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

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Outline

1. Brief summary of previous presentation
2. Moderna consent and proposal
3. The deferred vaccination design: a deeper dive
4. The evidential and ethical effects of partial and complete unblinding of the placebo group.
5. Design evolution

1

Summary:
Ethics & Evidence

3

Ethical summary

- **Ethical dilemma:** Not a choice between "right and wrong" actions, but between different "right" actions, each justifiable under a different moral framework.
- **Trust**: Societal permission to do clinical research depends on collective trust that what is best for research participants and for society is acceptably balanced. Trust is fragile, and what happens in one study affects others.
- **Context**: Ethical calculus is affected by context, which includes what we "know", what we don't, and availability of vaccine outside the trial.
- **Ethically relevant benefit?** The absolute 3 mo. mortality benefit of immunized group is on average, roughly 1/2000.

Epistemic/Evidential summary

All of the following can generate valid evidence, or with different degrees of certainty:

- Randomized controlled trials
- Quasi-experimental and observational designs
- Knowledge of mechanism and biology

- RCTs are best to assess some vaccine properties, but not necessarily all (e.g. rare effects).

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."

2

Moderna Consent and Proposal

7

Moderna consent

You are being invited to take part in a clinical research study, sponsored by ModernaTX, Inc. It is important that you know the following:

- Your participation is voluntary.
- You may or may not benefit from participating in this study. However, your participation may help others in the future as a result of knowledge gained from this study.
- You may choose to leave the study at any time.
- If you choose not to take part or if you leave the study, it will not harm your relationship with your study doctor or the research center.

Moderna consent, cont.

What will happen at the end of the study?

- After completing all of your study-specific visits, you will be discharged from the study at the discretion of the study doctor.

Will you be informed if new information becomes available during the study?

- Your study doctor will inform you in a timely manner of any new information learned during the study that may affect your willingness to continue your participation in this study.

Can you continue getting the study vaccine after the study?

- If you choose to withdraw from the study or are taken out of the study, you will not continue receiving the study vaccine. Also, if the study is terminated early, or when the study is ended, the Sponsor will not continue providing the study vaccine.

Moderna proposal re continuation

- Large crossover anticipated b/c of 25% healthcare workers and others with early vaccine eligibility.
- Proactively reconsent participants who received placebo to be offered mRNA-1273 vaccination and to remain in the trial, enabling ModernaTX to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial.
- Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

But unblinding participants destroys the randomization and thereby a valid comparison group.

What is "owed" to placebo participants.

- What is in the consent.
- That they won't be denied vaccine (e.g. through an exclusion in the EUA) if it becomes otherwise available to them through societal prioritization and local availability.
- Potentially, reciprocity for participation through higher priority for vaccine *within their priority group.*
- Not unblinding on demand.
- Not immediate vaccination in the trial before their turn is called outside of the trial.

