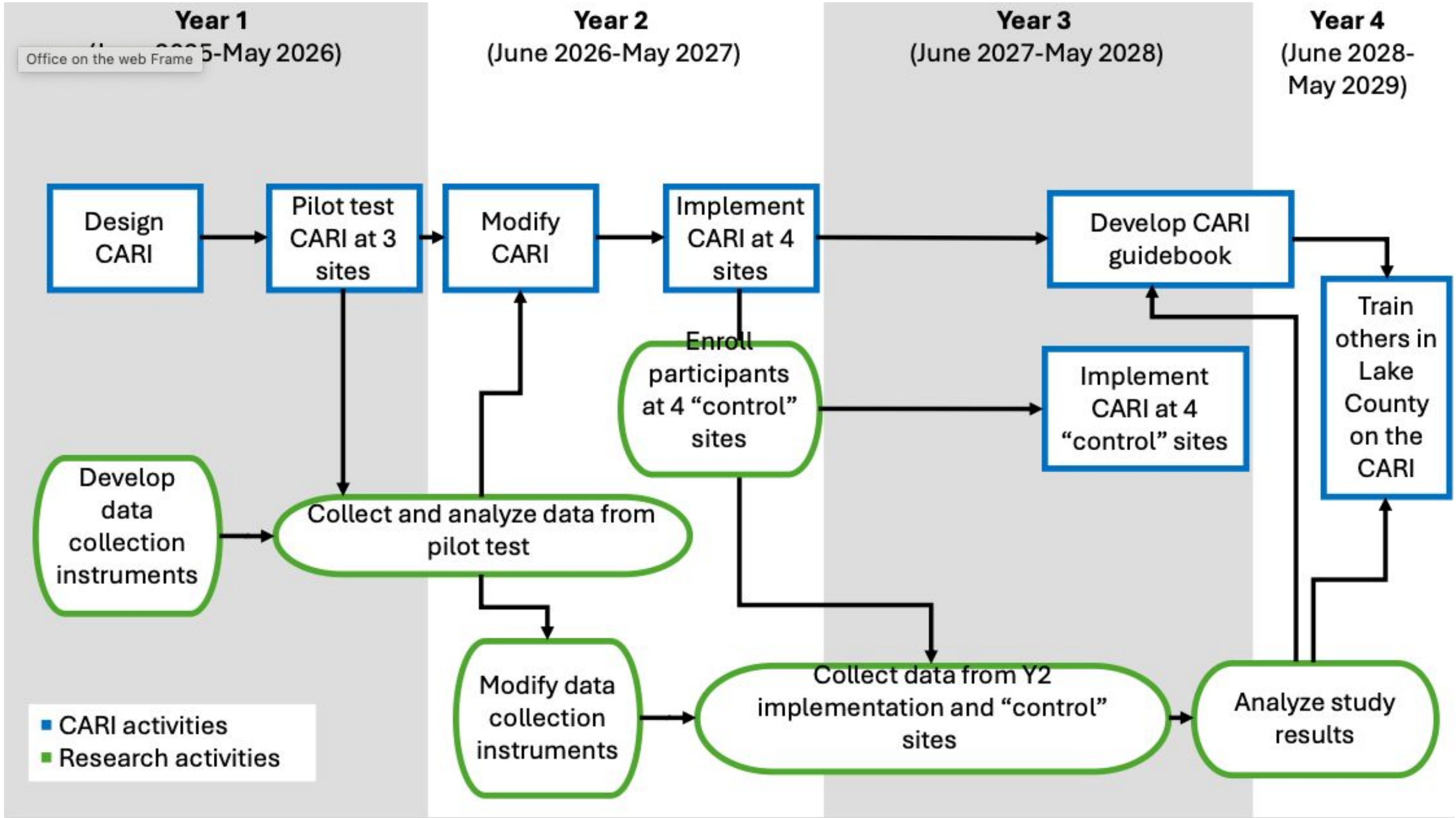
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CARI activities
Research activities

RCT Example: Practice (with CHARM!)

What is the unit of randomization?

- Each resilience hub site (e.g., senior centers, Tribal organizations, peer-support centers).

Why would the investigators decide to use a cluster randomized trial?

- To prevent spillover between participants at the same site, since individuals interact closely within hubs.

What if the investigators rolled out this trial in two waves (Year 1 and Year 2), with half the hubs receiving the intervention each year? What kind of randomization might they use?

- Block randomization
  - **What would the blocks be?**
    - Year of rollout (Year 1 vs Year 2).

What if the hubs serve very different populations (e.g., Tribal members, seniors, unhoused individuals, outdoor workers), and investigators want to ensure equal representation across intervention and control groups? What kind of randomization might they use?

- Stratified randomization
  - Stratification by population type.

Is this an effectiveness or efficacy trial?

- Effectiveness — it is testing CHARM as delivered in real-world community settings, not under ideal or tightly controlled conditions.

Will the investigators be using an Intention-to-Treat analysis or a Per-protocol analysis? Why?

- ITT (Intention-to-Treat)
  - **Benefits of ITT:**
    - Provides a more realistic estimate of effectiveness in practice.
    - Preserves the benefits of randomization, even if some participants don’t fully engage with the intervention.

What does building an intervention with community partners actually look like?

What does building an intervention with community partners actually look like?

(hint: it’s messy!)

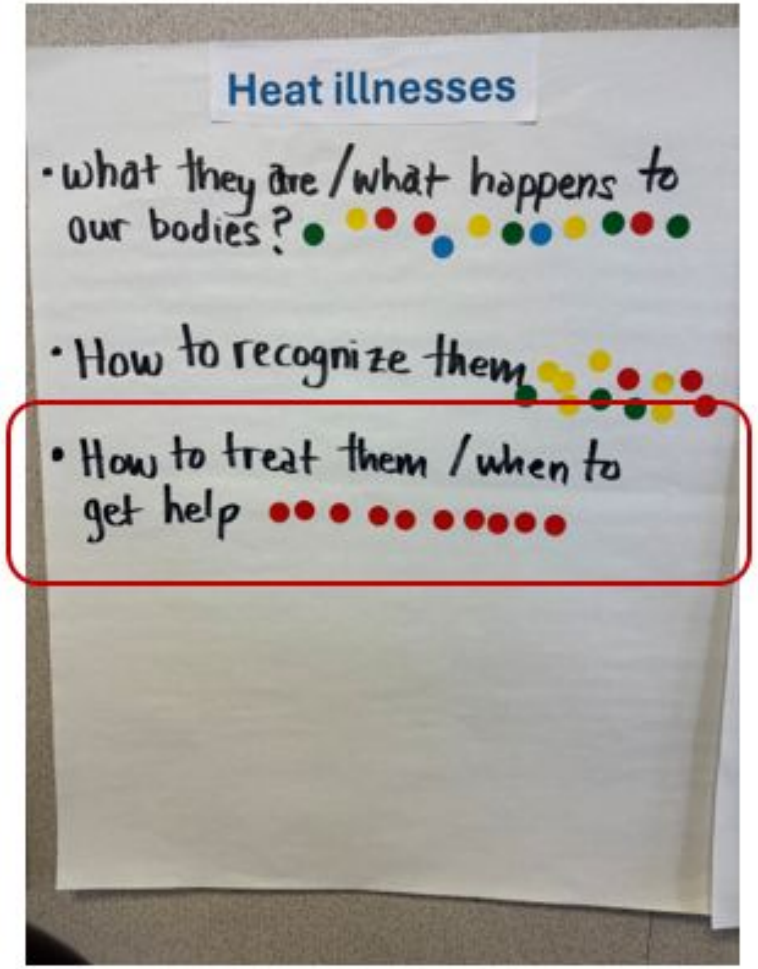
What will the program look like? What we heard from the CRC

