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On April 9 2020, WHO's R&D Testing group published a draft call for a large international single trial of SARS-CoV-2 vaccine candidates.[i] This single trial would compare candidates to one another and to a single placebo, as different candidates become ready to test and others, upon sufficient failure per pre-defined criteria, drop out of the platform (1).

With 78 confirmed vaccine candidates in development, five of which are already in clinical evaluation (2), such a shared platform carries great scientific and logistical promise. But would it be ethical, given that some participants would be denied vaccines that, at that point in time, strike the platform's data monitoring committee as more promising? Because the WHO's R&D Testing draft is now up for approval or revision, the new ethical question is pressing. This article explains why this question is novel in the vaccine development realm, and why the answer is affirmative.

How this question is new

Let us relay the fundamental ethical question using for simplicity only two competing vaccines, indicating its novelty.

Suppose that in coming months, Phase III (efficacy) testing is already under way for one vaccine candidate—call it 'A'—*vs.* placebo, and that at that point, the evidence for efficacy is suggestive but not (yet) statistically convincing; or the efficacy is convincingly positive but its degree remains highly uncertain. This is almost certain to happen if A is truly efficacious (because not enough evidence has yet accumulated). It may even happen if A is not efficacious (because of chance differences that happen to show less disease in the vaccinated group). If the testing of A has not been completed, the preliminary evidence regarding efficacy would usually be known to the trial's data safety monitoring board, but not to the investigators; if testing is complete but not yet fully analyzed or not yet peer-reviewed, it may be known to the investigators as well. Imagine further that during this period, another vaccine candidate—call it 'B'—passes Phase II testing and becomes ready for Phase III.

Assuming that some form of testing for the efficacy of these two vaccine candidates is ethical, what would be most ethical—adding B to the existing trial of A (turning it into one of A *vs.* B *vs.* placebo), starting a new trial of only B *vs.* A, or starting a new trial of B *vs.* placebo? Is there some further ethical way to test both?

Existing debates on testing vaccine and treatment candidates usually focus on circumstances different than the one at this "decision point" (as we shall call the moment at which the decision on efficacy testing must be made). Some debates pertain to circumstances where only one candidate countermeasure is being tested. In that case, many would agree that it is ethical to test most vaccines against placebo. Indeed, the efficacy of vaccines against human papillomavirus, dengue, and other infections have been recently tested with placebo control, when there was no licensed alternate vaccine candidate.

Other ethical debates pertain to circumstances at the other extreme, in which an alternative intervention is already approved or otherwise available to some patients (e.g. to patients in richer countries). In that case, debates rage on the ethics of testing alternatives instead of giving the ready countermeasure to all study participants, even if it would not ordinarily be available to

them outside the study. This debate has focused mainly on treatments (3-5), but sometimes on vaccines as well (6).

But our situation falls in the middle, between no alternative and an approved or otherwise available alternative (see Figure 1). The situation we may well face is that an alternative vaccine exists, but it remains experimental. This would not pose special challenges if neither option looked more promising overall (e.g. because while one looked safer in phase I, the other had higher or more rapidly-achieved immunogenicity in phase II). But it is more likely that at the decision point, there will be signs that one of the two alternatives is superior overall (e.g., that by the time of the partly-finished trial of A, all reasonable experts would agree that A is looking superior to B on balance, all things considered, at that point, albeit not proven efficacious enough to terminate phase III early). In such circumstances, where one of the alternatives appears in prospect better than the other, or where A appears better than placebo (but remains unproven), which of the possible designs—continuing evaluation of A vs. placebo, starting B vs. placebo, or comparing A *vs*. B with or without placebo, is ethically permissible?
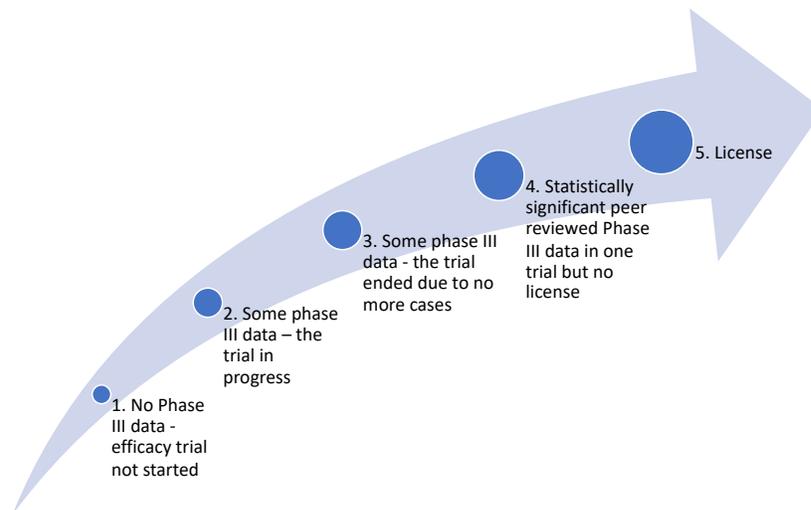