3

The Deferred Vaccination Design:
A Deeper Dive

12

Alternative designs

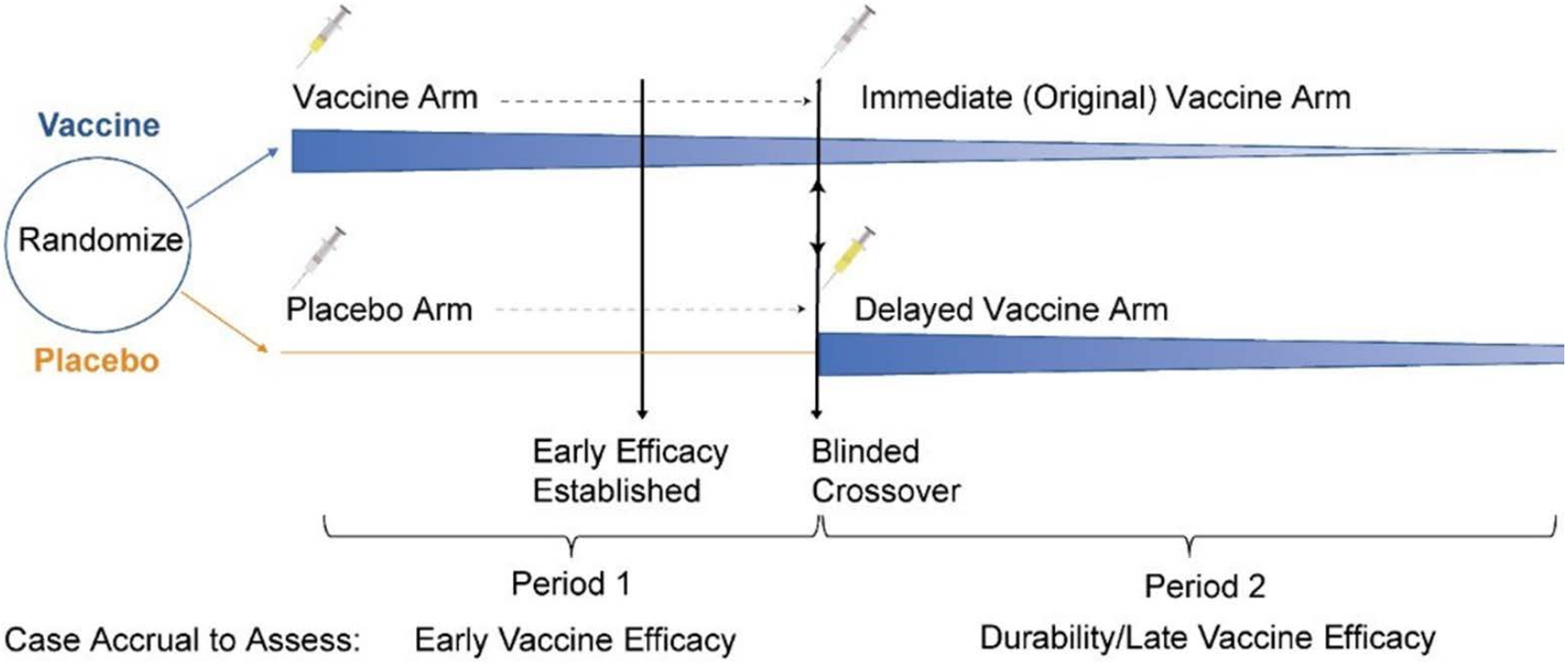
1.) Deferred immunization (Blinded crossover designs)

