

Considerations for placebo-controlled trial design if an unlicensed vaccine becomes available

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Considerations:

➤ Ethical

- › What is the “right” thing to do?

➤ Epistemic

- › What do we know now, with what uncertainty?
- › What do we need to know in the future?

Ethics consultants

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Questions

- 1.) Are investigators obligated to provide the vaccine (if likely effective) to those in the placebo group? If so, when and under what circumstances? If not, does society?
- 2.) At what point should trial participants be given access to the vaccine?
 - a) Whenever they ask?
 - b) Whenever the vaccine in their trial has been declared effective? When an EUA has been issued for that vaccine? If so, immediately or later?
 - c) When vaccination becomes available in their area for people like them?
 - d) Whenever another vaccine has been declared effective?
 - e) At the end of the minimum period of time specified in the consent & protocol?
 - f) At the end of the planned trial monitoring period for the vaccine group?
- 3.) Under what conditions should a placebo arm be prohibited in planned or ongoing vaccine trials? Under what conditions should assignment to or maintenance of a placebo arm be discontinued?
- 4.) Can alternative designs ameliorate these tensions?



Ethical preliminaries, I

- **Ethical dilemma**: Not a choice between “right and wrong” actions, but between different “right” actions, each justifiable under a different moral framework.
 - › e.g. actions that are good for an individual vs. those that produce the most good for society.
- Resolution almost always requires compromise.
- Compromise minimizes moral injury (a “wrong” or a “harm”), from unfairness, violations of autonomy, or personal or societal harm.

Ethical preliminaries, II

- Societal permission to do clinical research depends on collective trust that the tension between what is best for research participants and what is best for society is acceptably balanced.
- Trust and permission, essential for continued or subsequent participation in future trials, is fragile.
- Trust is reinforced by fairness, transparency and respect for participants in the balancing process.

Ethical preliminaries, III

- Actions deemed most “ethical” can vary in different contexts (aka “background conditions”).
- Context includes the current state of knowledge and uncertainty, and availability of vaccine to an individual in a country or region.
- As the context changes, the ethical calculus can change as well.
- Safety is judged relative to efficacy.

Epistemic preliminaries

- Randomized controlled trials, when they can be performed, provide the most reliable knowledge in biomedicine about specific interventions.
- But!...we can and have derived reliable knowledge from non- or quasi-randomized designs, e.g. vaccine safety surveillance, all of epidemiology, stepped wedge, etc..
- Knowledge of mechanism and biology allow some degree of generalization to people or groups excluded from or not well represented in trials, and strengthen conclusions from non-randomized studies.
- There are many things to learn about these vaccines, not all needing a placebo-controlled RCT design.

There should be No. Bright. Lines.

- **Bright lines are almost always unjustified, the enemy of ethical and epistemic compromise.**
- **Ethics: No ethical perspective dominates another.**
 - › Bright line: “It is unethical to deny an effective vaccine to a trial participant in the placebo arm.”
- **Epistemology: We can learn from both randomized and non-randomized studies.**
 - › Bright line: “You can’t learn anything from a study without randomization.”

What should RCT participants know....

- The study is for the benefit of society, not them, and that the study will benefit society.

But they trust that...

- They will not be exposed to known serious harms w/o commensurate benefit.
- They will be apprised of information relevant to continued research participation.
- They can withdraw at any time.

Pfizer consent

“This study is different from your regular medical care. The purpose of regular medical care is to improve or otherwise manage your health, but the purpose of research is to gather information to advance science and medicine....”

What are possible benefits of this study?

- **“It is not known yet whether the study vaccines may reduce the chance of you getting COVID-19, so you may not directly benefit from participating in the study. Information learned from the research study may help other people in the future.”**

What other choices do I have if I do not join this study?

- **This study is for research purposes only. Your alternative is to not take part in this study.**

Pfizer consent, cont.

What if I join this study and then change my mind?

- If you agree to participate and then change your mind for any reason, you are free to stop participating at any time.
- ...the study team will tell you in a timely manner if new information is learned during the course of the study that could change your mind about continuing in this study. If you decide to withdraw from the study, you may be asked to continue to participate in the study procedures even though you would no longer receive the study vaccine.



