PUBH 526 Randomized Trials

Homework 3

1. Read "Eggs in Early Complementary Feeding and Child Growth: A Randomized Controlled Trial" by Iannotti et al. (2017), available on Brightspace.

    a. Describe the study population. (1 point)

    b. Describe the intervention and control treatments in this study. (2 points)

    c. List the inclusion and exclusion criteria. (2 points)

    d. Who among researchers or participants were blinded? (1 point)

    e. List and describe two considerations the responsible IRBs may have considered when reviewing the protocol and tools for this study. (These may be considerations that would have been addressed on an informed consent form, for example.) (2 points)

    f. The authors note, "Children in the egg group showed a higher prevalence of stunting and underweight than the control group at baseline." Why was this surprising? (1 point)

    g. How did the authors attempt to address the baseline imbalance in their analysis? (1 point)

    h. Describe and discuss one limitation of this study. (1 point)

    i. Describe one potential threat to the internal validity of this study. (2 points)

    j. Describe one potential threat to the external validity of this study. (2 points)

    k. What power and significance level were used for the power calculations? (1 point)

    l. Find and review the entry for this trial at clinicaltrials.gov. What are the listed primary and secondary outcomes? How do these compare with the outcomes reported in the paper? (2 points)

NOTE: The following questions are not related to the Iannotti et al. paper.

2. What is one statistical risk of adding a new primary aim after a study has started? (3 points)

3. Your colleagues have conducted a randomized study, but they need help analyzing the data. They have asked you to join them as a collaborator. They will pay you for your time and include you as a co-author on their publications. You agree and start working on the data. The study participants were adults recently diagnosed with a chronic disease, and the study is evaluating a new treatment compared with the standard of care. As you get to know the study better, you learn that the participants were not actually randomized to the study arms; instead, the researchers, who are

physicians, examined each case and decided whether a participant should receive the new treatment or the standard of care. What do you do next? Explain your reasoning:

a) Describe clearly what the ethical issue is here. Do you need any more information to understand the issue? If so, write a question you can ask your collaborators. (2 points)

b) What are some possible alternative actions you can take in this situation? (4 points)

c) Which alternative action would you choose? Which principles or frameworks would you use to make and justify your decision? (There is no single right answer here; you should explain your reasoning.) (4 points)

4. Select the vignette that you found most interesting from the two webinars assigned in Topic 3. Then answer the following:

a) Who experienced the ethical challenge and which sector did they come from (academia/research, government, industry, …)? (1 point)

b) Describe in your own words the ethical challenge they faced. (2 points)

c) How did they resolve the challenge? Which specific ethical guideline(s) informed how they handled the challenge, and how? (4 points)

Homework 3

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PUBH 526: Design and Analysis of Randomized Trials in Public Health

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Read "Eggs in Early Complementary Feeding and Child Growth: A Randomized Controlled Trial" by Iannotti et al. (2017), available on Brightspace.

Question 1.a (1 point)

Describe the study population.

- Infants 6–9 months old and their mothers/primary caregivers from five rural parishes in Cotopaxi Province, Ecuador; n = 163 enrolled.
- Majority of households were rural, indigenous, or mestizo; most mothers were young (mean age $\approx$ 25) and infants were firstborns.
  - At baseline, $\approx$ 41% were firstborn.

Question 1.b (2 points)

Describe the intervention and control treatments in this study.

- **Intervention**: One medium egg ($\approx$ 50 g) daily for 6 months, provided weekly, with reminders and monitoring.
- **Control**: No eggs supplied; both groups received weekly home visits and social marketing for the "Lulun Project" to encourage participation.

Question 1.c (2 points)

List the inclusion and exclusion criteria.

- **Inclusion**: Participants are infants between 6 and 9 months old, singleton birth, in good health, and a caregiver willing to participate.
- **Exclusion**: Participants with congenital heart disease, acute severe malnutrition, and/or known egg allergy.

Question 1.d (1 point)

Who among researchers or participants were blinded?

- In this study, the field team investigators were masked to group assignments (except one staff member managing enrollment/logistics).
- Participants (caregivers and infants) could not be blinded due to the nature of the intervention (eggs are obvious).
- During data analysis, some investigators were blinded for sensitivity analyses.

Question 1.e (2 points)

List and describe two considerations the responsible IRBs may have considered when reviewing the protocol and tools for this study. (These may be considerations that would have been addressed on an informed consent form, for example.)