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

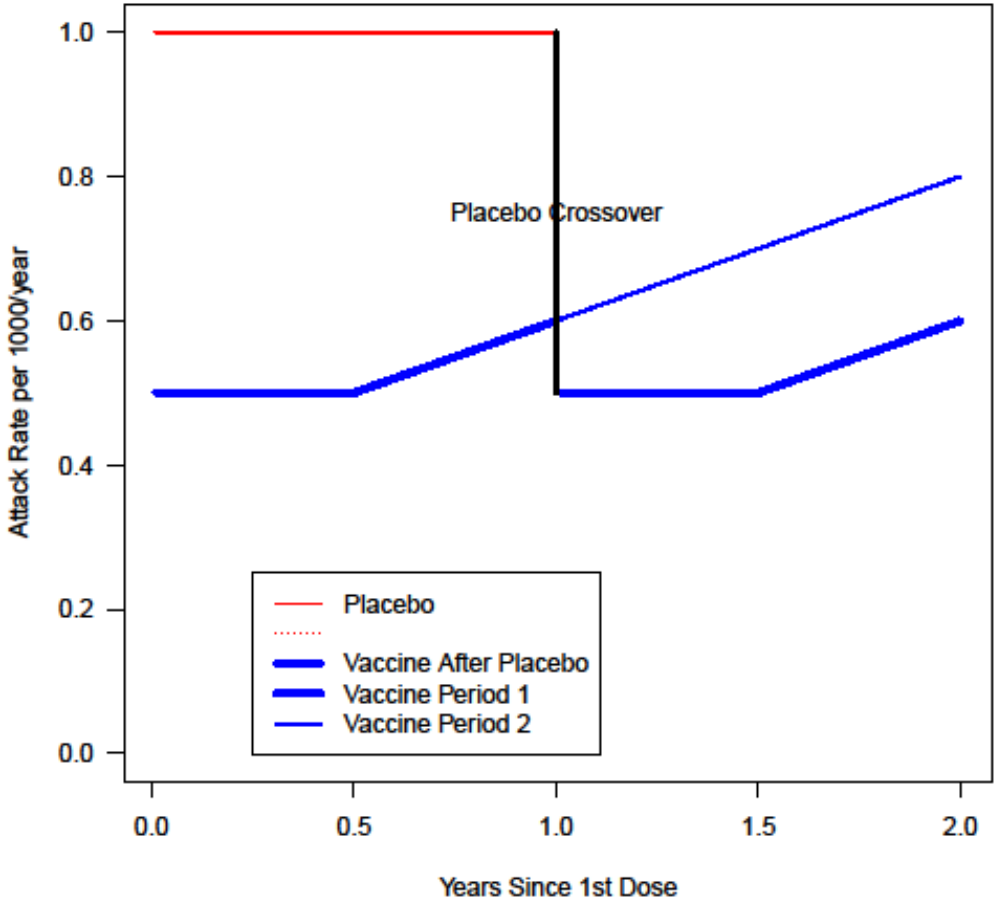
Plus

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

Both approaches require evidential and ethical compromise.



From Dean Follman, NIAID
https://www.medrxiv.org/content/10.1101/2020.12.14.20248137v1



