Duties towards research participants in vaccine trials for Covid-19

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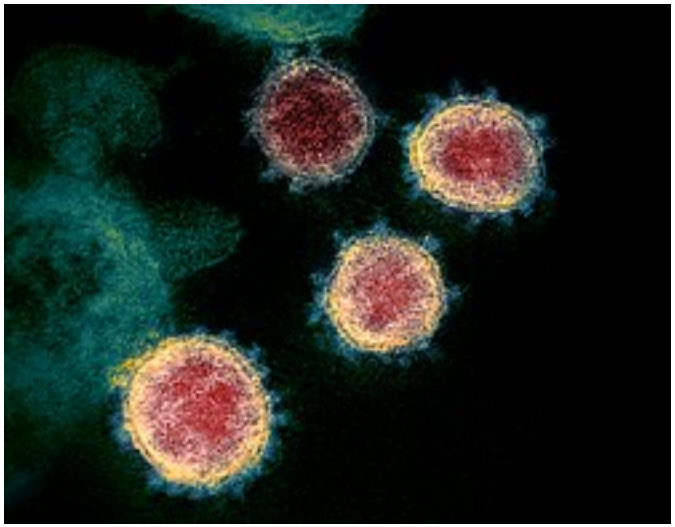
On-going Covid-19 vaccine trials

- 154 vaccine candidates in pre-clinical evaluation
- 44 vaccine candidates in clinical evaluation, including 10 vaccine candidates in or entering Phase 3 testing

(WHO, 19 October 2020)



Guidance

- “Efficacy trials should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial). In that case, discussion with the agency may be necessary to address ethical arguments to break the blind and offer vaccine to placebo recipients.”

(US FDA, 2020)

Two questions

1. If a trial assessing a vaccine candidate shows efficacy, should the vaccine be offered to the placebo recipients in that trial?
2. If a trial assessing a vaccine candidate shows efficacy, should the vaccine be offered to the participants in other vaccine trials?

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Why not provide the vaccine to all?

- Scientific reasons to continue a placebo-controlled trial:
  - More precise estimate of effectiveness
  - Measure duration of immunity
  - Power subgroup analyses
  - Identify rare side effects

The ethical dilemma

- Participants in the placebo arm are known to be at greater risk than participants in the experimental arm
- But, there may be very important scientific questions that can only be answered by continuing the study

Can there be risks of omission?

- Yes
- E.g. a research study that takes patient-participants off effective medication

Is withholding the effective vaccine imposing a risk?

- Would participants have access to the vaccine outside of the study?
- Ought the participants to have access to the vaccine (inside or outside of the study)?

Would participants have access?

- If vaccine authorized by regulatory authorities, *and*
- Participants are from groups that would receive high priority

Ought participants to have access?

- Reciprocity for contribution to research

  But, is this a good reason to stop a socially valuable study?

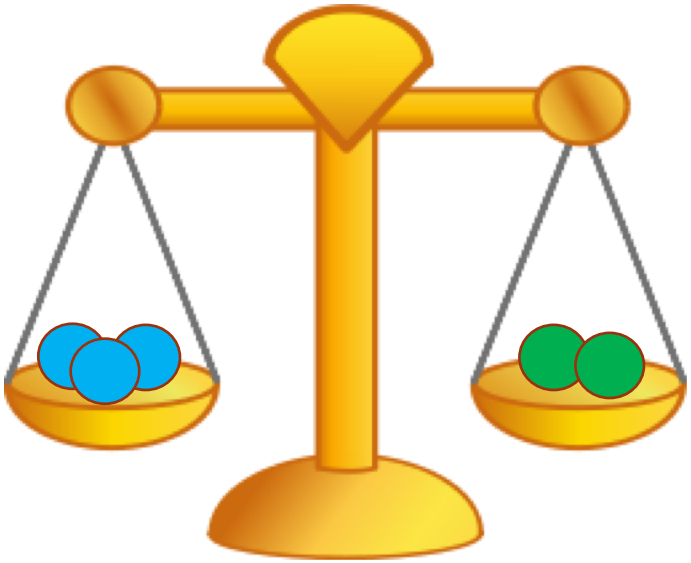
- Duty of beneficence

  But, expected benefit to each participant is low

- If participants in the placebo arm would or should have access to the effective vaccine, then we must evaluate the risk of asking them to forgo it

Risk/benefit assessment

- Risks to participants are minimized
- Net risks to participants are not excessive
- Net risks to participants are balanced by social value of the knowledge gained