Figure 1: The continuum of evidentiary stages for vaccine candidates around phase III testing:

Note: The future coronavirus vaccine trial dilemma is likely to be 2, while the DRC Ebola situation was a combination of 3 and 4 (for a vaccine candidate that is now at 5).

Note that the main ethical question about WHO's draft—whether at that point it is ethical to randomize between these comparators—is different from the more familiar questions whether treatment assignment should be individually- or cluster randomized (7); whether randomization should be between arms or stepped wedge (7); and whether exposure should be natural or artificial (8).

We shall argue that in the likely near-future situation we described, any of the trial designs—A *vs*. B (with or without placebo), A *vs*. placebo, and B *vs*. placebo—if judged scientifically helpful, could be ethical. Consequently, the WHO draft proposal could be ethical.

How is that possible, given that dramatic compromise of participants' clinical interests in the service of even substantial public health needs would usually be considered unethical (9, 10)? While even a placebo comparator (and hence, a somewhat promising alternate active comparator) is usually considered legitimate for testing vaccines against a disease that is not highly infectious and lethal, or where no better alternative is approved, denial of the most promising countermeasure to people at high risk for SARS-CoV-2 may seem very different. In the mid-90s, both placebo control and less promising arms were controversial in trials for preventing mother-to-child HIV transmission (3-5). And closer to home, in spring 2019, testing new vaccine candidates against Ebola in the Democratic Republic of Congo (DRC) was fiercely opposed by the health ministry, given that a different vaccine (rVSV-ZEBOV) had already been deemed safe and efficacious/effective enough to be dispatched there (11).

Our conclusion, that any of the comparators outlined above could be permissible, and hence that the WHO draft proposal could be permissible as well, is based on several considerations.

No better option for participants outside the trial

In the months immediately following the decision point, at stage 2 in Fig 1, an approved vaccine is unlikely to be rolled out for SARS-CoV-2. Why? Simply because at that point, testing of A is not yet complete (and may still fail) and, if it succeeds, testing, licensure, and scaled manufacturing of A are unlikely to be completed in the period of time for testing B. For this reason, participants receiving B (rather than A) would not be giving up on anything that they would have received outside the trial.

Importantly, this situation would be very different from the spring 2019 circumstances in DRC (better represented by stages 3 and 4 of Figure 1). There, one of the arms contained a vaccine candidate that was already being dispatched. So there was a reasonable case to be made that that candidate could be otherwise available to the participants in the routine care system. Anyone who felt torn about the situation in DRC could therefore remain unambivalently supportive of the most efficient trial designs in the current crisis.

No better option for anyone outside the trial

It may also be said to be wrong to exploit the candidate participants' desperate or unjust situation in the face of a lethal outbreak. But in the SARS-CoV-2 case we imagine, the trial does not exploit the participants' deprivation of a vaccine available to richer or more connected patients, because the trial discussed by WHO would be taking place before a vaccine is available to anyone outside the trial. At that point, there would be no just or ideal 'standard of care' to depart from.

Again, this is crucially different than the circumstances in DRC (and from those surrounding HIV treatment in the mid-nineties). There, the tested alternative candidate countermeasure could have reasonably been described as the standard of care, so denying it to participants in one or in both arms of a trial would deprive those participants of the standard of care, which some ethicists think is duly deserved by all, potentially exploiting their unjustly dire circumstances. In contrast, at our own decision point, no one in either poor or rich countries, in high-risk or low-risk

populations, is in receipt of the alternative candidate countermeasure. There is no deviation from what would have been *ideal* care for those invited to participate, either.

