

Equipoise, standard of care and consent: responding to the authorisation of new COVID-19 treatments in randomised controlled trials

Soren Holm ,^{1,2} Jonathan Lewis ,¹ Rafael Dal-Ré ³

¹Centre for Social Ethics and Policy, The University of Manchester, Manchester, UK
²HELSAM, Center for Medical Ethics, University of Oslo Faculty of Medicine, Oslo, Oslo, Norway
³Health Research Institute-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid, Madrid, Spain

Correspondence to

Professor Soren Holm, The University of Manchester, Manchester M13 9PL, UK; soren.holm@manchester.ac.uk

Received 28 January 2022
 Accepted 13 May 2022

ABSTRACT

In response to the COVID-19 pandemic, large-scale research and pharmaceutical regulatory processes have proceeded at a dramatically increased pace with new and effective, evidence-based COVID-19 interventions rapidly making their way into the clinic. However, the swift generation of high-quality evidence and the efficient processing of regulatory authorisation have given rise to more specific and complex versions of well-known research ethics issues. In this paper, we identify three such issues by focusing on the authorisation of molnupiravir, a novel antiviral medicine aimed at reducing the ability of SARS-CoV-2 to multiply in the body, for clinical use by the National Health Service in England and the concomitant testing of molnupiravir through the large-scale Platform Adaptive trial of Novel antiVIRals for eARly treatMent of COVID-19 In the Community randomised control trial. By analysing the ways in which the authorisation and clinical use of molnupiravir complicate standard approaches to clinical equipoise, standard of care and participant consent in the PANORAMIC randomised control trial, we will explain some of ethical implications for clinical trials that aim to study the efficacy and safety of new COVID-19 and other therapeutics when conditional authorisation has already been granted and when such treatments have already been made available to patients by national health providers.

INTRODUCTION

One of the research success stories during the COVID-19 pandemic has been the speed at which a few very large, adaptive, randomised, platform trials of potential COVID-19 treatments/interventions have been rolled out and conducted (eg, The RECOVERY trial in the UK National Health Service).¹⁻⁴ These trials have enabled evidence in relation to efficacy to be produced very quickly to inform evidence-based clinical practice. One of the regulatory success stories has involved the modification of medicinal product regulatory processes to provide rapid authorisations of new, pharmaceutical products (eg, the very fast approval of COVID-19 vaccines in the USA, UK and EU).

Because both success stories involve a speeding up of processes that usually proceed at a more stately pace, they can, however, combine to produce research ethics issues relating to: (1) definitions of equipoise in a fast moving environment; (2) decisions about the 'standard of care' or the 'best proven intervention' at a given time; and, consequently, they may (3) create problems in relation

to adequate participant information and informed consent.

By describing and analysing these issues, we do not seek to call into question the suitability of randomised control trials (RCTs) either in general or for the testing of new COVID-19 clinical therapeutics. Rather, by focusing on the concurrent start of large-scale research on molnupiravir and its clinical introduction in the UK, we seek to address some of the normative implications for RCTs when a particular COVID-19 treatment has already been authorised for clinical use.

There is already a considerable literature on whether research ethics processes and/or principles should be modified during a public health crisis like the COVID-19 pandemic. On the one side of this debate, it is argued that there should not be COVID-19 research ethics exceptionalism.⁵⁻⁷ Research ethics processes can undoubtedly be made more efficient and quicker, but they should continue to provide an equivalent level of scrutiny and protection to trial participants. Furthermore, we should not jettison long-established research ethics principles simply in order to facilitate COVID-19 research. On the other side, it is argued that the COVID-19 pandemic presents an opportunity to fundamentally reconsider our research ethics principles and, for instance, change our approach to consent for research-related risks. It is argued that we should allow competent participants to consent to any risk that is equivalent to the risks of the riskiest occupations and activities permitted in our societies.^{8,9} These debates about fundamental questions in research ethics are interesting and important, but the issues we consider here are, in some ways, much more mundane. The particular trial we use as a case study was approved under the existing research ethics framework and the trial protocol itself explicitly commits to ensuring that '... this study is conducted in accordance with the principles of the Declaration of Helsinki'¹⁰ (p. 28).