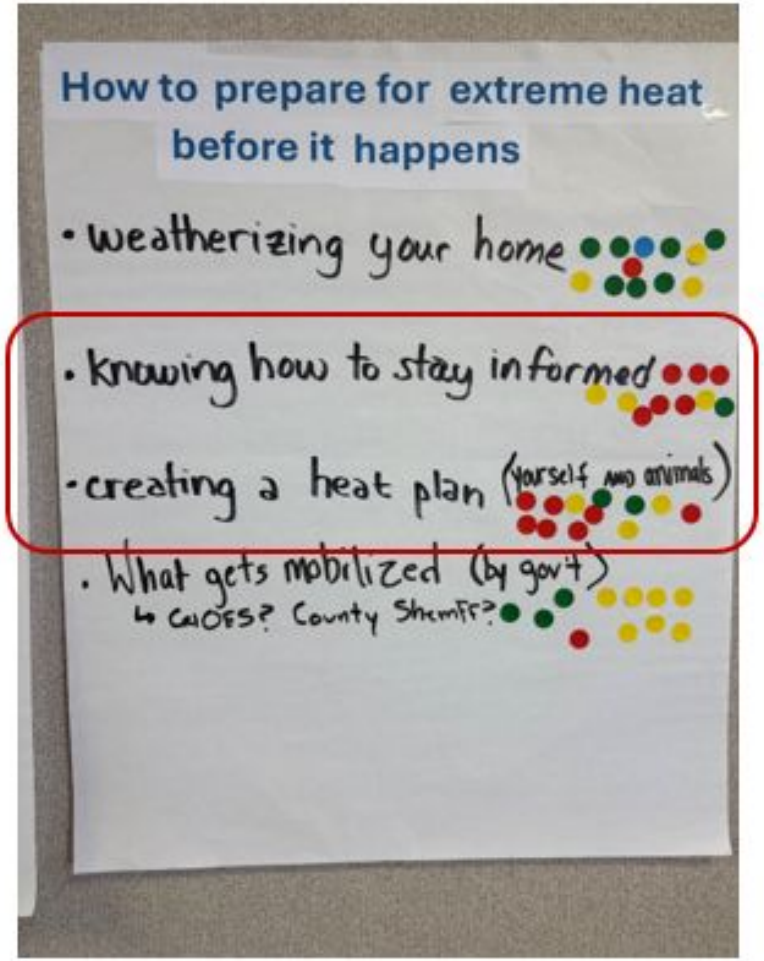
What participants should learn?

What encourages participation in the program?

What keeps participants engaged?

What will the program look like? What we heard from the CRC





NO death by power point!

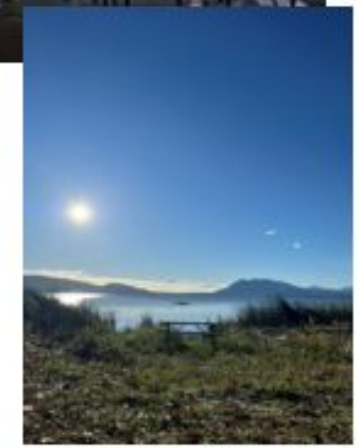
Action-oriented content: HOW to treat heat illness, not necessarily body biology

Delivery paired with incentives, games, existing activities at centers (e.g., bingo)

Practice and reminders: repeat skills often, and use simple tools (like fridge notes or phone alerts) to help people remember what to do

Make it fun!

PHEW...we did a lot in Phase 1!



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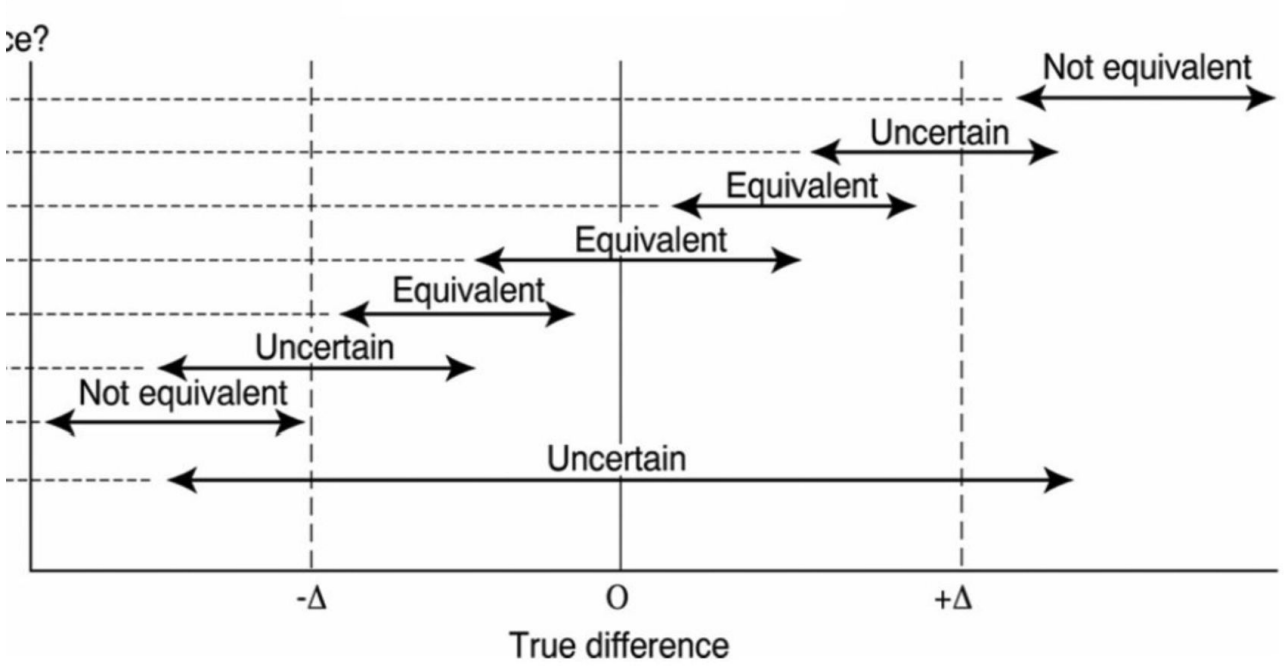
Additional review & practice problems

(not covered in live session)