What is “owed” to placebo participants.

- Accurate information about the EUA, if granted.
- Freedom to withdraw.
- That they won't be denied vaccine if it becomes otherwise available to them through societal prioritization and local availability.
- Not immediate vaccination in the trial before their turn is called outside of the trial.
- Not necessarily unblinding on demand.
- Potentially, higher priority for vaccine *within their societal prioritization group*.

COVID-19 Context

- We are in a pandemic! Massive health and economic devastation.
- 285K deaths in US in 7 months, and 1K+ deaths/day = roughly 1/1000 average risk of death in next 6 months, and 1/200 chance of hospitalization.
- Individual mortality risks vary by risk of becoming infected (exposure) and mortality risk of infection (age, co-morbidity).
- COVID burden falls disproportionately on minority and economically disadvantaged communities.
- Long term risks from non-fatal COVID are real but poorly understood.
- Large proportions of the US population will not be immunized for many months, and of other countries, perhaps years.



Ethical implications of COVID risks

- Maximum 6 mo. vaccine benefit \approx 1/200 reduction in serious disease and \approx 1/1000 reduction in death.
- This degree of benefit is far lower than the effect of most therapeutics for which we routinely allow placebo-controlled trials, as can be seen in meta-analyses.
- Also, w/o a vaccine many people can lower their risk of infection and thereby lower their COVID risks.
- Therefore placebo-controlled vaccine trials are ethically permissible as long as there are still important things to learn, whose importance are amplified by the pandemic. Such trials may be *infeasible*, but they are not “unethical”.

Vaccine context: What we know (about Pfizer vaccine)

- No long-term experience with similar vaccines.
- Short term efficacy of the 2-dose regimen appears to be very high (95%, CI 90-98%), both for sx and serious disease. Less certainty in age >55 (94%, CI 81% to 99%)
- Short term AEs are minor and reversible.
- Not enough current supply to immunize a majority of Americans over the next 6 months.
- Cold storage and other logistical issues may inhibit potential distribution in middle/low income regions or countries.
- Participants with knowledge and resources can unblind themselves through antibody testing.
- A proportion of the US population is vaccine hesitant or resistant. Some others see early approval as a disincentive to acceptance.

Vaccine context: What we don't know

High priority / concern

- Duration of immunity > 2 mos.
- Effectiveness and safety in kids and in pregnant women
- Subgroup variability in effectiveness or safety
- Long-term vaccine AEs
- Effect on asymptomatic infection or infectiousness
- Effect in previously infected patients

Moderate priority/concern

- Enhanced respiratory disease
- Protection against long-term COVID risks
- Efficacy w/viral changes
- Effect on mortality

FDA Briefing document (pp: 46-48)



Possible adverse scenario

If placebo participants who want vaccine when otherwise eligible are not given access within the trial in the name of scientific rigor:

- 1.) Many will lose trust in the investigators and the trial.
- 2.) Many will leave the trial w/o further follow-up.
- 3.) Some may seek any available vaccine, and may get mixed vaccines, with uncertainty safety and efficacy.
- 4.) Recruitment to future vaccine trials will be more difficult through loss of trust in the vaccine testing system.
- 5.) Appealing to the non-licensure as a reason to deny the vaccine will not get much traction when millions are being urged to get it.

Once a vaccine is made widely available and encouraged, maintaining a double-blinded control group for more than a nominal period is no longer in the investigator's (or regulators') control and undue pressure to do so may undermine the entire vaccine testing enterprise.

Pfizer proposal re continuation

- Offer vaccination to placebo participants > 16 who become eligible for receipt of BNT162b2 according to local or national recommendations. Unblind upon request, and offer vaccine as part of the study.
- Regardless of unblinding, all placebo recipients to be offered vaccination at 6 months and followed for 18 mos. [FDA brief]
- Pharmacovigilance: HERO, DOD, VA, Health care workers, VAERS

“We have an ethical responsibility to inform all ongoing study participants of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA. We will appeal to participants to remain in the ongoing Phase 3 study as originally randomized for as long as possible, ideally until a COVID-19 vaccine has full regulatory approval following the accumulation of 6 months of safety follow-up data after Dose 2. The study team responsible for study conduct would remain blinded ...”