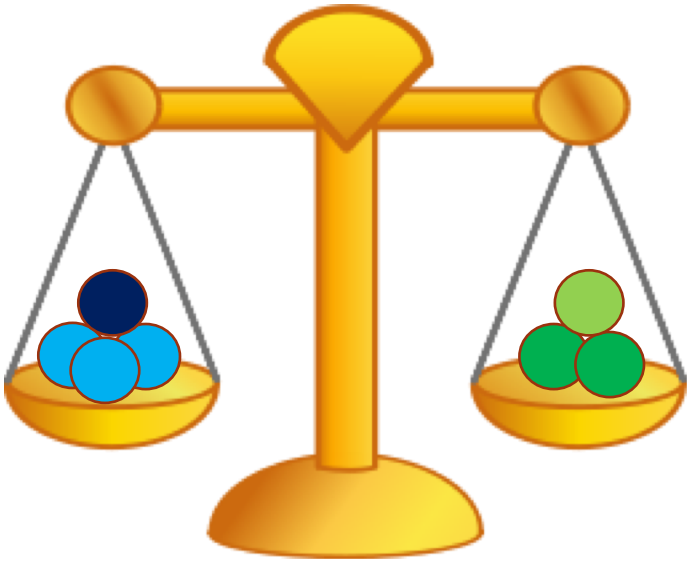


The comparative nature of risk/benefit assessment

- Risks: What is the probability of a participant becoming infected with SARS-CoV-2 with and without vaccination? What are the probabilities and severity of the different Covid-19 outcomes with and without vaccination?
- Social value: What information would be obtained by continuing with a placebo arm versus unblinding and offering the vaccine to all?

Key question

- Does the additional social benefit of continuing a trial as designed justify the additional risks to participants?



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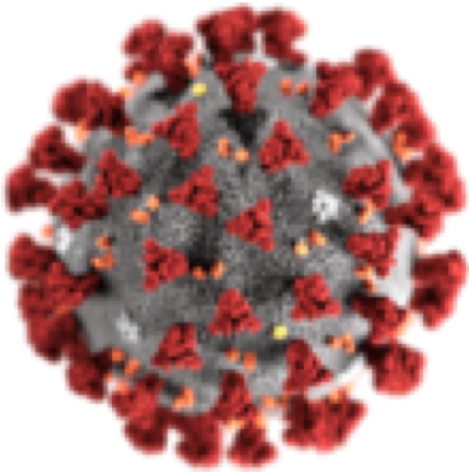
Why continue other trials?

- Alternative vaccines may still be valuable because
  - More effective
  - Longer protection
  - Work in different subpopulations
  - Limited supplies of first vaccine



Can the vaccine be provided?

- Researchers studying one vaccine candidate may not have access to other experimental vaccines

Ought ➡ Can

Cannot ➡ No obligation

Should the vaccine be provided?

- Consider scientific reasons to change trial design,

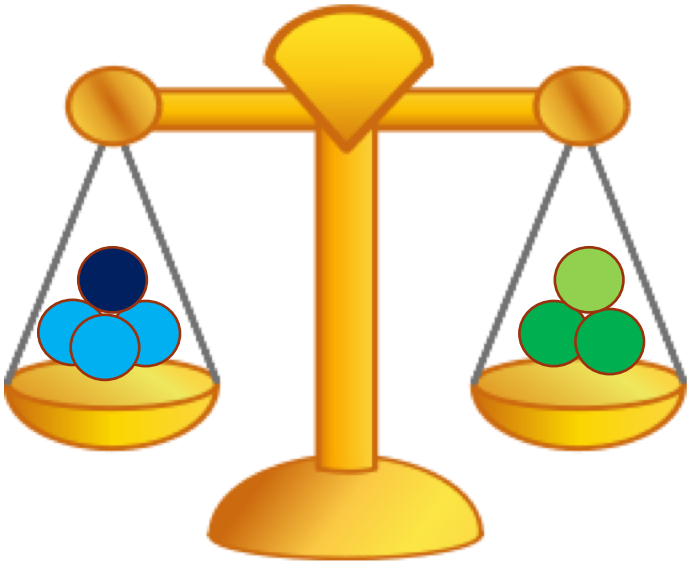
  e.g. relevant question for policy-makers is now: Is Vaccine B as effective as Vaccine A?

- Consider scientific reasons to continue with placebo-controlled trial,

  e.g. trial nearly complete, trial studying different population

Should the vaccine be provided?

- Withholding an available, safe, and effective vaccine is imposing a risk on participants
- Does the additional social benefit of continuing a trial as designed justify the additional risks to participants?



Disclosure and consent

- When knowledge about Covid-19 interventions changes, participants should be told
- If there are opportunities to obtain a vaccine elsewhere, participants should be told

Summary: effective vaccine trial

1. Continue the trial with a placebo group only if there are good scientific reasons to do so
2. Ethical obligation to provide the effective vaccine only if
   - Participants would or should receive the vaccine otherwise, *and*
   - Additional risk of withholding the vaccine is too high

Summary: other vaccine trials

1. Continue the trial as designed only if there are good scientific reasons to do so
2. Ethical obligation to provide the effective vaccine only if
   - It is available, *and*
   - Participants would or should receive the vaccine otherwise, *and*
   - Additional risk of withholding the vaccine is too high

Thank you!

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