1. **Food safety/allergy risk**: Informed consent needed to cover monitoring for egg allergy or food intolerance.
2. **Caregiver burden** & **safety**: Weekly visits, blood draws, and child morbidity monitoring to ensure confidentiality, informed consent, and referral to care if illness arose.

Question 1.f (1 point)

The authors note, "Children in the egg group showed a higher prevalence of stunting and underweight than the control group at baseline." Why was this surprising?

- At baseline, the egg group had higher stunting and underweight prevalence than controls. This may seem odd as randomization is expected to balance baseline characteristics across arms. Random imbalance in key outcomes undermines comparability.

Question 1.g (1 point)

How did the authors attempt to address the baseline imbalance in their analysis?

- To address the baseline imbalance in the analysis, the authors adjusted for baseline anthropometric measures, as well as age and sex of the child, using generalized linear models.

Question 1.h (1 point)

Describe and discuss one limitation of this study.

- Birth weight and gestational age were important determinants of growth; however, these factors were not measured in the study, which would limit the interpretation of growth trajectories.

Question 1.i (2 points)

Describe one potential threat to the internal validity of this study.

- A potential threat to the internal validity of this study would be the possible contamination/sharing, as eggs given to index child may have been shared with siblings, diluting the treatment effect.
- In addition, higher baseline diarrhea in the egg arm could confound results.

Question 1.j (2 points)

Describe one potential threat to the external validity of this study.

- A potential threat to the external validity of this study would be the limits regarding generalizability, as results apply to rural Ecuador with high stunting prevalence and cultural acceptance of eggs, but may differ in populations with low stunting, different dietary practices, or poor egg availability.

Question 1.k (1 point)

What power and significance level were used for the power calculations?

- Sample size calculations assumed an effect size of 0.35 SD, followed by an $\alpha = 0.05$, and power = $90\%(1 - \beta = 0.90)$.

Question 1.l (2 points)

Find and review the entry for this trial at clinicaltrials.gov. What are the listed primary and secondary outcomes? How do these compare with the outcomes reported in the paper?

- **ClinicalTrials.gov (NCT02446873)**:
  - **Primary outcomes**: Serum/plasma biomarkers such as vitamin B12, choline, betaine, polyunsaturated fatty acids, and amino acids.

  - **Secondary outcomes**: Attitudes/beliefs about eggs, dietary diversity/frequency (including egg consumption), and anthropometry (LAZ, WAZ, WLZ, BMI-z).

- **Paper (Iannotti et al., Pediatrics 2017)**:
  - Reported anthropometry (LAZ, WAZ, WLZ, BMI-z), stunting/underweight, dietary intake, and morbidity.
  - Biomarkers (the registered primary) were not in this article but appeared in a separate AJCN 2017 publication.

- **Comparison**:
  - The Pediatrics paper emphasized registered secondary outcomes (growth), while registered primary outcomes (biomarkers) were published separately—consistent with the paper's statement that biomarker outcomes are reported in a separate publication and that the trial is registered under NCT02446873.

Question 2 (3 points)

What is one statistical risk of adding a new primary aim after a study has started?

- Adding a new primary aim after a study has may introduce the risk of inflating the Type I error rate, as it effectively increases the number of hypotheses being tested without appropriate statistical correction (e.g., for multiple comparisons).
  - Appropriate statistical corrections include adjusting α (e.g., Bonferroni, Scheffé), using group sequential designs, and applying alpha-spending functions to reduce the risk of false-positive results.

- Adding new primary aim(s) may also undermine the integrity of pre-specified analyses, as the original power calculations and sample size were not designed to detect effects for the new outcome.
  - This risks data dredging, also known as p-hacking, where researchers capitalize on chance findings through statistical manipulation of data to find patterns which can be presented as statistically significant, ultimately reducing the credibility and reproducibility of the study.

(Homework 4) Your colleagues have conducted a randomized study, but they need help analyzing the data. They have asked you to join them as a collaborator. They will pay you for your time and include you as a co-author on their publications. You agree and start working on the data. The study participants were adults recently diagnosed with a chronic disease, and the study is evaluating a new treatment compared with the standard of care. As you get to know the study better, you learn that the participants were not actually randomized to the study arms; instead, the researchers, who are physicians, examined each case and decided whether a participant should receive the new treatment or the standard of care. What do you do next? Explain your reasoning:

Question 3.a (2 points)

Describe clearly what the ethical issue is here. Do you need any more information to understand the issue? If so, write a question you can ask your collaborators.