But unblinding participants destroys the randomization.....

Alternative designs, I

Where and when vaccines become widely available to potential participants, we might progress through several classes of designs that will maintain the benefits of randomization while not demanding an exceptional degree of altruism from participants, thereby preserving trust that scientists & regulators care both about the science and the participants.



Alternative designs, II

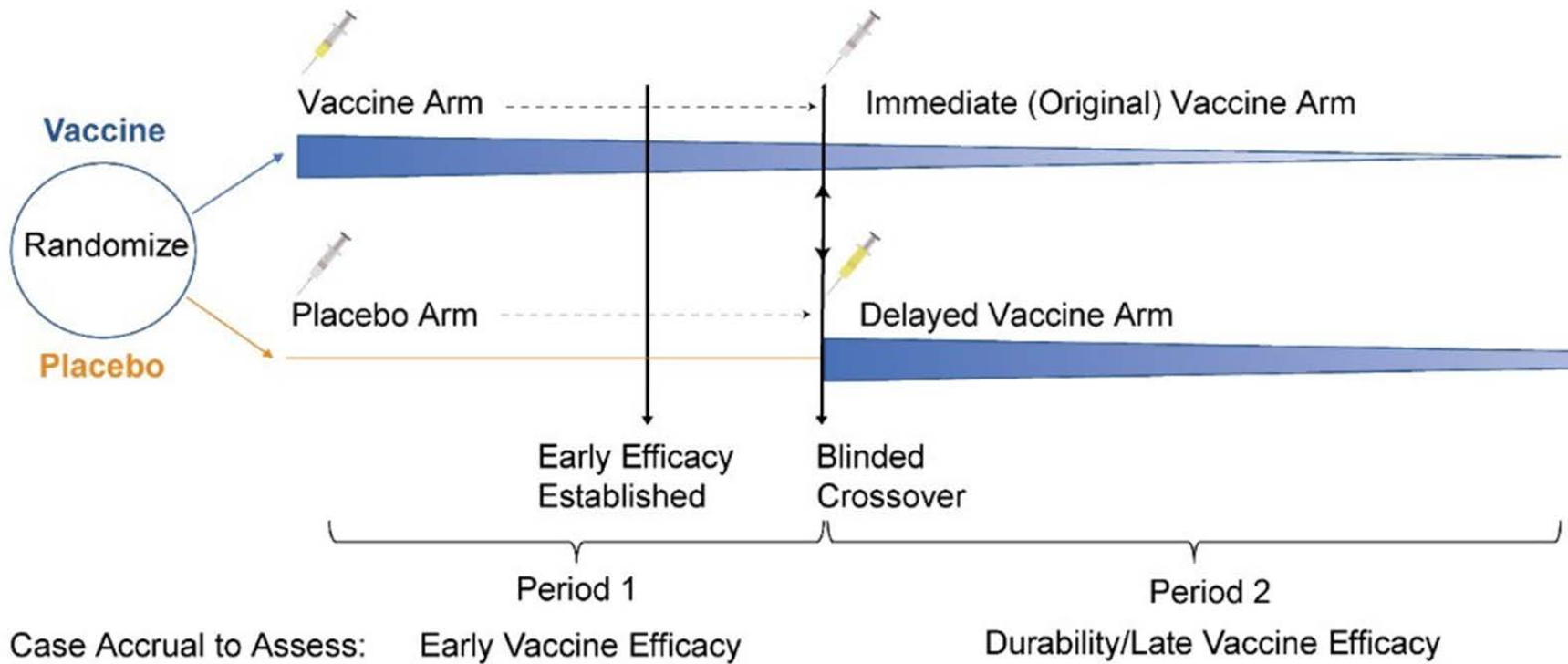
1.) Deferred immunization (Blinded crossover designs)

2.) Active control designs (Best with good surrogate endpoints)

