Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

COVID-19 vaccine trials: Duty of care and standard of prevention considerations

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1. Introduction

An efficacious COVID-19 vaccine is currently the world's leading research priority. Because of the extraordinary threat to global health posed by the COVID-19 pandemic, global regulators have decided that while it is necessary to characterize the immune response induced by a SARS-CoV-2 vaccine candidate by collecting data in animals, the efficacy of that vaccine candidate in animal challenge models need not be established prior to proceeding to first-in-human clinical trials [1]. As a result, the global effort to develop a vaccine in response to the COVID-19 pandemic has been unprecedented in terms of scale and speed [2]. To date, multiple COVID-19 vaccine trials are in clinical evaluation and pre-clinical trial evaluation, globally [3]. In June 2020, civil society and trade union actors demanded the suspension of a trial testing the preventive efficacy of the BCG vaccine against COVID-19 being conducted on South African healthcare workers (HCW) because of the failure of the trial to provide Personal Protective Equipment (PPE) to trial participants [4]. This is notwithstanding local occupational health and safety (OHS) regulations placing the onus on employers to provide PPE to their employees, and despite a critical shortage of PPE in the country. In September 2020, the AstraZeneca COVID-19 vaccine trial was temporality suspended globally after a previously healthy 37-year-old trial participant in the United Kingdom experienced confirmed transverse myelitis after receiving her second dose of the vaccine [5]. The participant required hospitalisation and treatment for this adverse event [5]. Such incidents highlight that while COVID-19 vaccine trials are proceeding at unprecedented speeds, the duty of care and standard of prevention issues implicit in these trials require urgent but sensitive navigation.

2. Duty of care in COVID-19 vaccine trials

Human volunteer "challenge" trials have been proposed to expedite COVID-19 vaccine trial progression [6,7]. In such trials, volunteers are deliberately infected with a virus to challenge a relevant candidate vaccine. If a participant of such a COVID-19 vaccine trial were to develop serious symptoms after contracting COVID-19, they would require hospitalisation, and, possibly, the provision of critical care services, such as high-flow oxygen or mechanical ventilation. Some may even require longer-term care and rehabilitation. Investigators of such trials would have an ethical duty to ensure that affected participants receive such care. Should human challenge trials come to pass, sponsors, reviewers, and oversight bodies of such trials must assess whether proposed candidate host settings possess such advanced care facilities. If critical care infrastructure is extremely scarce or non-existent in a proposed candidate host setting, or if a health facility that has such infrastructure in the proposed host setting is inaccessible to a study participant, that setting should not host a COVID-19 vaccine human challenge trial. COVID-19 human challenge trials would be inappropriate for some low and middle income settings which lack adequate critical care and rehabilitation services. For instance, at least 10 African countries lack even a single ventilator while dozens more African countries lack adequate functioning ventilators, oxygen supplies, and critical care beds [8]. Similarly, COVID-19 vaccine trials – especially phase 1 trials, where different dosages are being tested for the first time in humans – should not be hosted in settings that lack the capacity to manage potential unexpected severe reactogenicity events associated with vaccine administration that require hospitalization or are life-threatening. The hospitalisation of an AstraZeneca COVID-19 vaccine trial participant in the UK due to apparent vaccine-induced transverse myelitis [5] underscores the imperative to host COVID-19 vaccine trials in settings that are able to offer appropriate standards of care in the event of trial injuries. Had an adverse event of a similar nature to that experienced by the UK AstraZeneka trial participant occurred in a setting that lacked neurological clinical services, the affected trial participant may not have been accurately diagnosed and timeously provided with relevant treatment and care. Allegations that AstraZeneca was not forthright in disclosing the participant's exact diagnosis timeously [5] also underscores the importance of trial transparency, which is crucial to building trust in science, and overcoming vaccine misinformation, disinformation, vaccine hesitancy and vaccine denialism.

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3. Standard of prevention in COVID-19 vaccine trials

In the context of HIV prevention trials, the term 'standard of prevention' has come to mean the risk-reduction 'package' provided to all participants in a prevention trial to help minimise the risk of HIV infection [9]. In its guidance on ethical considerations in biomedical HIV prevention trials, UNAIDS notes that "Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial." [10] Similar ethics considerations apply in respect of COVID-19 vaccine trials. Infection prevention and control measures in the context of COVID-19 includes compliance with hand hygiene, physical distancing, and the use of relevant PPE. Health authorities in several countries [11,12,13] and regions [14,15] have issued guidance on PPE usage. Sponsors and investigators of COVID-19 vaccine trials will have to consider such guidance in determining an appropriate standard of prevention that ought to apply to trial participants in those settings. A differential approach may be necessary if trial recruitment is aimed at distinct cohorts, such as the general public, those who work in health care settings (including long-term care and residential facilities), and those who care for COVID-19 patients at home. In the absence of local guidance or regulations on mask use by the general public in the context of COVID-19, trial investigators and sponsors may wish to consider World Health Organisation (WHO) guidance. WHO recommends that the decision whether to recommend or make mandatory the use of masks should be based on 5 factors: (i) purpose of mask use; (ii) risk of exposure to the COVID-19 virus; (iii) vulnerability of the mask wearer/population; (iv) setting in which the population lives; (v) feasibility; and (v) type of face mask [16]. Further, that the local context, culture, availability of masks, resources required, and preferences of the population should also be taken into account in decision-making. In some settings, political leaders have resisted using or refused to promote the use of face-masks in public as a risk mitigation measure against COVID-19 infection [17]. If a COVID-19 vaccine trial is being hosted in such settings, ethics dictates that COVID-19 vaccine trial investigators should counsel and encourage trial participants who are drawn from the general public to use medical and non-medical masks in areas with known or suspected community transmission, regardless of the local political leadership's official policy or stance on the matter. Recognising that the use of medical masks in the community may divert this critical resource from HCW and others who need them the most, the WHO recommends that in settings where medical masks are in short supply, such masks should be reserved for HCW and at-risk individuals, when indicated. In such settings, COVID-19 vaccine trials would not be ethically obliged to provide medical masks to trial participants drawn from the general public. Should authorities in settings hosting COVID-19 vaccine trials not issue advisories on hand hygiene, physical distancing, and mask-wearing or promote behaviours or issue advisories that conflict with scientific consensus, COVID-19 vaccine trial investigators should consider it their ethical duty to provide trial participants with COVID-19 risk-reduction counselling, relevant PPE, and to advise them on the appropriate use and disposal of PPE. Such provision affirms the ethical principles of beneficence and justice.