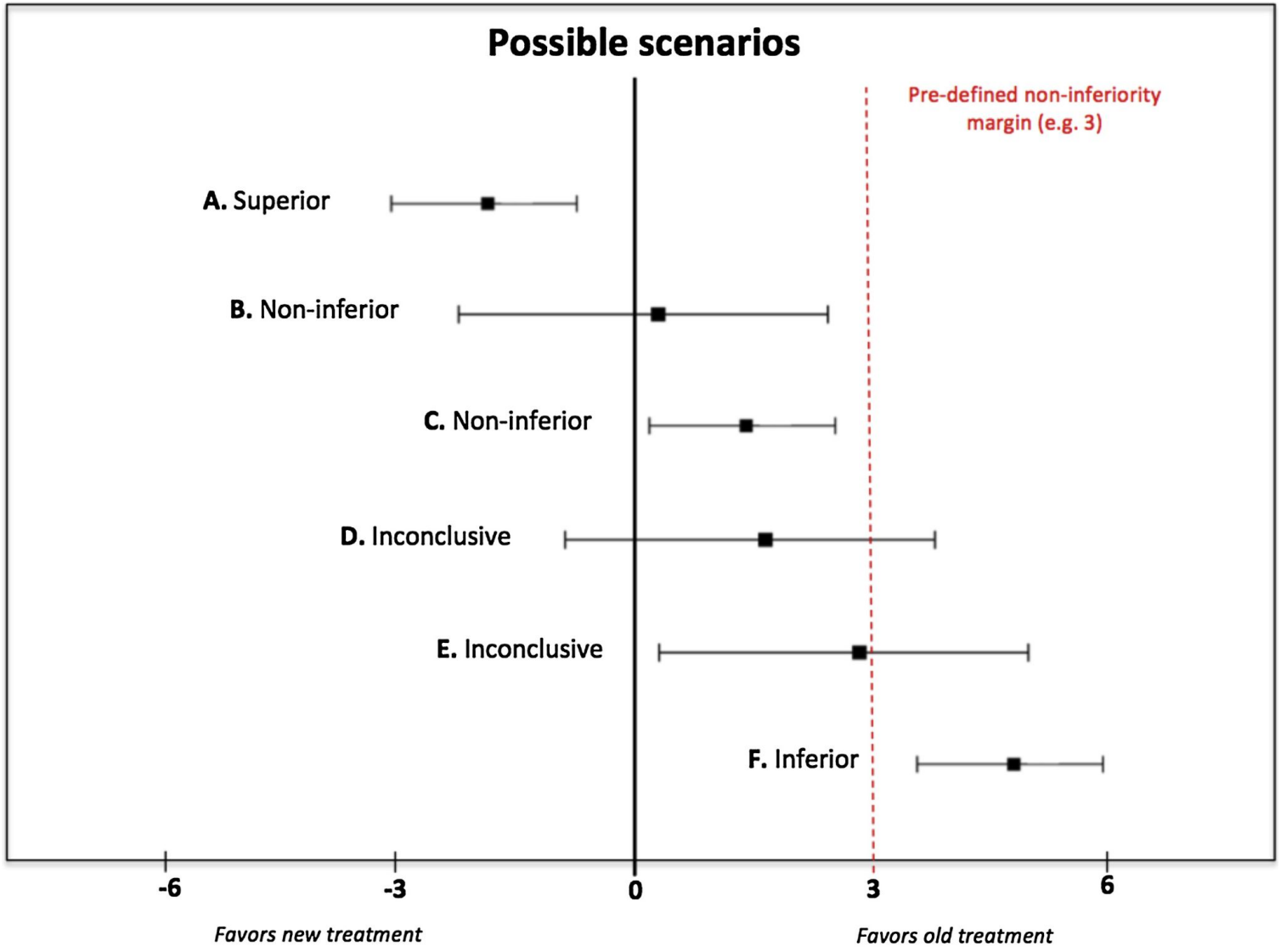
Superiority and Equivalence Trials

- **Superiority Trial**
  - Intended to determine if a new treatment is BETTER THAN a placebo or existing treatment
    - Null Hypothesis: There is no difference between treatments
    - Alt Hypothesis: The new treatment is different from the control (two sided) or the treatment is better than the control (one-sided)
- **Equivalence Trial**
  - Intended to determine that new treatment is NO WORSE THAN an active control
    - Null Hypothesis: Difference between treatments is greater than X (set amount)
    - Alt Hypothesis: Difference between treatments is less than X (set amount)
    - Note: We can never assess absolute equivalence; we assess equivalence within a prescribed margin
- **Non-inferiority Trial**
  - Intended to determine that a new treatment is NOT SUBSTANTIALLY WORSE than active control.
    - Null: new treatment is inferior to standard
    - Alternative: new treatment is non-inferior

Equivalence Margins



Interpreting non-inferiority chart

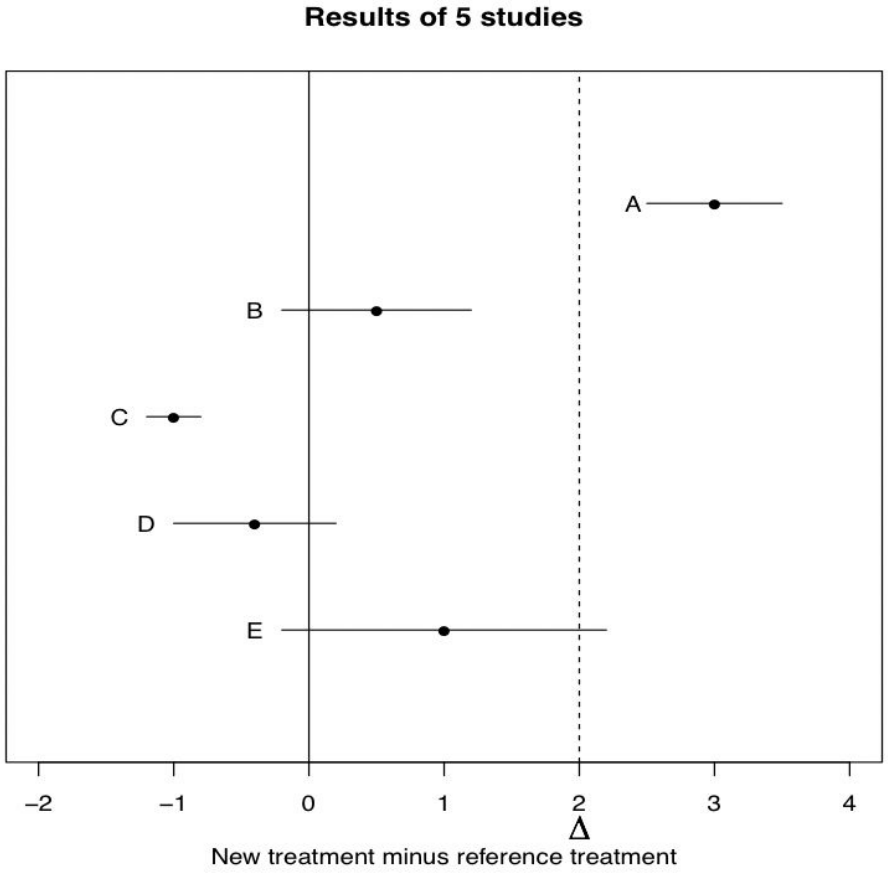


Randomized Controlled Trials: What context can they be used in?

- **Clinical Trials**
  - COVID-19 vaccines
- **Impact Evaluation** *(Ex: testing the impact of Interventions)*
  - A Randomized Controlled Trial of a Rapid Re-housing Intervention for Homeless Persons Living with HIV/AIDS: Impact on Housing and HIV Medical Outcomes (Towe et al, 2019)
    - Participants who were randomized to rapid-rehousing case managers were placed in housing faster than control participants (25% placed by 150 days vs 25% placed by 243 days) AND 2x as likely to achieve/maintain viral suppression over 12 months.
  - Can Housing and Service Interventions Reduce Family Separations for Families Who Experience Homelessness? (Shinn et al, 2016)
    - Families randomized to permanent housing subsidies (rent amount set to 30% of income) had HALF the rate of child separation and LESS than half the rate of foster care placement (compared to usual care) after 20 months.
- **RCTs & Observational Studies**
  - If your study question is about the impacts of smoking, depression, anxiety, racism, trauma on health… you cannot randomize these exposures, and observational studies are often used to understand impacts of these exposures.
  - If your study question is WHAT TO DO to reduce exposures such as smoking, depression, anxiety, racism, and trauma… your interventions can be tested using an RCT!

Week 5, Tab 1 Problems. #1

The figure below shows the results of five non-inferiority studies comparing an old and a new treatment. We are concerned with an adverse outcome. For each letter, label whether they are superior, inferior, noninferior, or inconclusive. The pre-specified delta for these studies is 2.



A: _

B: _

C: _

D: _

E: _

Week 5, Tab 1 Problems. #1

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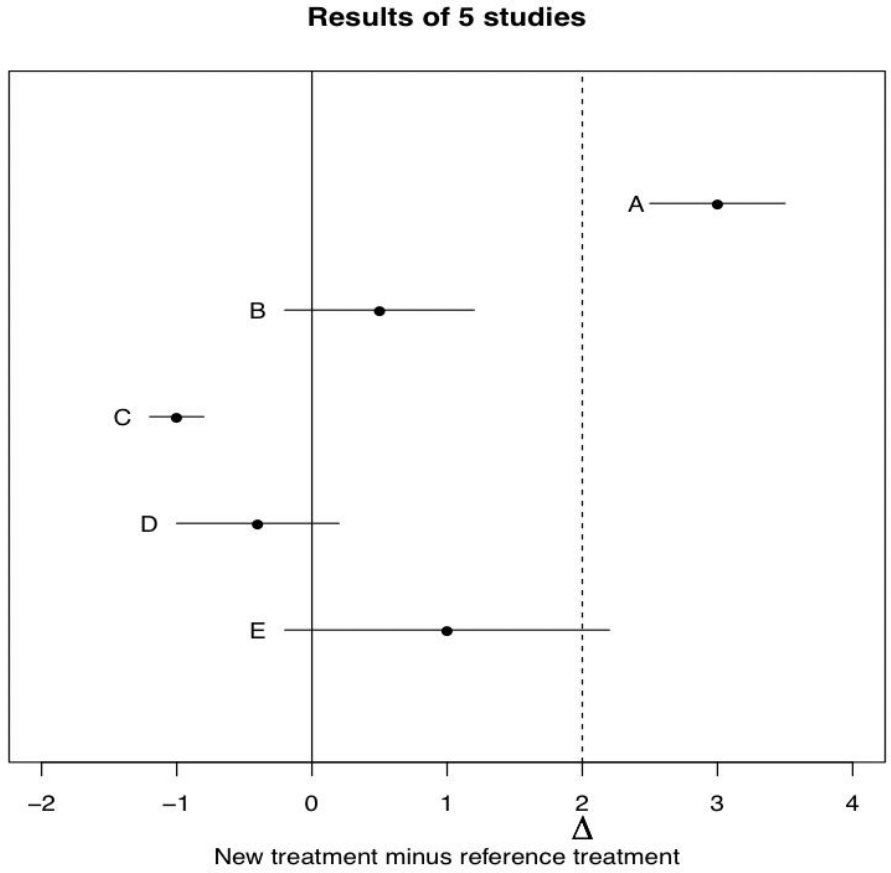

A: inferior

B: noninferior

C: noninferior/superior

D: noninferior

E: inconclusive

Week 5, Tab 1 Problems. #2

“The standard brand-name version of chronic obstructive pulmonary disease (COPD) treatment increases forced expiratory volume 1 (FEV1, a measure of respiration) by 15% on average. The newly developed generic version of this treatment will increase FEV1 by at least 12% on average.”