The UK 'Platform Adaptive trial of Novel antiVIRals for eARly treatMent of COVID-19 In the Community (PANORAMIC)' trial started recruiting in December 2021 to study the efficacy of molnupiravir.¹⁰ Molnupiravir is an oral antiviral medicine that reduces the ability of SARS-CoV-2 (the cause of COVID-19) to multiply in the body by interfering with viral replication.¹¹ It has been known for a considerable amount of time that antivirals for early treatment of COVID-19 are being developed and that they would, at some point, reach the stage where they could be included in a platform trial. The design of PANORAMIC and the



© Author(s) (or their employer(s)) 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Holm S, Lewis J, Dal-Ré R. *J Med Ethics* Epub ahead of print: [please include Day Month Year]. doi:10.1136/medethics-2022-108182

Table 1 Comparison of selection criteria

PANORAMIC inclusion criteria	NHS (England) prescription criteria	MOVE-OUT inclusion criteria
<p>Participant is able and willing to provide informed consent, or their legal representative is willing to provide informed consent; and symptoms attributable to COVID-19 started within the past 5 days and ongoing; and a positive PCR SARS-CoV-2 test; and aged ≥50 years; or aged 18–49 years with one of the following known underlying chronic health conditions considered to make them clinically vulnerable:</p> <ul style="list-style-type: none"> ▶ Chronic respiratory disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication). ▶ Chronic heart or vascular disease. ▶ Chronic kidney disease. ▶ Chronic liver disease. ▶ Chronic neurological disease (including dementia, stroke and epilepsy). ▶ Severe and profound learning disability. ▶ Down's syndrome. ▶ Diabetes mellitus (type or type II). ▶ Immunosuppression: primary (eg, inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood) or secondary due to disease or treatment (eg, sickle cell, HIV, cancer and chemotherapy). ▶ Solid organ, bone marrow and stem cell transplant recipients. ▶ Morbid obesity (BMI >35). ▶ Severe mental illness. ▶ Care home resident. ▶ Judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable. 	<p>Age ≥12 years; and positive PCR test; and at highest risk of getting seriously ill. This includes some people who have:</p> <ul style="list-style-type: none"> ▶ Down's syndrome. ▶ A rare condition affecting the brain or nerves (including multiple sclerosis, motor neuron disease, Huntington's disease or myasthenia gravis). ▶ Sickle cell disease ▶ Certain types of cancer. ▶ HIV or AIDS. ▶ A severe liver condition (such as cirrhosis). ▶ Chronic kidney disease stage 4 or 5. ▶ Had an organ transplant. ▶ Certain autoimmune or inflammatory conditions (such as rheumatoid arthritis or inflammatory bowel disease). ▶ A condition or treatment that makes you more likely to get infections. ▶ Had certain types of chemotherapy in the last 12 months. ▶ Had radiotherapy in the last 6 months. <p>A doctor or specialist will confirm if you are eligible for treatment.</p>	<p>Non-hospitalised adults with mild or moderate COVID-19 were eligible. Key inclusion criteria at randomisation were:</p> <ul style="list-style-type: none"> ▶ SARS-CoV-2 infection that had been laboratory confirmed no more than 5 days earlier. ▶ Onset of signs or symptoms no more than 5 days earlier. ▶ At least one sign or symptom of COVID-19 and At least one risk factor for development of severe illness from COVID-19: ▶ Age >60 years. ▶ Active cancer. ▶ Chronic kidney disease. ▶ Chronic obstructive pulmonary disease. ▶ Obesity, defined by a BMI ≥30. ▶ Serious heart conditions (heart failure, coronary artery disease or cardiomyopathies). ▶ Diabetes mellitus.
<p>PANORAMIC exclusion criteria</p> <ul style="list-style-type: none"> ▶ Patient currently admitted to hospital (inpatient). ▶ Previous randomisation in the PANORAMIC trial. ▶ Currently participating in a clinical trial of a therapeutic agent for acute COVID-19. ▶ Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendice of currently open trial arms. 	<p>MOVE-OUT exclusion criteria</p> <ul style="list-style-type: none"> ▶ An anticipated need for hospitalisation for COVID-19 within the next 48 hours. ▶ dialysis or estimated glomerular filtration rate less than 30 mL per minute per 1.73 m². ▶ Pregnancy. ▶ Unwillingness to use contraception during the intervention period and for at least 4 days after completion of the regimen severe neutropenia (absolute neutrophil count of <500 per millilitre). ▶ Platelet count below 100 000 per microlitre. ▶ SARS-CoV-2 vaccination. 	

BMI, body mass index; NHS, National Health Service; PANORAMIC, Platform Adaptive trial of Novel antivirals for eArly treatMent of COVID-19 In the Community.

ethical approval of the platform trial itself were, therefore, not conducted under any particular time pressure.

