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LETTER TO THE EDITOR

Ethical concern regarding the UK PANORAMIC COVID-19 trial

PANORAMIC is an open-label, multi-center, randomized, platform, adaptive, controlled trial, aiming to assess novel SARS-CoV-2 antivirals in the community.[1] This trial, funded by the UK NIHR, has started recruitment of up to 10638 adult participants that will be randomized to receive usual care plus molnupiravir *vs*. usual care, to assess whether this antiviral prevents hospitalization or death in higher-risk patients with confirmed positive SARS-CoV-2 PCR test result.[1] Molnupiravir conditional authorization was based on the interim results of a phase 3 trial (MOVe-OUT) that, on top of usual care, assessed molnupiravir *vs*. placebo.[2] MOVe-OUT included only *unvaccinated* non-hospitalized mild-to-moderate COVID-19 tested positive patients who have at least one risk factor for developing severe illness; these risk factors were related to renal, heart or respiratory chronic conditions, obesity, diabetes, or having >60 years of age.[3] The risks factors considered in PANORAMIC are the same (except for age: now ≥50 years) as in MOVe-OUT, but to 18- to 49-year-old participants several have been added like chronic liver disease, Down's syndrome, severe mental illness, being a care home resident or judged by the recruiting health professional to be clinically vulnerable.[1] Although participants with some risk factors in the MOVe-OUT trial were scarcely present (e.g., 29 cancer patients or 57 with chronic obstructive pulmonary disease)[3] and all participants were *unvaccinated*, molnupiravir's temporary authorization states that it is indicated for any tested positive for SARS-CoV-2 adult patient with at least a risk factor for developing severe illness and regardless of vaccination status.[2] PANORAMIC could be described as a trial assessing, on top of usual care, an 'intervention' (i.e., molnupiravir) *vs*. 'no intervention'.

The principles of the Declaration of Helsinki—to be followed by PANORAMIC investigators[1]—state that the new intervention must be tested against the best proven intervention, and that 'no intervention' could be used if participants not receiving any intervention 'will not be subject to additional risks or serious or irreversible harm as a result of not receiving the best proven intervention'.[4] PANORAMIC's sample size is based on a 33% relative reduction in hospitalization or death in the molnupiravir arm (absolute risk: 2%) relative to control arm (absolute risk: 3%).[1] So, investigators expected that 3% of participants in 'no intervention' arm ($n = 160$) will develop severe illness, that is, hospitalization or death.

Soon after PANORAMIC started recruitment, the NHS established requirements so any (vaccinated or unvaccinated) mild-to-moderate COVID-19 patient who is at highest risk to progress to severe illness could receive molnupiravir (or sotrovimab).[5] In PANORAMIC, there will be participants fulfilling the NHS requirements, such as patients with Down's syndrome, cirrhosis, or with chronic kidney disease: all will have 50% chance to receive 'no intervention'. We believe that PANORAMIC does not conform to the Declaration of Helsinki for *unvaccinated* participants fulfilling the NHS requirements since the trial is exposing these participants to 'additional risks or serious or irreversible harm'.[4] There are no ethical concerns regarding vaccinated participants, since they were not included in MOVe-OUT, and there is the need to gather information on the clinical effectiveness of this antiviral in the vaccinated population. But it would be ethically unacceptable if *unvaccinated* patients fulfilling the NHS requirements and hence eligible to receive active COVID-19 treatment (molnupiravir or sotrovimab) could have the possibility to receive 'no intervention' in PANORAMIC.

Investigators should amend PANORAMIC protocol to solve this issue. They should also amend the participants information sheet to include a description of the requirements that make patients eligible to receive molnupiravir (or sotrovimab) outside the trial, through the NHS. As of 6 February 2022, there are more than 7400 participants enrolled in the trial.[6] Therefore, since the NHS established the requirements to receive molnupiravir treatment on 16 December 2021, several thousands of participants have been inadequately informed in writing when they were invited to participate in this trial. The informed consent form should also include an item to ensure that the participant knows this information. Until the amended documents are approved by the research ethics committee, investigators should verbally inform any potential participant of the possibility of being treated with either of these two COVID-19 medications if they are eligible for it.

Since other novel antivirals will be assessed in PANORAMIC in the future (e.g., nirmatrelvir/ritonavir),[7] investigators and the research ethics committee must ensure that eligible participants for the trial would not be worse off than they would have been outside the trial: participating in PANORAMIC must not entail the possibility of being penalized by receiving 'no intervention'. To this end, the requirements established by the NHS for the prescription of any antiviral outside PANORAMIC, must always be taken into consideration when amending the trial protocol for the evaluation of new antivirals.

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COMPETING INTERESTS

There are no competing interest to declare.

AUTHOR CONTRIBUTIONS

RDR conceived the idea and wrote the first draft of the manuscript. Both authors provided comments and edits throughout the drafting process for important intellectual content. Both authors approved the final version of the manuscript and are accountable for all aspects included in it.

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