This statement is the alternative hypothesis for which type of clinical trial?

a. Superiority trial
b. Phase IV trial
c. Equivalence trial
d. Non-inferiority trial
e. Phase I trial

Week 5, Tab 1 Problems. #2

“The standard brand-name version of chronic obstructive pulmonary disease (COPD) treatment increases forced expiratory volume 1 (FEV1, a measure of respiration) by 15% on average. The newly developed generic version of this treatment will increase FEV1 by at least 12% on average.”

This statement is the alternative hypothesis for which type of clinical trial?

a. Superiority trial
b. Phase IV trial
c. Equivalence trial
d. Non-inferiority trial
e. Phase I trial

D, this is a non-inferiority hypothesis that the alternative treatment is not worse than existing treatment within a certain margin (new treatment < current treatment by no more than 3% points).

Week 5, Tab 1 Problems. #3

What is the null hypothesis in a superiority trial?

A. There is no difference between groups.
B. Treatment outcome is greater than control outcome
C. Control outcome is greater than treatment outcome

Week 5, Tab 1 Problems. #3

What is the null hypothesis in a superiority trial?

A. There is no difference between groups.
B. Treatment outcome is greater than control outcome
C. Control outcome is greater than treatment outcome

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

a. Name the type of trial that is best suited to addressing these research questions. List the study arms in this trial.

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

a. Name the type of trial that is best suited to addressing these research questions. List the study arms in this trial.

Factorial trial

Four study arms – one receives neither intervention, one gets just media campaign, one gets just playground improvements, one gets both interventions

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

b. Would you randomize exposures at an individual or a cluster level? Justify your choice in one sentence.

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

b. Would you randomize exposures at an individual or a cluster level? Justify your choice in one sentence.

Cluster. Both exposures are group-level exposures that could not be effectively randomized to individuals.

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

c. You would like to ensure that each arm of the study is balanced in terms of a key confounder of local sports league availability, which differs between urban and rural settings. You also hope to ensure that each arm of the study is approximately the same size even if it's a small study. Identify and justify a randomization strategy that addresses both of these concerns (1-2 sentences).

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

c. You would like to ensure that each arm of the study is balanced in terms of a key confounder of local sports league availability, which differs between urban and rural settings. You also hope to ensure that each arm of the study is approximately the same size even if it's a small study. Identify and justify a randomization strategy that addresses both of these concerns (1-2 sentences).

Blocked, stratified randomization. Blocking ensures equal numbers in each study arm; stratification by urban-rural setting prior to randomization guarantees that the distribution of urban to rural settings is even across study arms.

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

d. As the study progresses, study personnel raise a concern that information from the media campaigns is being reposted on social media platforms that all study participants have a chance to see. What potential problem is this? If it is occurring, how might it affect the effect you estimate?

Week 5, Tab 1 Problems. #4

Observational evidence has indicated that increasing access to playgrounds (building new playgrounds or renovating existing ones) for young children can reduce the risk of childhood obesity. In addition, data suggest that mass media campaigns can influence norms around gender roles, leading fathers to spend more time playing with their young children. You want to test whether these interventions (increasing playgrounds and mass media campaign) can improve children's physical activity. You hypothesize that the two interventions combined will have a synergistic impact of childhood obesity.

d. As the study progresses, study personnel raise a concern that information from the media campaigns is being reposted on social media platforms that all study participants have a chance to see. What potential problem is this? If it is occurring, how might it affect the effect you estimate?

Spillover or contamination. It would bias results towards the null by making all groups more similar to each other. Also accepted is non-adherence as this would lead to contamination.

Week 5, Tab 1 Problems. #5

A clinical trial of a drug to reduce hyperactivity in teenagers included 400 subjects, of which 324 took the complete course of medication (either active drug or placebo depending on assigned treatment arm). What analysis should they use to quantify effectiveness? How many subjects would be included?

Week 5, Tab 1 Problems. #5

A clinical trial of a drug to reduce hyperactivity in teenagers included 400 subjects, of which 324 took the complete course of medication (either active drug or placebo depending on assigned treatment arm). What analysis should they use to quantify effectiveness? How many subjects would be included?

The investigators should conduct an intent-to-treat analysis. For this analysis, the investigators should use all 400 subjects.

Week 5, Tab 1 Problems. #6

Which phase of a trial is most often designed as a RCT?

I

II

III

IV

Week 5, Tab 1 Problems. #6

Which phase of a trial is most often designed as a RCT?

I

II

III

IV

Week 5, Tab 1 Problems. #7

What is the ICC of the following data set? Provide an interpretation of this ICC

Cluster 1		Cluster 2		Cluster 3		Cluster 4	
2	2	3	3	5	5	7	7
2	2	3	3	5	5	7	7

Week 5, Tab 1 Problems. #7

What is the ICC of the following data set? Provide an interpretation of this ICC

Cluster 1		Cluster 2		Cluster 3		Cluster 4	
2	2	3	3	5	5	7	7
2	2	3	3	5	5	7	7

1

There is no within-cluster variance.

Week 5, Tab 1 Problems. #8

Compared to individually-randomized study, a cluster-randomized study almost always requires a sample size with _____ individuals.

A. More
B. Fewer
C. The same number of

Week 5, Tab 1 Problems. #8

Compared to individually-randomized study, a cluster-randomized study almost always requires a sample size with _____ individuals.

A. More
B. Fewer
C. The same number of

Week 5, Tab 1 Problems. #9

Fill in the blank.

In a clustered study design, cluster membership is not at all informative when the intraclass correlation coefficient (ICC) is equal to _____.

Week 5, Tab 1 Problems. #9

Fill in the blank.

In a clustered study design, cluster membership is not at all informative when the intraclass correlation coefficient (ICC) is equal to __ZERO_____.

Week 5, Tab 2 Problems. #1

Fill in the blank.

If individuals who choose to enroll in an intervention are systematically different from those who do not enroll, the study results will suffer from this threat to validity: _____

Week 5, Tab 2 Problems. #1

Fill in the blank.

If individuals who choose to enroll in an intervention are systematically different from those who do not enroll, the study results will suffer from this threat to validity: _____
Selection bias

Week 5, Tab 2 Problems. #2

Background: A previous trial in Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63).
Methods: ObaapaVitA was a trial undertaken in seven districts in Brong Ahafo Region in Ghana. The trial area was divided into fieldwork areas consisting of four contiguous clusters. All women of reproductive age (15–45 years) who gave informed consent and who planned to remain in the area for at least 3 months were recruited. Participants were randomly assigned by cluster of residence to receive a vitamin A supplement (25 000 IU retinol equivalents) or placebo capsule orally once every week. Two clusters in each fieldwork area were allocated to vitamin A supplementation and two to placebo. Capsules were distributed during home visits undertaken every 4 weeks, when data were gathered on pregnancies, births, and deaths. Primary outcomes were pregnancy-related mortality and all-cause female mortality.
Findings: 544 clusters (104,484 women) were randomly assigned to vitamin A supplementation and 542 clusters (103,297 women) were assigned to placebo. The main reason for participant drop out was migration out of the study area. In an ITT analysis, 1326 women died in 292,560 woman-years in the vitamin A supplementation group (453 deaths per 100,000 years) compared with 1298 deaths in 289,310 woman-years in the placebo group (449 per 100,000 years); adjusted rate ratio 1.01, 0.93–1.09; p=0.85.

a) Identify the study design – and be as specific as possible

Week 5, Tab 2 Problems. #2

Background: A previous trial in Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63).
Methods: ObaapaVitA was a trial undertaken in seven districts in Brong Ahafo Region in Ghana. The trial area was divided into fieldwork areas consisting of four contiguous clusters. All women of reproductive age (15–45 years) who gave informed consent and who planned to remain in the area for at least 3 months were recruited. Participants were randomly assigned by cluster of residence to receive a vitamin A supplement (25 000 IU retinol equivalents) or placebo capsule orally once every week. Two clusters in each fieldwork area were allocated to vitamin A supplementation and two to placebo. Capsules were distributed during home visits undertaken every 4 weeks, when data were gathered on pregnancies, births, and deaths. Primary outcomes were pregnancy-related mortality and all-cause female mortality.
Findings: 544 clusters (104,484 women) were randomly assigned to vitamin A supplementation and 542 clusters (103,297 women) were assigned to placebo. The main reason for participant drop out was migration out of the study area. In an ITT analysis, 1326 women died in 292,560 woman-years in the vitamin A supplementation group (453 deaths per 100,000 years) compared with 1298 deaths in 289,310 woman-years in the placebo group (449 per 100,000 years); adjusted rate ratio 1.01, 0.93–1.09; p=0.85.

a) Identify the study design – and be as specific as possible

Cluster randomized RCT, parallel arms

Full credit for cluster RCT.