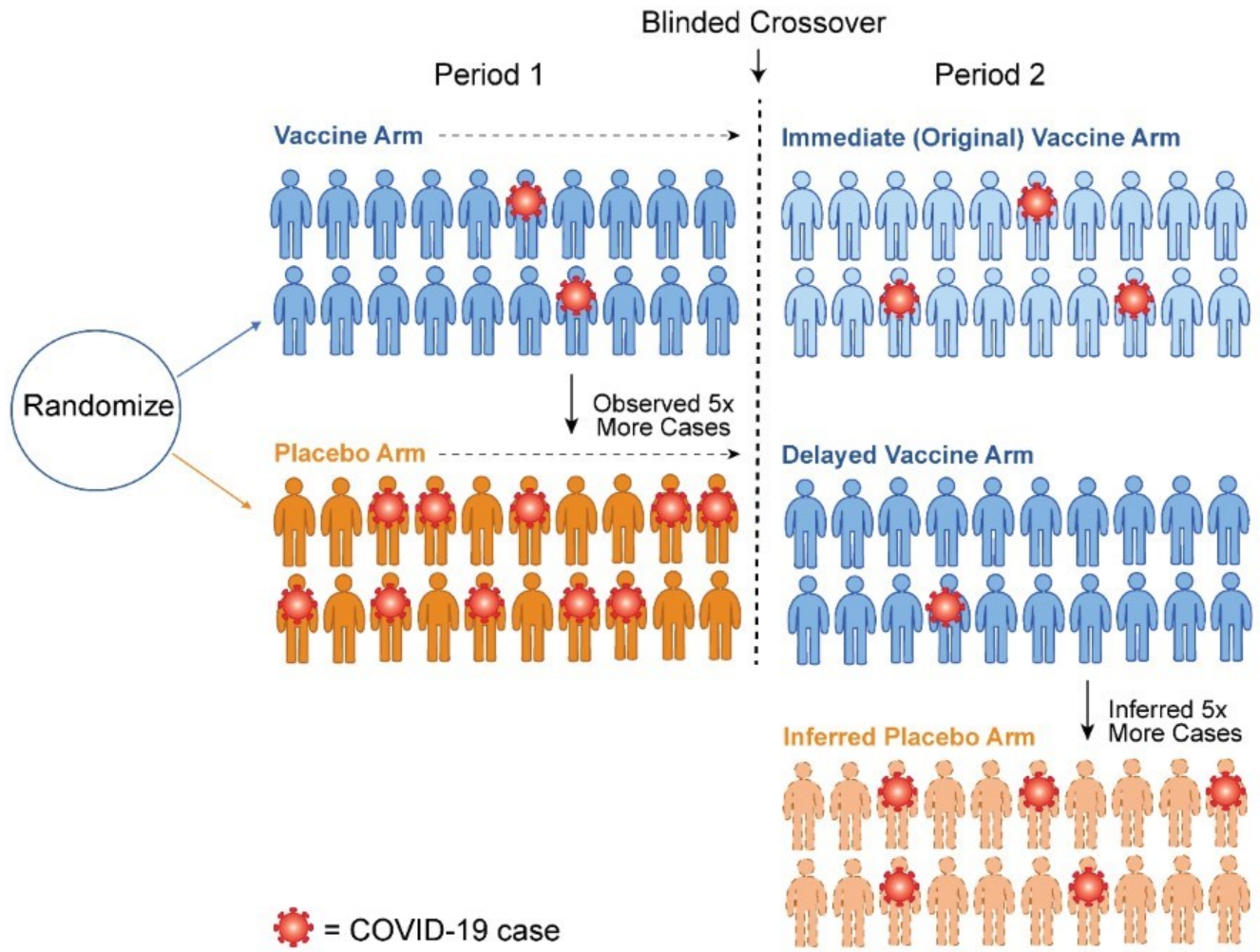
Plus

Active and passive observational studies of RCT participants and the population-based cohorts.

Both approaches require epistemic and ethical compromise.



From Dean Follman, NIAID



From Dean Follman, NIAID

Compromises

Ethical compromise

- We don't provide what is believed to be the best preventive treatment to some trial participants as quickly as desired.
- We conduct placebo controlled trials in areas or among populations for whom vaccine is not available.

Epistemic compromise

- We don't learn as reliably or as quickly about long term safety, infectiousness or other factors (but may strengthen evidence on durability).

Yield

- **Retain the ability to learn about key efficacy parameters in a randomized fashion from current and future vaccine trials.**

Thank you