PANORAMIC recruits mild-to-moderate COVID-19 patients in the community who are at increased risk of severe illness and hospitalisation on the basis that they present with at least one of the specified conditions that make them clinically vulnerable (table 1).¹⁰ It randomises participants to either the 'Usual Care' group or the 'Usual Care+Intervention' group. 'Usual Care' is defined as 'the currently recommended treatment delivered by responsible clinicians'¹⁰ (p. 10). The content of 'Usual Care' is not specified in the trial protocol as recommended treatments may change and will be tailored to suit individual characteristics. 'Usual Care+Intervention' is defined as usual care plus 'novel antiviral agents (or combinations) targeting SARS-CoV-2, specified by The Antivirals Taskforce (ATF) and with capacity for sequential introduction of each treatment regimen into the trial'¹⁰ (p. 10). PANORAMIC is designed to be able to evaluate up to three different intervention arms at the same time, and the randomisation is adaptive, allocating an equal proportion of patients recruited at a given time to each open arm. At the

time recruitment began in December 2021, 'Usual Care+Molnupiravir' was the only open intervention arm in PANORAMIC and randomisation was, therefore, 50% to each of the two arms. At the time of writing, PANORAMIC has recruited and randomised more than 5000 participants.

Molnupiravir was given conditional marketing authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA) in November 2021 with the indication 'treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness'¹² (s4.1). In December 2021, the National Health Service (NHS) in England issued criteria for the prescription of molnupiravir to patients in certain high-risk groups (see criteria in table 1).¹³ The patients in these groups, who could be automatically identified by the NHS centrally from their care records, were sent COVID-19 PCR diagnostic kits that they can use if they develop COVID-19

¹³Similar decisions have been made by the NHS in Northern Ireland, Scotland, and Wales but we are focusing on England for ease of exposition.

symptoms in order to speed up definitive diagnosis and initiation of treatment. Other patients who have not been preidentified can still be prescribed the treatment if they fulfil the criteria, for instance if they contact their general practitioner when they experience symptoms.

The main evidentiary basis for the issuing of the conditional marketing authorisation and for the NHS criteria for prescription is the phase 2–3 ‘MOVE-OUT’ RCT in *unvaccinated* patients who were over the age of 60 years or who had at least one specified chronic health conditions (table 1).¹¹ The primary end points in this trial were hospitalisation and death of any cause within 29 days. The analysis showed that: ‘... the percentage of participants who were hospitalised or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs 9.7% [68 of 699]; difference, –3.0 percentage points; 95% CI, –5.9 to –0.1)’¹¹ (p. 509). The MOVE-OUT trial raises many interesting questions in itself, not least in relation to the difference in the effect found on the primary endpoints at the interim analysis (n=775), where risk reduction was found to be approximately 50%, and at the final analysis (n=1433), where risk reduction was found to be approximately 30%. Pursuing an analysis of these issues is, however, outside the scope of this paper. The following argument will proceed on the assumption that the MOVE-OUT trial provided some high-quality evidence for the efficacy of molnupiravir as an intervention in the group of patients defined by the inclusion and exclusion criteria of the trial.

EQUIPOISE

It has been argued that a core element for the ethical and epistemological justification of running a RCT is that a situation of clinical equipoise obtains, where clinical equipoise is defined as ‘a state of genuine uncertainty on the part of the expert community regarding the comparative therapeutic merits of each arm in a RCT’¹⁴ (p. 465). It was initially suggested that physicians who recruit to trials should be in ‘personal equipoise’, that is, they should be indifferent to the therapeutic value of the experimental and control treatments.^{15 16} Others have suggested that both clinical and personal equipoise are necessary for a truly unbiased RCT. However, discussions have primarily focused on ‘clinical equipoise’ as a state of genuine disagreement within a community of bona fide expert practitioners.¹⁷ There is a large and complex critical literature on equipoise, and it is, therefore, important to clarify that the argument in this section does not assume the strong position—supported by some commentators, including the authors of this paper—that clinical equipoise is always necessary for a trial to be ethical. However, we also do not assume that a distinction can be made between research ethics and the ethics of care such that equipoise is no longer relevant to the justification of randomisation.¹⁸ Rather, our analysis does, for the sake of argument, assume a weaker claim that, in situations where the equipoise position is uncertain, there is a need for a closer scrutiny of: (1) how randomisation to a treatment known or thought by the expert community to be inferior to the established standard of care can be reconciled with the physician’s duty to protect and promote the best interests of the patient¹⁹; and (2) whether the research-related risk created by the trial is acceptable.²⁰ To clarify, we are not endorsing the view that this weaker claim should over-ride the claim for clinical equipoise, that is, we are not rejecting clinical equipoise in favour of closer scrutiny of research-related risk and the conditions by which randomisation can be reconciled with a duty of care. Rather, we aim to show that, even on this weaker account