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Unit of randomization: cluster, group or village (*1 point*)

Technique: blocked randomization (*1 point*)

Week 5, Tab 2 Problems. #2

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C. Calculate an unadjusted measure of association for all-cause mortality and name it. Compare this to the adjusted rate ratio that the authors report. What does this indicate about the randomization?

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C. Calculate an unadjusted measure of association for all-cause mortality and name it. Compare this to the adjusted rate ratio that the authors report. What does this indicate about the randomization?

You can calculate an IDR

(1326 deaths/292560 woman years)/(1298 deaths/289310woman-years)=1.009

This is equivalent to the adjusted estimate (1.01) of the IDR reported by the authors, indicating that randomization was successful.

Week 5, Tab 2 Problems. #2

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D. Do these results support inclusion of vitamin A supplementation for women in either safe motherhood or child survival strategies in Ghana? Why or why not?

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D. Do these results support inclusion of vitamin A supplementation for women in either safe motherhood or child survival strategies in Ghana? Why or why not?

The adjusted results for female mortality do not support vitamin A supplementation as a risk reduction strategy. The adjusted rate ratio 1.01 is very close to the null.

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E. Are these results generalizable to all women? Why?

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E. Are these results generalizable to all women? Why?

No, the eligibility criteria limit the generalizability of this study to reproductive aged women. These criteria challenge the external validity of the results. In addition the target population of reproductive aged women in Ghana is certainly not generalizable to all women in other contexts.

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F. If the authors had done a per-protocol analysis and found different results from the ITT would you expect the result to be closer to or farther from the null than and why?

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F. If the authors had done a per-protocol analysis and found different results from the ITT would you expect the result to be closer to or farther from the null than and why?

The PP analysis would be farther from the null. ITT is generally more conservative and closer to the null because it includes groups as randomized at baseline. Poor adherence would cause this difference between PP and ITT.

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G. If the authors measured adherence by pill counts, and found a 75% adherence rate in the treatment group, but a 50% adherence rate in the placebo group, what would that imply about the placebo control in this trial?

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G. If the authors measured adherence by pill counts, and found a 75% adherence rate in the treatment group, but a 50% adherence rate in the placebo group, what would that imply about the placebo control in this trial?

If adherence rates were substantially different it may indicate that the placebo was not actually a good one, and did not assure blinding among participants.

Week 5, Tab 2 Problems. #2

H. In another study, the investigators had been unable to randomize women to vitamin A supplementation, but knew that about 7% of Ghanaian women regularly used vitamin A. They consider conducting either a cohort study or a case-control study to investigate this question. List a potential strength and limitation of each design for addressing this research question. (2 points)

Week 5, Tab 2 Problems. #2

H. In another study, the investigators had been unable to randomize women to vitamin A supplementation, but knew that about 7% of Ghanaian women regularly used vitamin A. They consider conducting either a cohort study or a case-control study to investigate this question. List a potential strength and limitation of each design for addressing this research question. (2 points)

They could have conducted a cohort study, which would be useful for a rare exposure. Cohort studies can be expensive and time consuming, and are challenging with a rare outcome. Since the outcome itself is rare, the authors could have conducted a case-control study. However, a case-control study can be challenging for the rare exposure we see here. It depends on the budget and time of the study.

Other relevant and correct answers about case-control and cohort studies also accepted.

Week 5, Tab 2 Problems. #2

Imagine that you are having a conversation with a colleague who is interested in conducting an epidemiologic study but has not taken 250F. She refers to RCTs as “the gold standard of epidemiologic research”, and says that if she conducts an RCT her results will be “free of bias”. Write a brief (2-3 sentences) explanation for your colleague of <u>one</u> way in which that assumption could be false and results of an RCT could, indeed be biased.

Week 5, Tab 2 Problems. #2

Imagine that you are having a conversation with a colleague who is interested in conducting an epidemiologic study but has not taken 250F. She refers to RCTs as "the gold standard of epidemiologic research", and says that if she conducts an RCT her results will be "free of bias". Write a brief (2-3 sentences) explanation for your colleague of one way in which that assumption could be false and results of an RCT could, indeed be biased.

There were a number of different answers that received full credit:

1. A discussion of differential adherence in arms of the trial leading to bias in a trial.
2. A discussion of imbalance in baseline covariates and/or unmeasured confounding leading to bias in a trial.
3. A discussion of differential loss to follow-up leading to bias in a trial.
4. A discussion of the consequences of not blinding investigators, analysts, or participants leading to bias in a trial, or of any of them becoming non-randomized
5. A discussion of insufficient randomization/ lack of true randomization.
6. A discussion of poor allocation concealment leading to selection bias

Week 5, Refresher Tab Problems. #1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719054/pdf/pmed.1000125.pdf

Background: Solar drinking water disinfection (SODIS) is a low-cost, point-of-use water purification method that has been disseminated globally. Laboratory studies suggest that SODIS is highly efficacious in inactivating waterborne pathogens. Previous field studies provided limited evidence for its effectiveness in reducing diarrhoea.

Methods and Findings: We conducted a cluster-randomized controlled trial in 22 rural communities in Bolivia to evaluate the effect of SODIS in reducing diarrhoea among children under the age of 5 y. A local nongovernmental organisation conducted a standardised interactive SODIS-promotion campaign in 11 communities targeting households, communities, and primary schools. Mothers completed a daily child health diary for 1 y. Within the intervention arm 225 households (376 children) were trained to expose water-filled polyethyleneteraphtalate bottles to sunlight. Eleven communities (200 households, 349 children) served as a control. We recorded 166,971 person-days of observation during the trial representing 79.9% and 78.9% of the total possible person-days of child observation in intervention and control arms, respectively. Mean compliance with SODIS was 32.1%. The reported incidence rate of gastrointestinal illness in children in the intervention arm was 3.6 compared to 4.3 episodes/year at risk in the control arm. The relative rate of diarrhoea adjusted for intracluster correlation was 0.81 (95% confidence interval 0.59–1.12). The median length of diarrhoea was 3 d in both groups.

Conclusions: Despite an extensive SODIS promotion campaign we found only moderate compliance with the intervention and no strong evidence for a substantive reduction in diarrhoea among children. These results suggest that there is a need for better evidence of how the well-established laboratory efficacy of this home-based water treatment method translates into field effectiveness under various cultural settings and intervention intensities. Further global promotion of SODIS for general use should be undertaken with care until such evidence is available.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

a) Describe the randomization process used in this study. Specifically, discuss the unit of randomization and method of randomization.

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This study is a cluster randomized trial. The unit of randomization is the community (n=22). Communities were pair-matched on baseline incidence of child diarrhea and randomized within each pair to either treatment of control. Treatment allocation was randomized during a public event through a lottery/ball-drawing – note how well described the randomization process is!

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

B. What is the main benefit of randomization? What is a worry you might have regarding randomization when conducting cluster-randomized trials?

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The main purpose of randomization is to ensure that characteristics of participants are as similar as possible across groups at the start of the study – i.e., to control for confounding factors, both measured and unmeasured. Worries regarding randomization may vary. Here are two examples. Because the participants are clustered, the sample size must be larger than if they were randomized as individual participants in order account for the loss of independence among observations. Another worry with cluster randomization is that there could be "contamination" across the clusters; that is, the concern that the outcome of participants who were not randomized to "treatment" will be influenced by the treatment assignments of those participants who were randomized to treatment due to geographic or social proximity to participants randomized to treatment. This will bias the results because some members of the control (or comparison) group are now exposed to treatment.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

C. The authors explain how they assessed compliance (page 3 column 2). Describe why it is important to evaluate compliance (adherence) in trials. How would conducting an intention-to-treat analysis compared to a per-protocol analysis affect the results in this study?