No better option for participants in any differently-designed trial

Some may however argue that trialists ought to promote the very best interests of study participants, regardless of what is available for them or for others outside the trial. They may claim that it is crucial to do so even at the expense of the scientifically best study design. Any of the alternatives we are discussing gives the participants in at least one arm of the trial less than the very best prospects. If candidate vaccine A looks more promising than candidate vaccine B at the decision point, then any arm in receipt of B or placebo is receiving less than what is most promising at that point. A patient's clinician, thinking only of her clinical benefit, might advise her to take A rather than randomization, which risks allocation to B (if the evidence is strong enough that A is beneficial). It may further seem as though there is a way to test vaccine candidates without these ethically concerning comparators, and the inevitable exposure of participants in at least one arm to less than what is the best prospect for them, namely, vaccine A.

However, there is no way to test A by giving all trial participants vaccine A. Put differently, to offer the very best prospects to everyone in the trial would make it hard or impossible to have a valid trial. For what would the trial consist in, if not in comparison of A to something else—to these candidates, or to placebo? Admittedly, early on in discussions of the Ebola outbreak in West Africa, some proposed a single arm follow-up which compares the trial results to the grim realities in the surrounding population; or rolling out an untested vaccine candidate and following up later; or combining these approaches with early monitoring for any striking results, e.g. many of those vaccinated/unvaccinated die or become infected (12, 13). Tellingly, these alternatives were completely abandoned after initial conversations. No one now thinks a nonrandomized observational study with historical comparators is a way to test a vaccine. To prevent even temptation to revert to these proposals, let us explain why.

When it comes to an *emerging* infection, we always know very little about its infection rates and what local and temporal factors may affect them; put another way, infection risks have natural dynamics, rising due to contagion and falling due to the buildup of herd immunity and/or imposition of control measures (14). The numbers on Coronavirus notoriously keep fluctuating. This means that historical controls are in no way representative of what would have happened to an individual at a later time, if they had not been vaccinated. So the results of such an observation would be almost entirely uninterpretable – a problem even greater than that faced by historically-controlled trials of treatments, which have been judged uninterpretable (15). And even if we could somehow make sense of them, statistical credibility warranting the mass-scale production of vaccines for large parts of humanity would take years of observational research, or never reach completion. Assuming, therefore, that some valid form of testing would be ethical, the single-arm option is already off the table.

To be fair, there is always a small chance that a striking result would emerge early in a one-arm trial. But that chance is, well, small. Given the stakes, it would be reckless to adopt a solution that gives us only a small chance of saving millions of lives through a proven vaccine.

The broad acceptability of similar designs for therapeutics

The WHO R&D Blueprint draft can be seen as a proposal for an adaptive platform trial, a recent newcomer in drug testing, only applied to vaccines in the circumstances of a global public health emergency.

Adaptive platform trials "study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm" (16). Many use "response-adaptive randomization… rules to preferentially assign interventions that perform most favourably, rules to trigger the addition or termination of a study arm, or rules to transition from one study phase to another" (16). Such a common protocol has been recommended for emerging infections in the past, albeit for therapeutics not vaccines (17). While adaptive platform trials may have never been used for evaluating vaccines, the WHO group's proposal translates this strategy for therapeutics to vaccine testing in public health emergency.

Tellingly, even bioethicists who are generally committed to a requirement of "equipoise" in clinical research approve of adaptive platform trials and consider their risk-benefit balances for participants to be fair (18, 19). Since stakes for individual participants of therapeutics trials are usually higher than in ones of prophylactic vaccines, the risk/benefit balance for participants under this strategy should arguably be widely accepted for vaccine testing in the current public health emergency.

A word of warning. In one form of platform trial, "once a drug is proven effective, it's incorporated into the supportive care that all trial patients receive, and the study may continue in order to evaluate the added benefit of other investigational drugs" (17). The parallel of this would usually defeat the purpose in a vaccine study—inasmuch as the proven vaccine already prevents infection. Thankfully, the WHO group's draft includes no such plan. A better way to combine the most valid and expedient trial designs with near-optimal service of the participants' medical interests is committing in advance to offering the most promising candidate vaccine candidate to all participants who did not receive it (and are not known to have been infected yet), at least once data collection is completely over—if they wish to receive it and it remains promising (1, 20).

Practical implications

Comparison of the efficacy of vaccine candidate A to that of vaccine candidate B; or of that of A to placebo; or of that of B to placebo can all be permissible even after preliminary efficacy testing results about A and/or B start coming in and make A presumptively preferable. Indeed, an adaptive platform trial would be very suitable, and WHO's R&D Testing draft offers participants a fair balance of risks to benefits.

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