of the necessity of equipoise, the inclusion of molnupiravir in PANORAMIC raises very significant ethical questions. The simplest way of explicating the notion of ‘closer scrutiny’ is by drawing a parallel between: (1) standard research-related risks (ie, risks specifically caused by research procedures that are additional to the risks caused by the patient’s condition and the interventions conducted under the auspices of usual care); and (2) what could be called ‘randomisation risk’ (ie, the risk of being randomised to an arm that is known or strongly suspected to be less effective than the clinically prescribed treatment the patient could have received if they declined trial participation (see also Fully informed consent). It is generally accepted that participants can provide informed consent to research-related risk, even though the questions of whether there should be an upper threshold for such risks and how that threshold should be defined are hotly disputed. ‘Closer scrutiny’ could, therefore, be understood as paying specific attention to the risk inherent in being allocated to a known or suspected inferior arm and ensuring that: (1) this randomisation risk falls below the threshold for consentable risk; and (2) that potential participants are fully informed about that risk.

To what extent and for what indications can clinical equipoise be said to exist in relation to treatment with molnupiravir after the publication of the results of the MOVE-OUT trial, the conditional marketing authorisation provided by the MHRA and the drug being made available for prescription by the health system in the jurisdiction in which the platform trial is conducted (in this case the NHS)?

It might be claimed that the decisions of the MHRA and the NHS directly indicate that clinical equipoise has been disrupted. This would, however, be a mistake. These official decisions are, in themselves, only indirect evidence of clinical equipoise. They produce no new evidence as to the efficacy of molnupiravir but merely indicate that the relevant bodies find the existing evidence at a specific moment of time sufficiently convincing to: (1) allow the drug to be prescribed to patients (MHRA); and (2) make the drug available if they meet certain requirements (NHS). It could still be possible that the clinical expert community believed molnupiravir to be of no value. There are drugs that are currently available for prescription where the clinical equipoise position suggests that they have very little or no effectiveness. It is also noteworthy that both decisions allow for the extension of the use of molnupiravir beyond those uses for which direct evidence was provided by the MOVE-OUT trial. Both decisions, for instance, make no distinction between vaccinated and unvaccinated patients, even though the trial only recruited *unvaccinated* patients. In addition, the NHS criteria include adolescents between 12 and 17 years old, a group that was excluded from the trial, as well as those adults with underlying chronic health conditions not studied in the MOVE-OUT trial unless they happened to have been included as a result of being over the age of 60 years. Even though decisions made by regulators or by healthcare systems are not direct evidence of equipoise in themselves, they may influence clinical equipoise. For instance, since some members of the expert community may be aware that their own view is only based on partial knowledge of the available evidence, they may perceive these decisions as being based on a search for and synthesis of *all* the available evidence.

It seems reasonable to assume that the original position in the relevant clinical community was one of equipoise in relation to molnupiravir and that expert members of the community only started to form a view on the efficacy of the intervention as research evidence gradually became available, which pointed to

molnupiravir as a potentially efficacious intervention. From an epistemological point of view, the pre-existing equipoise should be more disturbed as more and better evidence becomes available and should be more disturbed in relation to those questions where the evidence is most directly relevant.¹⁴ For instance, this follows if we model the expert clinical community as consisting of a population of decision makers who update their knowledge and, therefore, decision making following a Bayesian approach.²¹ The members of the community will access different information and their updating will, in most cases, not be perfectly Bayesian. We should, therefore, expect a distribution of views to arise. However, this does not undermine the epistemological point that, as more evidence becomes available, we should expect a predictable evolution of the equipoise positions.

At the point in time where PANORAMIC started recruitment to the molnupiravir intervention arm, the best evidence for the efficacy of molnupiravir came from the MOVE-OUT trial, which had only included unvaccinated patients who were over the age of 60 years or who had at least one of the specified chronic health conditions (table 1). As noted, this evidence was crucial for both the MHRA and the NHS decisions relating to molnupiravir. We should, therefore, expect the equipoise position in the community to have moved the furthest in relation to the prescription of the drug to unvaccinated patients with the specified chronic health conditions detailed in the MOVE-OUT selection criteria who are at high risk of developing severe COVID-19. It is possible—perhaps even likely—that the community had moved away from equipoise towards a position whereby molnupiravir treatment was seen as clinically indicated for this group of patients. This would not require all members of the expert community to have formed this view but would require it to be the majority view. By contrast, given that the MOVE-OUT trial did not include vaccinated individuals, clinical equipoise regarding the efficacy of molnupiravir should have, in principle, obtained for this group of patients. Nevertheless, in practice, as we have already observed, the decisions to allow the drug to be prescribed to patients and to make it available if patients meet certain requirements may have contributed to a change to the equipoise position for vaccinated patients. Therefore, there is no guarantee of a state of clinical equipoise even for vaccinated patients. Given that an empirical analysis of the state of clinical equipoise in relation to vaccinated patients is beyond the scope of this paper, the following explicitly ethical discussion, for principled reasons, focuses on the equipoise position as it relates to specifically unvaccinated patients who are recruited to the PANORAMIC trial.