Week 5, Refresher Tab Problems. #1

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If compliance/adherence is low, then there is potential for bias (in particular, selection bias – we will cover this in detail later in the course). People who drop out of studies or who do not comply with treatment are usually different, and potentially have different outcomes, than those who remain in the study and have good compliance. These systematic differences can lead to selection bias. Using intention-to-treat (ITT) analysis in situations where participants have deviated from their assigned treatment means that the outcomes in the treatment and control groups will be more similiar – i.e., you are less likely to observe an effect of treatment. This means that ITT analysis is "conservative" with respect to potential selection bias (versus a per-protocol/as-treated analysis, which would include in the treatment group only those individuals who actually received treatment, and thus potentially introduce bias). In this study, compliance was particularly low, so the observed effect is likely lower than it would be in a per-protocol analysis.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

D. Discuss how compliance affected efficacy vs. effectiveness in the laboratory setting, previous RCTs and in the Mausezahl study.

Week 5, Refresher Tab Problems. #1

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The authors explain that SODIS has been shown to be highly efficacious in laboratory settings. SODIS has also seemed to be *effective* in previous randomized controlled trials, but the authors note that these previous trials were conducted under highly controlled, unusual settings that enforced high compliance rates. Therefore, such trials might be better described as providing evidence for *efficacy*, since they did not have normal field conditions in which to assess compliance rates. In the Mausezahl study, field conditions were much more typical of the kind of community the intervention is normally deployed in. In this setting, compliance rates were quite low, which meant that the effectiveness of SODIS was also low – in fact they did not find a statistically significant effect of the intervention.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

E. Would it have been possible to blind participants and/or assessors in this trial? Please explain your response.

Week 5, Refresher Tab Problems. #1

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Blinding participants and assessors in this trial would be extremely difficult, if not impossible, as noted by the authors (see pg. 8). The intervention does not lend itself to blinding: the treatment requires active, knowledgeable participation by the families (i.e., leaving plastic water bottles out in the sun), and whether they are participating is visible to all observers, including the community field workers who are assessing compliance. However, this was inherent in the design of the study, and the geographic distribution of the communities helped ensure no cross-contamination.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

F. There were 52 households lost to follow up in intervention communities and 51 households lost to follow up in control communities. Discuss whether their loss to follow up biased the estimate of impact. If not, when would loss to follow up be a concern?

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

F. There were 52 households lost to follow up in intervention communities and 51 households lost to follow up in control communities. Discuss whether their loss to follow up biased the estimate of impact. If not, when would loss to follow up be a concern?

Loss to follow up (attrition) was balanced between both arms, thus we expect that this did not likely bias our estimate of impact. Attrition is a serious concern when there is differential loss to follow-up – this means your groups are no longer balanced.

Week 5, Refresher Tab Problems. #1

Focus on the introduction and methods sections to answer the following questions.

G. The authors included the following ethics statement in the paper: *"The study was approved by the three human subjects review boards of the University of Basel, Switzerland, the University of California, Berkeley, and the University of San Simon, Cochabamba, Bolivia. The Cochabamba and Totora municipal authorities also approved the study and informed consent was obtained from community leaders and male and female household heads prior to implementation of the study. Informed consent was obtained before randomization to the treatment arms. Mildly ill children from households participating in the study were provided with and instructed to use oral rehydration salts, or they were referred by field staff to the local health system where clinical services were provided free of charge. The project provided transport and treatment costs for those patients. All project staff completed training on research ethics."*
SODIS has been shown in lab settings to reduce the number of waterborne pathogens in water. Why is it then considered ethical in this study to randomize the treatment in an experiment?

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SODIS has been shown in lab settings to reduce the number of waterborne pathogens in water. Why is it then considered ethical in this study to randomize the treatment in an experiment?

+2 The intervention was being rolled out to all households in the area at the end OR
+2 There is mixed evidence on the effectiveness of SODIS in real-world settings so there is equipoise
(Also accepted: This is also an easily copied intervention with widely available materials – you are not excluding anyone from using SODIS method on their own volition.)

Week 5, Refresher Tab Problems. #2

- Bent S, Kane C, Shinohara K, Neuhaus J, Hudes ES, Goldberg H, Avins AL. Saw Palmetto for Benign Prostatic Hyperplasia. 2006. New Engl J Med; 354: 557-66.

BACKGROUND Saw palmetto is used by over 2 million men in the United States for the treatment of benign prostatic hyperplasia and is commonly recommended as an alternative to drugs approved by the Food and Drug Administration.
METHODS In this double-blind trial, we randomly assigned 225 men over the age of 49 years who had moderate-to-severe symptoms of benign prostatic hyperplasia to one year of treatment with saw palmetto extract (160 mg twice a day) or placebo. The primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate. Secondary outcome measures included changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values, and the rate of reported adverse effects.
RESULTS There was no significant difference between the saw palmetto and placebo groups in the change in AUASI scores (mean difference, 0.04 point; 95 percent confidence interval, –0.93 to 1.01), maximal urinary flow rate (mean difference, 0.43 ml per minute; 95 percent confidence interval, –0.52 to 1.38), prostate size, residual volume after voiding, quality of life, or serum prostate-specific antigen levels during the one-year study. The incidence of side effects was similar in the two groups.
CONCLUSIONS In this study, saw palmetto did not improve symptoms or objective measures of benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00037154.)

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

A. What type of randomization procedure did the study investigators use?

B. What do you think was the purpose of the run-in period?

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

A. What type of randomization procedure did the study investigators use?

Randomization was *stratified* according to AUASI (symptom severity) score and *blocked* with randomly chosen even-numbered block sizes of <10.

B. What do you think was the purpose of the run-in period?

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

A. What type of randomization procedure did the study investigators use?

Randomization was *stratified* according to AUASI (symptom severity) score and *blocked* with randomly chosen even-numbered block sizes of <10.

B. What do you think was the purpose of the run-in period?

The investigators used the run-in period primarily to assess adherence and exclude people that would not be adherent. It also provided baseline data (reported in the results section) and, though not explicitly stated, might have allowed time for the effects of other medications to “wash out” so that they would not confound the results.

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

C. Who was blinded in the study? Why might you want to conceal treatment allocation from the study investigators? Did the investigators make any attempt to assess if the blinding was successful? How?

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

C. Who was blinded in the study? Why might you want to conceal treatment allocation from the study investigators? Did the investigators make any attempt to assess if the blinding was successful? How?

Study participants, study investigators who administered interventions and assessed outcomes, and data analysts were all blinded throughout the study. Concealing allocation of treatment (or allocation concealment) can help to prevent confirmation bias, or the tendency to try to confirm preconceptions, among investigators.

To assess the success of the blinding of study participants, the investigators asked participants whether they believed they were taking saw palmetto or placebo capsules. At 12 months, 40% of the men in the intervention group believed they were truly taking the intervention, compared with 46% of the men in the placebo group (p=0.38) (This was reported in the results section; apologies for directing you to the intro and methods only). Blinding of participants appeared to be successful. This may have helped prevent noncompliance, underreporting or over reporting of outcomes, and selection bias.

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

D) Why do you think the investigators were comfortable performing an intent-to-treat analysis?

Week 5, Refresher Tab Problems. #2

Focus on the introduction, methods and results sections to answer the following questions.

D) Why do you think the investigators were comfortable performing an intent-to-treat analysis?

The investigators note that loss to follow-up was minimal and balanced between the two groups (see Figure 1). Their assessment of blinding also suggests that non-compliance due to treatment allocation was not an issue.

Week 5, Refresher Tab Problems. #3

Researchers are conducting a placebo-controlled randomized trial to test whether anti-inflammatory medication can prevent preeclampsia (preeclampsia = gestational hypertension = high blood pressure during pregnancy). (5 points)

a. Draw a DAG to show the causal structure underlying the trial data; include the exposure, outcome, and pre-pregnancy blood pressure.