International labour law stipulates that employers have the overall responsibility of ensuring that all practicable preventive and protective measures are taken to minimize occupational risks [18]. Employers are responsible for providing, where necessary and so far as is reasonably practicable, adequate protective clothing and protective equipment, at no cost to the worker [19]. Employers are also responsible for providing adequate information and appropriate training on OHS, and consulting workers on OHS aspects associated with their work [20]. Such standards have been codified in domestic OHS regulatory frameworks in many settings. While the provision of relevant occupational PPE is generally the duty of the employer, some settings may not have issued dedicated COVID-19 PPE guidance. Where there is scientific consensus on the efficacy of a particular PPE, COVID-19 trials should make all efforts to provide such PPE to trial participants as standard of prevention even if doing so precedes the issuance of national guidelines on the issue. South Africa's experience with its COVID-19 BCG vaccine trial [4] highlights that standard of prevention concerns amongst HCWs can undermine the conduct of COVID-19 vaccine trials and spur mistrust of scientists. Accordingly, investigators and sponsors of COVID-19 vaccine trials recruiting HCW will have to give careful consideration to what duties are owed to this study cohort if relevant PPE is unavailable or in short supply in the study setting because of unprecedented global demand and supply chain disruptions associated with the COVID-19 pandemic [21].

HCWs who work in COVID-19 care settings where aerosol generating procedures (AGPs) are performed (e.g. COVID-19 intensive and semi-intensive care units), require specialised PPE. In such contexts, WHO recommends that health workers should wear filtering facepiece respirators (N95 or FFP2 or FFP3 standard, or equivalent) [16]. In the absence of AGPs, WHO recommends that health workers providing direct care to COVID-19 patients, should wear a medical mask (in addition to other PPE that are part of droplet and contact precautions) [16]. As many countries are experiencing critical PPE shortages [21,22], trial investigators should give consideration to appropriate alternatives to preferred PPE. WHO notes that in the context of severe medical mask shortages, face shields may be considered as an alternative to medical masks and respirators [16]. WHO considers the use of cloth / fabric masks as an alternative to medical masks inappropriate for the protection of health workers [16]. As such, cloth or fabric masks should not be provided to COVID-19 vaccine trial participants for occupational use in healthcare settings or to those who care for COVID-19 patients at home. Instead, all attempts should be made to provide such trial participants with appropriate medical masks.

In contexts where an employer is not providing PPE because of resource constraints and/or shortages, the provision of relevant PPE to COVID-19 vaccine trial participants, especially HCW cohorts, should be carefully weighed against the risk of such provision becoming an undue inducement to participate in COVID-19 vaccine trials. Prospective stakeholder and community engagement efforts will be crucial pursuant to the conduct of COVID-19 vaccine trials and applicable standards of prevention. As COVID-19 vaccine trials are targeting a wide variety of cohorts (for example, the general public and healthcare workers in different care settings), trial investigators will need to undertake bespoke engagement approaches with different cohort communities to avoid mismatched expectations regarding applicable standards of care and prevention [4]. Vaccines aimed at the elderly, for example, will require engagement efforts that are appropriate for this vulnerable cohort. Similarly, COVID-19 vaccine trials in healthcare settings may necessitate prospective engagement with relevant professional associations and trade unions. The provision of relevant PPE to COVID-19 vaccine trial participants will have budgetary implications and will require engagement with host country authorities, trial sponsors, and relevant civil society stakeholders, such as healthcare and research advocacy groups, unions and professional associations. If trials are providing PPE as standard of prevention, investigators and trial sponsors will have to engage in stringent supply chain management to ensure supply continuity.

4. Conclusion

An efficacious COVID-19 vaccine is currently the world's greatest research priority. While such trials have been rightfully fast-tracked, the moral imperative to pursue a COVID-19 vaccine is not absolute and still entails preconditions for conducting such trials with transparency and integrity. Further, moral imperative is not carte blanche for inattentive trial implementation. Instead, the duty of care and standard of prevention consideration implicit in the conduct of such trials warrant urgent but sensitive consideration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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