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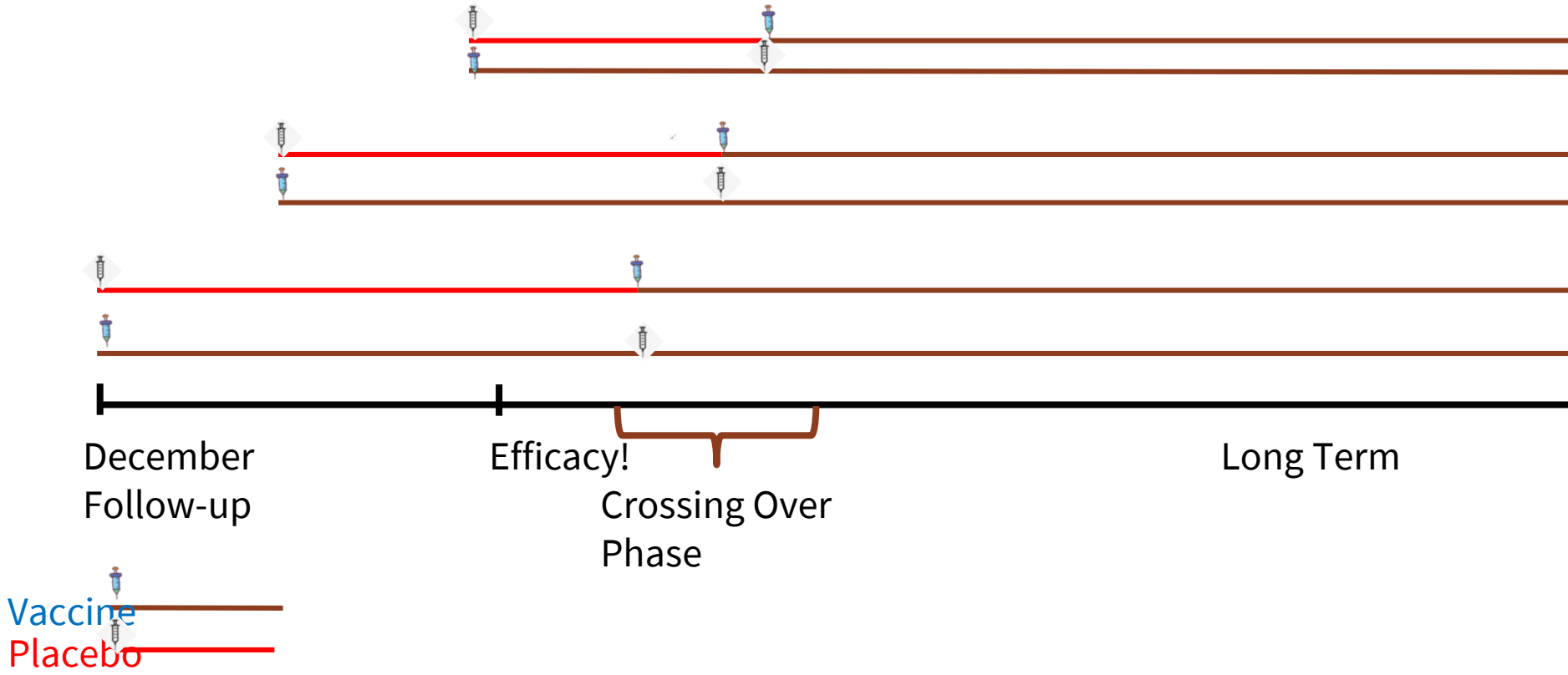
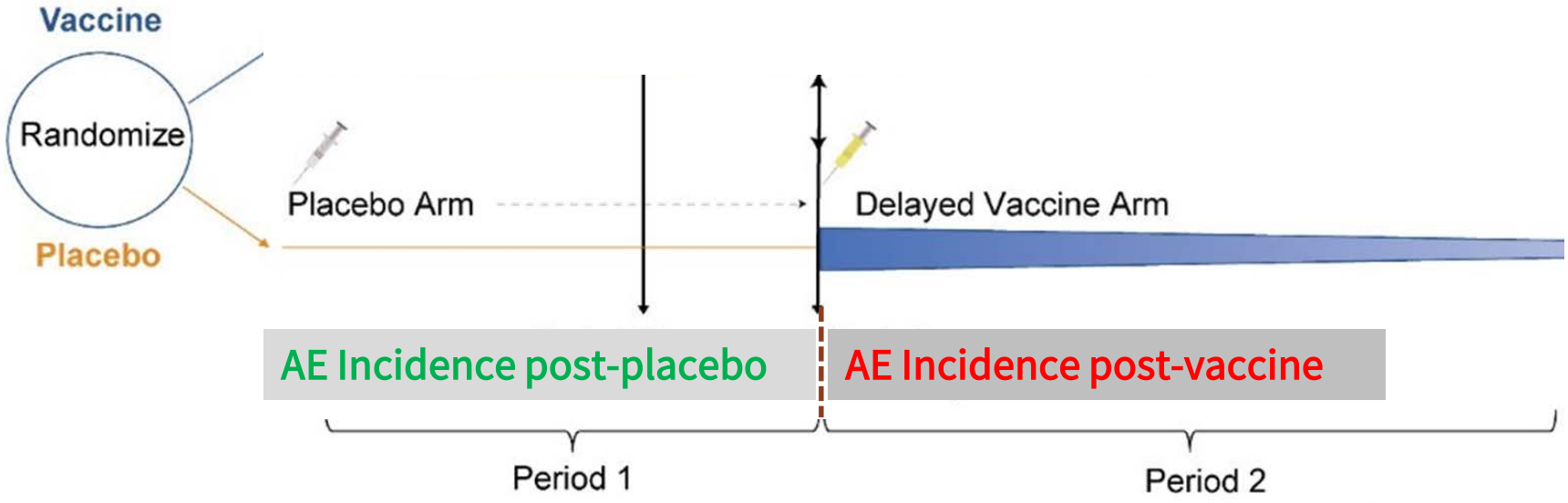
Crossover can occur whenever participant becomes eligible for an available vaccine outside the trial