Week 5, Refresher Tab Problems. #3

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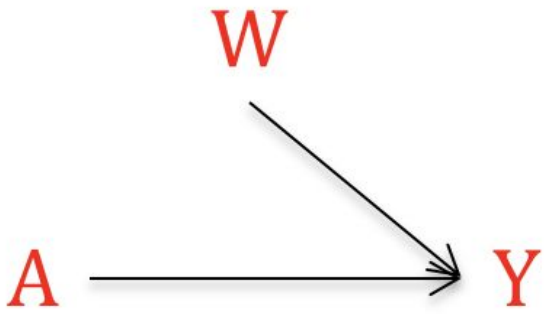
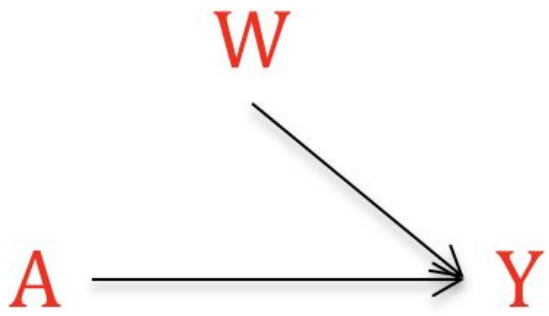
a. Draw a DAG to show the causal structure underlying the trial data; include the exposure, outcome, and pre-pregnancy blood pressure.

A is exposure, Y outcome, and W pre-pregnancy BP in the graph below. There is no line between A and W because A is randomized.



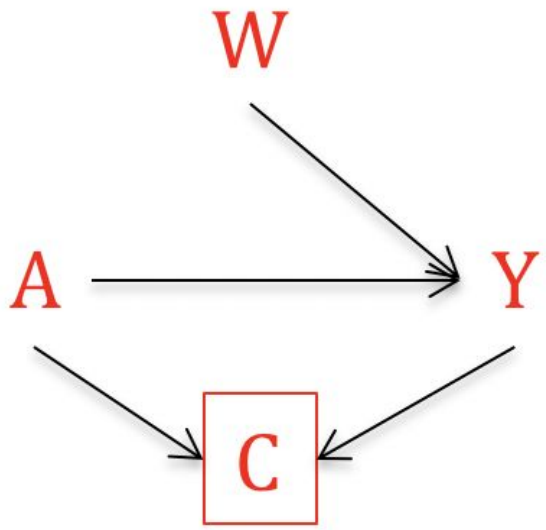
Week 5, Refresher Tab Problems. #3

b. During the trial, participants report minor side effects of the medication; these reports are more common in the treatment arm than the placebo arm. 80% of the cohort remains in the trial throughout while 20% withdraw. Researchers do not know for certain if side effects contributed to retention in the study. The researchers do know that those showing early signs of preeclampsia were more likely to stay in the study. Update your DAG above or re-draw it to include retention in the study and how loss to follow up impacts the existing variables in the DAG.



Week 5, Refresher Tab Problems. #3

b. During the trial, participants report minor side effects of the medication; these reports are more common in the treatment arm than the placebo arm. 80% of the cohort remains in the trial throughout while 20% withdraw. Researchers do not know for certain if side effects contributed to retention in the study. The researchers do know that those showing early signs of preeclampsia were more likely to stay in the study. Update your DAG above or re-draw it to include retention in the study and how loss to follow up impacts the existing variables in the DAG.



Week 5, Refresher Tab Problems. #4

Read the following abstract and answer the related questions below:

Study Objective: This study was designed to evaluate whether immediate (versus delayed) use of Anti Retroviral Treatment (ART) by HIV-infected individuals would reduce transmission of HIV to their HIV-uninfected partners.
Methods: 1,763 HIV-serodiscordant couples (couples with one member who is HIV-infected and one member who is HIV-uninfected) were enrolled. The HIV-infected person was required to have a CD4 cell count that did not require ARV treatment for his/her own health at the time the study began. Couples were randomized to one of two groups. In one group, the HIV-infected person immediately began taking ART (immediate ART group). In the other group, the HIV-infected person began ART only when his or her CD4 cell count fell below the requirement for treatment (delayed ART group).
Results: Among the 877 couples in the delayed ART group, 27 HIV transmissions occurred in one year. This was in contrast to only one (1) transmission that occurred among the 866 couples in the immediate ART group in one year. This difference was highly statistically significant.
Adapted from: HIV Treatment for Prevention Trial (modified from original: www.hptn.org)

Week 5, Refresher Tab Problems. #4

a) What was the unit of randomization in this study? Explain how randomization relates to counterfactuals in 1-3 sentences.

Week 5, Refresher Tab Problems. #4

a) What was the unit of randomization in this study? Explain how randomization relates to counterfactuals in 1-3 sentences.

The unit of randomization for this study was “couples”. Sero-discordant couples were randomized to receive “immediate ART” in the intervention group or “delayed ART” in the control group. The goal of randomization is to create two groups that are as similar to each other as possible at baseline in terms of measured and unmeasured covariates. These groups represent the closest approximation to the true counterfactual populations as we can get. The ideal counterfactual would be to have a group take the intervention (e.g., immediate ART) and assess their outcomes, rewind time, have them take the control (e.g., delayed ART) and assess their outcomes, and then compare the two sets of outcomes

Week 5, Refresher Tab Problems. #4

b) This trial was not a placebo-controlled trial. Explain in 1-2 sentences why you think the authors did not include a true placebo group (i.e., one that received no active treatment).

Week 5, Refresher Tab Problems. #4

b) This trial was not a placebo-controlled trial. Explain in 1-2 sentences why you think the authors did not include a true placebo group (i.e., one that received no active treatment).

Ethical concerns are paramount when conducting randomized controlled trials. ART is highly effective treatment of HIV and it would be unethical to deprive individuals with ART of at least the same level of access to ART they would have without the study (i.e. ART once their CD4 levels fell below the treatment threshold). In addition, because there is an existing standard of care that is believed to partially prevent the transmission of HIV, there would not be true equipoise between providing immediate ART and not providing ART at all. Thus, the investigators chose the existing standard of care as the 'control' and immediate ART as the 'intervention'.

Week 5, Refresher Tab Problems. #4

C. Assuming that the authors believe the results from this study to be *causal,* calculate the *most appropriate* measure of association from the data given in the abstract and provide an interpretation of that measure for the study data.

Week 5, Refresher Tab Problems. #4

C. Assuming that the authors believe the results from this study to be *causal,* calculate the *most appropriate* measure of association from the data given in the abstract and provide an interpretation of that measure for the study data.

From the data given in the abstract, the most appropriate MoA would be a risk difference if the causal effect of the intervention is of interest (no information on person-time is provided so a rate difference is not an option)

Immediate ART group: 866 couples

Delayed ART: 877 couples

	HIV transmission	No HIV transmission
Immediate ART	1	865
Delayed ART	27	850

Week 5, Refresher Tab Problems. #4

C. Assuming that the authors believe the results from this study to be *causal,* calculate the *most appropriate* measure of association from the data given in the abstract and provide an interpretation of that measure for the study data.

From the data given in the abstract, the most appropriate MoA would be an attributable risk if the causal effect of the intervention is of interest (no information on person-time is provided so attributable rate is not an option)

Immediate ART group: 866 couples

Delayed ART: 877 couples

	HIV transmission	No HIV transmission
Immediate ART	1	865
Delayed ART	27	850

$AR = R_e - R_u = (1/866) - (27/877) = -.0296$

Couples in the "immediate ART" group had a 0.0296 lower one-year risk of HIV transmission than couples in the "delayed ART" group.

Among every 100 couples in the "immediate ART" group there were 2.9 fewer HIV transmissions over one year compared with couples in the "delayed ART group"

Week 5, Refresher Tab Problems. #4

D. Despite the fact that there may have been issues with adherence to ART in both the "Immediate ART" and the "Delayed ART" groups, the authors of this study analyzed the HIV outcomes of couples in their study according to the arm of the trial that the couples had initially been randomized to.

I. What kind of analysis is this?

II. Name the primary reason why the authors would have analyzed the data in this way rather than by the actual treatments received.

Week 5, Refresher Tab Problems. #4

D. Despite the fact that there may have been issues with adherence to ART in both the "Immediate ART" and the "Delayed ART" groups, the authors of this study analyzed the HIV outcomes of couples in their study according to the arm of the trial that the couples had initially been randomized to.

I. What kind of analysis is this? Intention to Treat

II. Name the primary reason why the authors would have analyzed the data in this way rather than by the actual treatments received.

Acceptable answers included:
1) a discussion of preserving the benefits of randomization.
2) a discussion of the benefits of estimating effectiveness instead of efficacy.

