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The best of one, but not both worlds

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Many thousands of volunteers are participating in clinical studies of vaccines against COVID-19. What happens to those of them who were not vaccinated when the vaccine is rolled out to the rest of the population?

Photo: Einar Nilsen

Over the next few months, parts of the population will be offered a vaccine against COVID-19 (1). At the time of writing, only the mRNA vaccine from Pfizer and Biontech is available in Norway, having been granted *conditional* approval in Europe just before Christmas (2). In the United States, both this and the vaccine from Moderna have been granted so-called emergency use authorisation (2, 3). The preconditions for these schemes are not exactly the same, but in both cases are non-permanent and the manufacturers need to provide more data (2).

So far, there are sound data to indicate that the vaccines protect against development of clinical illness and that the adverse effects are mild and transient (2). The benefits of the vaccine are considered to far outweigh the risks (2). However, it is still uncertain whether vaccinated persons can be infected (and infect others), and the efficacy in different population groups and how long the protection lasts are also unclear (2).

Thereby, a dilemma arises. On the one hand, the authorities are requesting more data in order to grant a permanent approval. The best way to obtain such data is to continue the double-blind trials. This means that for the time being, those 70 000 persons who have participated in the trials of the abovementioned vaccines will remain unaware of whether they have been given an active vaccine or a placebo. This could represent an ethical problem, since a vaccine is in fact available (4, 5). Moreover, participants in clinical trials can

reasonably expect to receive the vaccine as soon as it is rolled out, as a reward for risking their own health for the common good (6). This is understandable. But should they really, as long as we do not have all the knowledge that we want?

According to the WHO expert group, continuing the trials is ethically defensible, provided that the participants are informed about their options (7). The alternative, which is favoured by some of the pharmaceutical companies, is to inform all participants as to what group they belong (7). This means losing the control group, and the remaining observation data will be especially vulnerable under unstable conditions with varying infection pressures and behaviours (7). For this reason, the US Food and Drug Administration (FDA) already in October requested the pharmaceutical companies to prepare a plan for what was to happen once the vaccines had been granted emergency use authorisation. The FDA specified that this approval did *not* constitute grounds for terminating the trials (8).

> ***«It is impossible to combine quick vaccination with data of the very best quality»***

Participants who fulfil the criteria for a vaccine in accordance with the regular vaccination programme will nevertheless be entitled to information about their status (7). As the offer of a vaccination is gradually extended to more and more groups, there will be selective attrition from the placebo-controlled trials, and this will complicate the interpretation of the data. In other words, it is impossible to combine quick vaccination with data of the very best quality. At a meeting between the pharmaceutical companies and the American health authorities in December, an alternative design was discussed: a blinded crossover trial, in which all participants are 're-vaccinated', but where those who first had received the placebo now receive the vaccine, and vice versa (9, 10). As a result, everybody will be vaccinated, while the trial retains its controlled conditions with regard to the timeline for immunity, and the cohorts can be monitored going forward.

At the time of writing it is uncertain whether agreement on such a solution can be reached (9, 10). However, if this is the best possible solution in a situation where quick action is called for, we can only hope that it will be feasible. This will bode well for collaboration and development in the new year. Letting the trial participants thereby also jump the vaccine queue could be a well-earned bonus.

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