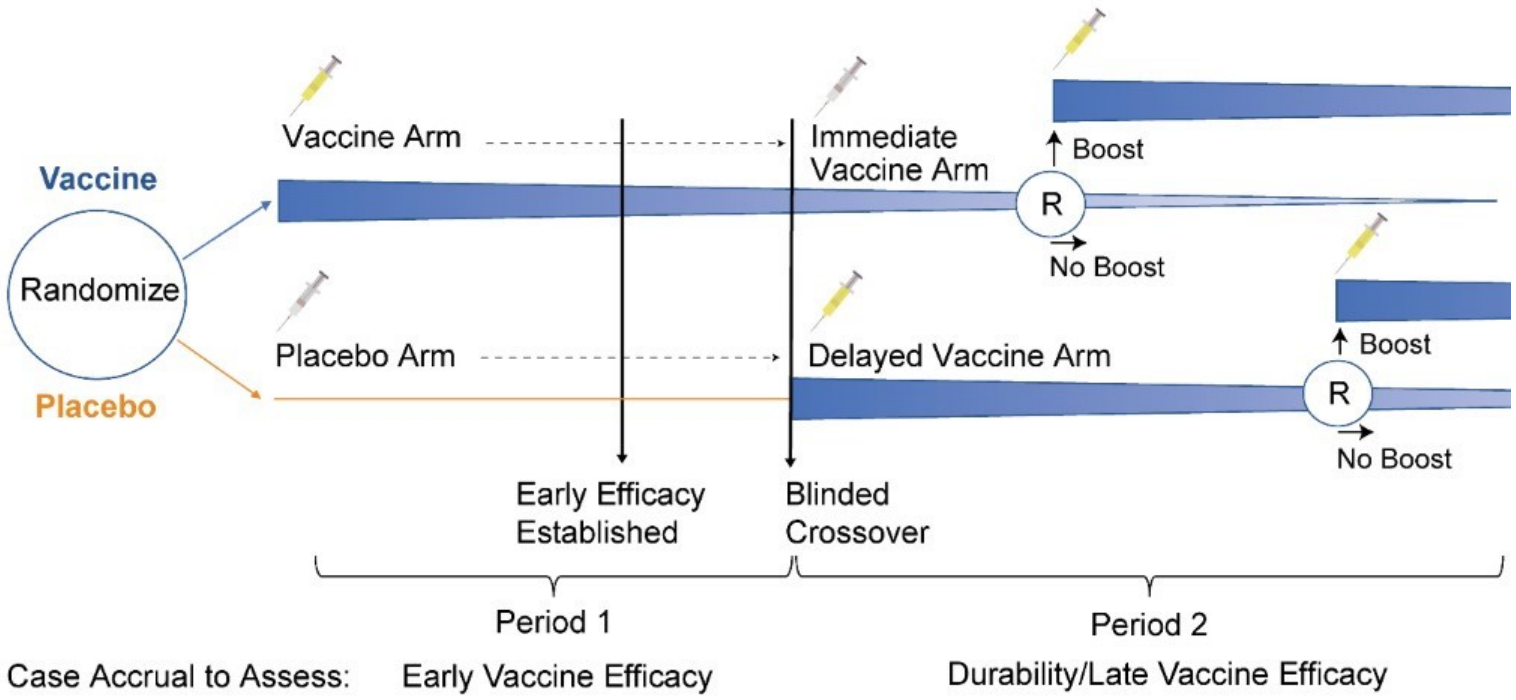


Blinded crossover allows more safety assessment via self-controlled design

AE distribution is compared before and after vaccine *within the same participant.* Powerful technique with 100% control for confounding.



Booster Trial: Ready to go, if needed



Logistics of maintaining blind

- Mandatory crossover serology + a dummy shot
- 1 more visit for 2nd dummy shot for 2 dose regimens
- Possibly more blood draws, which must be at the same times after immunization as in the original immunized group.
- Reconsent – but this is necessary for any major design change, including unblinding.

- BUT! In theory no one knows their assignment and knows this is to guarantee vaccine administration.