Week 5, Refresher Tab Problems. #5

The Physicians' Health Study was a randomized, double-blind (participants and investigators blinded), placebo-controlled trial designed to assess the effects of low-dose aspirin on cardiovascular disease and of beta-carotene on risks of cancer. A total of 22,071 U.S. male physicians aged 40 to 84 years were randomized to one of four treatment groups: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or both placebos. Aspirin therapy (compared with placebo) was associated with a reduced rate of myocardial infarction among participants with chronic stable angina (RR = 0.30; 95% CI = 0.14-0.63; p = 0.003).

Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

a) Fill in the blank spaces *(2 points)*:
"This _____(*type of study*) used a _____(*type of design)* to assign treatment."

Week 5, Refresher Tab Problems. #5

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Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

a) Fill in the blank spaces *(2 points)*:
"This randomized controlled trial (*type of study*) used a factorial design (*type of design)* to assign treatment."

Week 5, Refresher Tab Problems. #5

The Physicians' Health Study was a randomized, double-blind (participants and investigators blinded), placebo-controlled trial designed to assess the effects of low-dose aspirin on cardiovascular disease and of beta-carotene on risks of cancer. A total of 22,071 U.S. male physicians aged 40 to 84 years were randomized to one of four treatment groups: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or both placebos. Aspirin therapy (compared with placebo) was associated with a reduced rate of myocardial infarction among participants with chronic stable angina (RR = 0.30; 95% CI = 0.14-0.63; p = 0.003).

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b) Describe the treatment arms used in the Physicians' Health Study.

Week 5, Refresher Tab Problems. #5

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Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

b) Describe the treatment arms used in the Physicians' Health Study.

A+B = active aspirin and active beta-carotene

A = active aspirin and beta-carotene placebo

B = aspirin placebo and active beta-carotene

Placebo (or standard of care) = both placebos

Week 5, Refresher Tab Problems. #5

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c) What was the unit of randomization? Explain in 2-3 sentences how randomization relates to counterfactuals.

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Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.
c) What was the unit of randomization? Explain in 2-3 sentences how randomization relates to counterfactuals.

The unit of randomization was the individual.
Randomization approaches the counterfactual world. The goal of randomization is to create two groups that are as similar to each other as possible at baseline in terms of measured and unmeasured covariates. These groups represent the closest approximation to the true counterfactual as we can get. The ideal counterfactual would be to have a group take the intervention (e.g., aspirin) and assess their outcomes, rewind time, have them take a different intervention (e.g., placebo) and assess their outcomes, and then compare the two sets of outcomes.

Week 5, Refresher Tab Problems. #5

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Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

d) What is the purpose of blinding in the context of this study? *(1 point)*

Week 5, Refresher Tab Problems. #5

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d) What is the purpose of blinding in the context of this study? *(1 point)*

Possible answers:
- Blinding keeps the treatment assignment unknown, so that the participants and the researchers cannot be influenced by its knowledge.
- Blinding reduces bias.

Week 5, Refresher Tab Problems. #5

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Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

e) In the article, the authors state that they "conducted intention-to-treat analysis". i. Explain what is meant by "intention-to-treat" analysis.

Week 5, Refresher Tab Problems. #5

The Physicians' Health Study was a randomized, double-blind (participants and investigators blinded), placebo-controlled trial designed to assess the effects of low-dose aspirin on cardiovascular disease and of beta-carotene on risks of cancer. A total of 22,071 U.S. male physicians aged 40 to 84 years were randomized to one of four treatment groups: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or both placebos. Aspirin therapy (compared with placebo) was associated with a reduced rate of myocardial infarction among participants with chronic stable angina (RR = 0.30; 95% CI = 0.14-0.63; p = 0.003).
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e) In the article, the authors state that they "conducted intention-to-treat analysis". i. Explain what is meant by "intention-to-treat" analysis.

An intention-to-treat (ITT) analysis compares the groups as they were randomized (not based on whether they adhered to the protocol or not).

Week 5, Refresher Tab Problems. #5

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f) What is the advantage of using the "intent-to-treat" analysis compared to the "per protocol" analysis, with respect to bias?

Week 5, Refresher Tab Problems. #5

The Physicians' Health Study was a randomized, double-blind (participants and investigators blinded), placebo-controlled trial designed to assess the effects of low-dose aspirin on cardiovascular disease and of beta-carotene on risks of cancer. A total of 22,071 U.S. male physicians aged 40 to 84 years were randomized to one of four treatment groups: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or both placebos. Aspirin therapy (compared with placebo) was associated with a reduced rate of myocardial infarction among participants with chronic stable angina (RR = 0.30; 95% CI = 0.14-0.63; p = 0.003). Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

f) What is the advantage of using the "intent-to-treat" analysis compared to the "per protocol" analysis, with respect to bias?

Possible answers:

- The original randomization is preserved when the "intent-to-treat" analysis is used. On the other hand, when conducting a "per protocol" analysis the groups (exposed and unexposed) are not randomized and this lack of randomization may introduce bias [2 points for this answer]
- "Intent-to-treat" analysis is more conservative than "per protocol" and has a lower probability of introducing bias [0.5 points for this answer]
- "Intent-to-treat" analysis quantifies effectiveness or how does the treatment work under circumstances similar to those found in daily practice (real world) [0.5 points for this answer]

Week 5, Refresher Tab Problems. #5

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g) Give one reason why the results from this study might not be generalizable to the general population.

Week 5, Refresher Tab Problems. #5

The Physicians' Health Study was a randomized, double-blind (participants and investigators blinded), placebo-controlled trial designed to assess the effects of low-dose aspirin on cardiovascular disease and of beta-carotene on risks of cancer. A total of 22,071 U.S. male physicians aged 40 to 84 years were randomized to one of four treatment groups: active aspirin and active beta-carotene, active aspirin and beta-carotene placebo, aspirin placebo and active beta-carotene, or both placebos. Aspirin therapy (compared with placebo) was associated with a reduced rate of myocardial infarction among participants with chronic stable angina (RR = 0.30; 95% CI = 0.14-0.63; p = 0.003). Adapted from: Ann Intern Med 1995;114(10):835-9; Am J Prev Med 1991;7(3):150-4.

g) Give one reason why the results from this study might not be generalizable to the general population.

1. Trials often have strict eligibility criteria
2. Volunteers might be different from the general population

Week 5, Refresher Tab Problems. #6

A clinical trial of a drug to reduce hyperactivity in teenagers included 400 subjects, of which 324 took the complete course of medication (either active drug or placebo depending on assigned treatment arm). What analysis should they use to quantify effectiveness? How many subjects would be included?

Week 5, Refresher Tab Problems. #6

A clinical trial of a drug to reduce hyperactivity in teenagers included 400 subjects, of which 324 took the complete course of medication (either active drug or placebo depending on assigned treatment arm). What analysis should they use to quantify effectiveness? How many subjects would be included?

The investigators should conduct an intent-to-treat analysis. For this analysis, the investigators should use all 400 subjects.

Example: Testing the Effectiveness of Houvast: A Strengths-based Intervention for Homeless Young Adults

Abstract

Objective:

To test the effectiveness of Houvast: a strengths-based intervention for homeless young adults.

Method:

A cluster randomized controlled trial was conducted with 10 Dutch shelter facilities randomly allocated to an intervention and a control group. Homeless young adults were interviewed when entering the facility and when care ended. Repeated-measures analyses and logistic regression analyses were conducted by the principle of intention-to-treat framework (*N* = 251).

RCT Example: Practice

- **What is the unit of randomization?**
    - Each Shelter
- **Why would the investigators decide to use a cluster randomized trial?**
    - Spillover!
- **What if the investigators rolled out this trial in 10 different counties, 1 county at a time. If they wanted to be sure that the trial has an equal number of control and treatment facilities at each stage of the trial, what kind of randomization might they use?**
    - Block Randomization
        - What would the blocks be?
            - Counties!
- **What if all of the shelters are organized by sex (ie - men's shelters, women's shelters), and investigators are worried about sex as a confounder. They want to make sure there are an equal amount of intervention groups and control groups within each strata of the confounder. What kind of randomization might they use?**
    - Stratified randomization
- **Is this an effectiveness or efficacy trial?**
    - Effectiveness
- **Will the investigators be using an Intention-to-Treat analysis or a Per-protocol analysis? Why?**
    - ITT
        - Benefits of ITT:
            - Gives a better estimate of the *effectiveness* of your intervention
            - Preserves Randomization