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CORRESPONDENCE

Large Simple Double-Blind Randomized Trials for the Rapid Assessment of the Effectiveness of COVID-19 Vaccines

TO THE EDITOR—The coronavirus disease 2019 (COVID-19) pandemic has brought not only far too many losses of human lives but an economic crisis as well. Thus, effective treatments and vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are urgently needed. Eyal et al have discussed challenge studies [1] to accelerate the assessment of vaccine effectiveness. In a challenge study, all participants are vaccinated with placebo or with the test vaccine and are then intentionally exposed to doses of SARS-CoV-2. There is already a worldwide initiative to register volunteers for such studies [2]. As all participants have been exposed, the effectiveness of a vaccine can be assessed with smaller sample sizes and possibly more quickly compared to the conventional trial with community participants; however, challenge studies are accompanied by serious ethical issues [3].

First, the characteristics of a distinct group of volunteers without risks for fatal progression or serious late complications of COVID-19 need to be reliably known. Second, a highly effective and safe treatment should be available for patients with COVID-19, so that fatalities and persistent adverse consequences can be avoided. Both these problems are not yet solved. Third, the consent of the volunteer must be with their full understanding of comprehensive information, including appreciation of potential long-term consequences. It may be questioned, however, whether someone at age 20 years or so can imagine the consequences of a scarred lung occurring many years later. Finally, it cannot be taken for granted that a vaccine that works in a challenge study with young, healthy volunteers will work in elderly patients with possible comorbid conditions [4]. Thus, even the social value of challenge trials can be questioned.

Fortunately, there is an ethically more acceptable alternative for an accelerated evaluation of SARS-CoV-2 vaccines. The large, simple, randomized trial (LSRT), as proposed by Yusuf et al in 1984, is a reliable, methodologically and ethically sound alternative [5]. Characteristics of this design include: wide, simple eligibility criteria; central randomization; recording of only few baseline data; simple and short-term treatment; reduced or no follow-up visits; and outcome assessments of hard endpoints, preferably by registries. Using this design, truly large randomized trials with sample sizes beyond 40 000 patients have been carried out and answered important questions [6]. Probably due to the increasing bureaucratization of clinical research activities, including very costly monitoring, in the last 20 years there has been an almost complete disappearance of this trial design. At the current stage of evaluation of the effectiveness of SARS-CoV-2 vaccines, this design should be revived as it is ideally suited for this task. There would be wide eligibility criteria with very few exclusion criteria as the vaccine should become available for almost everybody. The investigational vaccine is a 1 or 2-time treatment only and no follow-up visits are needed. The outcomes, COVID-19 or death, can be collected either by registries available in many countries (eg, in the United States, United Kingdom, or Scandinavia) or by patient reporting. Vaccine safety information can be collected by established systems like the Vaccine Safety Datalink in the United States [7], prescription event monitoring programs (eg, the Drug Surveillance Research Unit in the United Kingdom [8]), or by direct patient safety reporting on websites, including those accessible with smartphones [9], which can be specifically designed for vaccine trials. Among the advantages of using the LSRT design are that it allows central randomization of large numbers of volunteers within a short time and rapid collection of the relevant outcomes at a low cost compared to the conventional phase 3 trials with many follow-up visits and extensive monitoring. Adaptive design features (eg, modification of the eligibility criteria considering the accruing safety information) are feasible as well. Given the wide entry criteria, the results provide external validity for large parts of the population compared to any challenge trial, which would need to focus on participants with extremely low risks for developing serious COVID-19. As there will be very many people who would like to participate in such a vaccination trial, the sample sizes needed should be achieved within a very short time.

When the LSRT double-blind design is used, the validity of the results is assured and it does not generate the serious ethical issues inherent in challenge trials. Regarding the Salk vaccine, large randomized trials with sample sizes of more than 70 000 were done in the early 1950s [10] and such LSRTs should be feasible in 2020. Thus, the sponsors of vaccine trials and the drug regulatory agencies should start the preparatory work now to be ready once an investigational vaccine is ready to be administered on a large scale.

Notes

Disclaimer. The opinions expressed do not necessarily represent those of the Association of Medical Ethics Committees in Germany.

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