Effect of deferred vaccination design on what we need to learn

Efficacy

- Duration of immunity > 2 mos. - Enhanced
- Effect on asymptomatic infection and infectiousness – Other designs needed
- Protection against long-term or rare COVID risks – Partly preserved
- Efficacy w/viral changes – Limited, but partly preserved.
- Effect on serious disease and mortality (imprecise) – Partly preserved
- Correlates of immunity - Enhanced

Risk/benefit

- Effectiveness and safety in kids and in pregnant women
- Effectiveness & safety in subgroups: old, young, ethnicity, +comorbidities, etc. – Partly preserved

Safety

- Long-term vaccine AEs -
- Effect in previously infected patients
- Vaccine enhanced disease

FDA Briefing document (pp: 46-48)

4

Effects of complete or partial placebo unblinding: Evidential and Ethical

21

Effects of partial unblinding of placebo group: Evidential

- The same fraction of the vaccine recipients are unblinded.
- Remaining cohort will probably be lower risk, as higher risk will preferentially request unblinding.
- Higher risk behavior earlier for unblinded vaccine recipients.
- Patient-reported outcomes for unblinded group biased; no clear comparison group. (Headache, myalgia, fatigue, etc.)
- Impaired ability to evaluate waning vaccine efficacy in first 6-8 weeks.
- Unpredictable effect on trial retention, particularly safety assessment visits post-crossover.

Effects of completely unblinding placebo group: Evidential

- No comparison group to compare rates of infection or safety, so duration of protection and long term hazard will be poorly assessable.
- Unpredictable effect on retention.
- Quality of evidence for licensure will be only marginally different than that for the EUA.
- Weakens the scientific value of the trial that is pledged to the participants on enrollment. This should not be done if there are good alternatives.
- This may make placebo controlled trials more difficult for other vaccines, and we have an interest in develop good efficacy and safety evidence for as many vaccines as possible.

What is the value of more vaccines?, I

Efficacy and safety

- Longer or higher vaccine efficacy?
- Vaccines may have different risk/benefit profiles overall or in subpopulations.
- Vaccines in combination or in sequence may be needed to protection against or prevent new viral strains.
- Safety issues may derail some, or a class of vaccines.

What is the value of more vaccines?, II

Distribution / Uptake

- Easier delivery systems; less severe cold chain, single shot, etc.
- Larger collective supply in US and globally.
- Better local manufacturing and distribution of some vaccines.
- More fault-tolerant manufacturing system with diverse pipelines.
- Some countries won't accept vaccines not tested there, or with enough of their citizens.
- Certain vaccine types (e.g. mRNA vs. inactivated virus) may have different acceptability/uptake in various countries or groups.