- The ethical issue is that the study was being treated and presented as a randomized controlled trial (RCT), but participants were **not actually randomized**. Instead, physicians assigned treatment based on clinical judgment. This misrepresentation raised concerns about the scientific integrity of the study and may lead to invalid causal inferences.
- The study violated the **ASA's Ethical Guidelines** below:
  - **Principle A.4**: opposes selective interpretation of data or study design
  - **Principle B.1**: requires transparency about how data were generated
  - **Principle D.5**: protects the rights and expectations of research subjects, especially if informed consent was based on randomization.
- **Yes**, I would need more information to understand the issue. I would ask the question:
  - "Did the IRB protocol and informed consent documents mention randomization, and were participants being told that their treatment would be assigned by researchers who were physicians?"

Question 3.b (4 points)

What are some possible alternative actions you can take in this situation?

- **Clarify** from the study investigators to fully understand how treatment assignment occurred and how the study was described in the IRB protocol and consent forms.
- Recommend **reclassifying** the study as observational, since treatment was assigned by physicians rather than randomly. The analysis should then use methods appropriate for observational data, such as regression adjustment and/or propensity scores.

- Advise investigators to **inform** and update the IRB about parts that have been incorrectly represented as random.
- **Withdraw** from the project if the research team refuses to correct the misrepresentation, to avoid participating in unethical scientific conduct.

Question 3.c (4 points)

Which alternative action would you choose? Which principles or frameworks would you use to make and justify your decision? (There is no single right answer here; you should explain your reasoning.)

- I would start by having a direct conversation with the research team to confirm how treatment assignments were made and whether the study was ever described as randomized in the IRB or consent forms.
  - If the participants were not actually randomized, I would recommend changing the description of the study to an observational design and adjusting the analysis accordingly.
- If the team is open to making that correction, I would be willing to stay on as a collaborator. But if they insist on presenting the study as randomized when it wasn't, I would choose to step away from the project.
  - Misrepresenting the study could lead to misleading and unethical conclusions.
- My decision reflects the ASA principles and frameworks mentioned in *Topic 3*:
  - **Recognizing the issue, weighing options, minimizing harm, and acting with transparency.**
  - Being honest about how data were collected (**Principle B**), being accountable for the way research is presented (**Principle A**), and protecting the rights of participants (**Principle D**).

Select the vignette that you found most interesting from the two webinars assigned in *Topic 3*. Then answer the following:

The following answers are based on the first vignette, **Principles A, B, C, and D.**

Question 4.a (1 point)

Who experienced the ethical challenge and which sector did they come from (academia/research, government, industry, ...)?

- The ethical challenge was experienced by **Marsha Levinson**, a statistician who worked in the industry sector, specifically at Pfizer and later as a leader overseeing statistical teams.

Question 4.b (2 points)

Describe in your own words the ethical challenge they faced.

- Marsha described situations during the publication process for clinical trials, where statisticians were sometimes excluded from **authorship**, even when they had made major contributions to the study design, analysis, or interpretation.
- Instead, most were offered only in the acknowledgments section, or worse, nothing at all. Meanwhile, others with less direct contributions were included as co-authors, raising concerns about fairness, transparency, and professional recognition in collaborative research.

Question 4.c (4 points)

How did they resolve the challenge? Which specific ethical guideline(s) informed how they handled the challenge, and how?

- **Individual level**: Initially, Marsha handled these issues individually through conversations with collaborators to argue for the inclusion of statisticians as authors.
- **Organizational level**: Eventually, they took a more formal approach by adopting specific **authorship guidelines** based on established publication standards, such as ICMJE, and implementing an SOP that clarified the process for authorship decisions.
  - Marsha concluded by saying that having procedures helped ensure that statisticians were **appropriately credited** for their work across projects.
- Marsha's decision reflects the ASA principles and frameworks mentioned in *Topic 3*:
  - **Principle A**: Accurately represent the team's contributions and resist unfair authorship exclusion.

- **Principle B**: Proper authorship to achieve transparency on responsibility for the statistical methods and analyses in the publication.
- **Principle C**: SOP ensured fair recognition and respect for all members involved for clear communication with external collaborators.
- **Principle D**: Recognizing authors promotes research accountability to protect the integrity of research findings shared with the public and research participants.