Effect on ongoing or future trials: Ethical, I

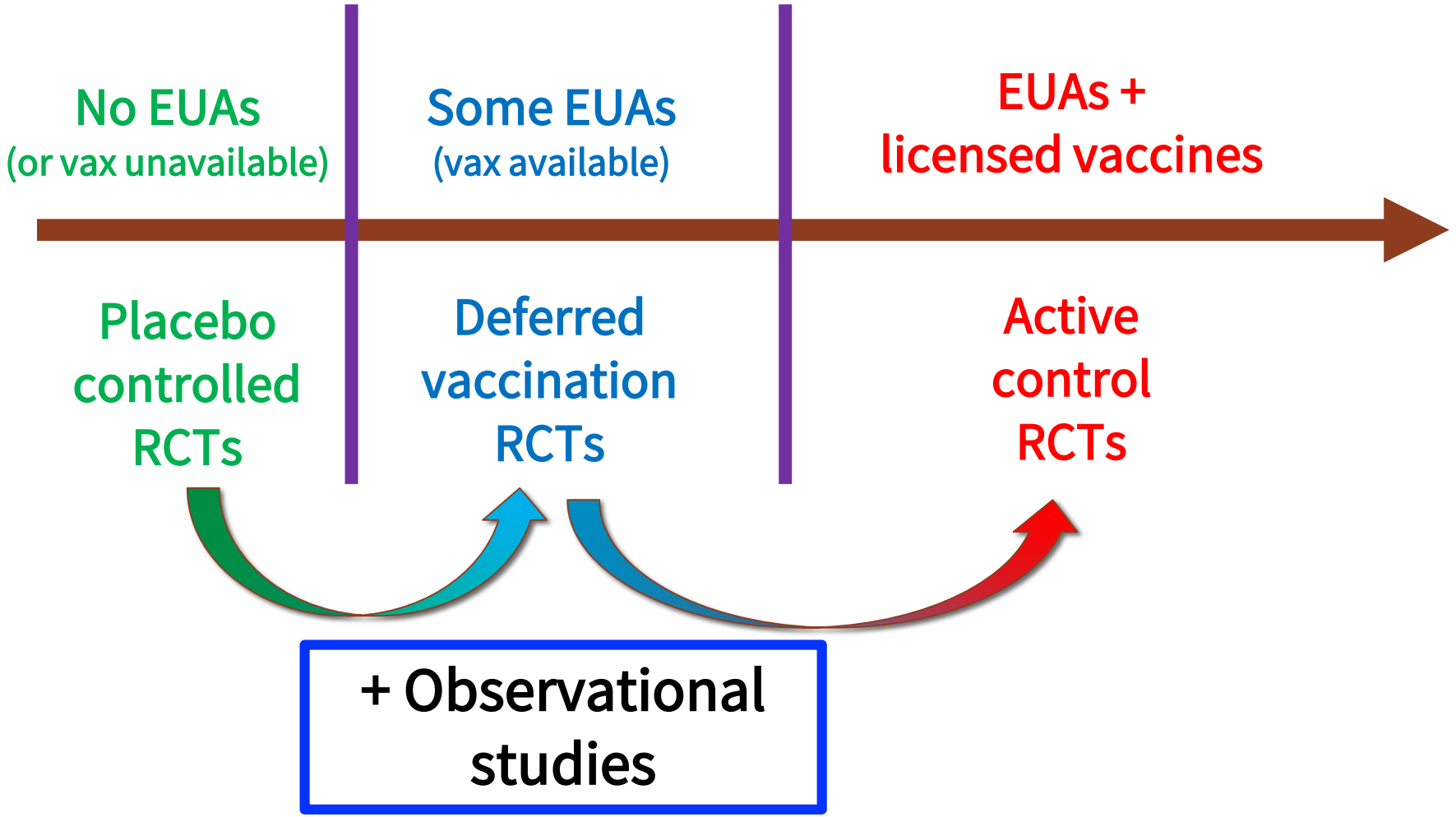
- Immediate unblinding and vaccination will become a precedent and de facto expectation for others, perhaps undermining ongoing or new placebo trials. A sense could take hold that even temporary withholding of vaccination within a trial is “unethical”.
- The images of young, low risk trial participants being knowingly vaccinated before much higher risk community members could adversely affect trust in the fairness of the vaccine testing and allocation system.
- We will then start scrutinizing closely the trial recruitment and enrollment procedures to see how we are choosing those who can jump the queue.

Effect on ongoing or future trials: Ethical, II

- It may be dangerous to have different ethical-evidential tradeoffs made in each trial, by each company, and thereby also bypassing societal priority setting for vaccine access. Those priorities are currently generally regarded as fair, partly because processes that created them is perceived as fair. If these are overridden in individual trials there could be unpredictable effects on perceptions by under-represented groups and the public.
- If these trade-offs are trial and company specific, then there will be a rush by some current and prospective participants to game the system in their individual favor, thereby undermining an ethos that we are all in this together and need to act collectively for the greater good.

5

Design evolution



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Thank you

..and thanks to participants in the trials so far who have enabled us to have this conversation today. Your contribution was and will continue to be an invaluable gift to all of us.