If the evaluation of the state of equipoise in relation to unvaccinated patients at the relevant time is correct, or even merely plausible, then it strongly raises the question of whether unvaccinated patients who are over the age of 60 years or who have at least one of the chronic health conditions specified in the MOVE-OUT inclusion criteria should be recruited to the PANORAMIC trial at all. The absence of equipoise means that most experts believe that treatment would be to the benefit of these patients.ⁱⁱ However, it is important to note that this particular expert belief is fully compatible with the belief,

ⁱⁱIf the physician treating the patient believed this, recruiting the patient to the study might be a contravention of Article 14 of the Declaration of Helsinki: “Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects”.²²

held by the same experts at the same time, that it would be desirable to have more and better evidence on the efficacy of molnupiravir in this group of patients. In less urgent, non-pandemic contexts, ‘more and better evidence’ would likely have been generated through additional phase 3 trials with slightly different patient groups before molnupiravir received marketing authorisation. However, as we acknowledged in the introduction, because the regulatory processes were (rightly) sped up to enhance access to clinical interventions in response to the pandemic, less evidence than usual was available at the point when the product became available for clinical prescription. This creates a situation where further evidence on the efficacy of molnupiravir for high-risk, unvaccinated patients that fall within the inclusion criteria of MOVE-OUT can no longer be ethically produced through placebo or ‘usual care’ controlled trials. If we take into account this equipoise situation on its own, then there is a principled reason to question the justifiability and permissibility of the randomisation risk for patients in this group who are recruited to the PANORAMIC trial and, as we shall discuss in the following section, to claim that PANORAMIC’s duty of care to unvaccinated patients is not being adequately met.

Finally, it is worth acknowledging that the PANORAMIC trial includes unvaccinated participants with certain risk factors not covered by the MOVE-OUT trial. For these groups of patients, it is more difficult to ascertain with any certainty whether clinical equipoise existed, and whether it was already significantly disrupted when PANORAMIC started recruitment.

STANDARD OF CARE

What is the standard of care or the best proven intervention at the point in time when PANORAMIC started recruitment to the molnupiravir intervention arm?

This question can be interpreted as either an epistemological question or a pragmatic question. The epistemological question about the standard of care is roughly equivalent to the question of the existence of equipoise in the whole clinical community combined with the intervention in question having successfully negotiated the clinical translation gap. We have discussed the epistemological issues involved in interpreting the state of evidence following the MOVE-OUT trial in the preceding section of the paper, so we will primarily consider the pragmatic question here. In the research ethics literature, there is a considerable body of argument that interprets the standard of care as roughly the treatments and interventions that patients in a particular healthcare system can routinely access, even if those treatments and interventions are known not to be the best available.^{23–25} This understanding is, for instance, the basis for the argument that if interventions that are routinely available in high-income countries are not available to potential participants in low-income countries, then it is acceptable to run placebo-controlled trials with those interventions in low-income countries. If, for the sake of argument, we accept this interpretation of the standard of care, then the standard of care in England is minimally defined by the interventions that are provided by the NHS. In the present context, this means that molnupiravir treatment for anyone who falls within the NHS criteria (table 1) is the standard of care or the best proven treatment.

This creates a problem for PANORAMIC given that the investigators declared in the protocol that they would comply with the principles of the Declaration of Helsinki¹⁰ (p. 28). According to Article 33 of the Declaration:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.²²

It is important to note that this research ethics issue, which is based on a pragmatic understanding of standard of care as defined by availability, primarily arises because recruitment to the PANORAMIC trial takes place at a time when the intervention, molnupiravir is, in principle, already available to potential participants who fulfil the NHS requirements. Indeed, given that there is an element of general practitioner discretion allowed by the NHS in determining whether a patient is eligible to access molnupiravir (on the basis that they are deemed to be ‘at highest risk of getting seriously ill from COVID-19’),¹² then, in practice, all potential PANORAMIC participants could access the standard of care treatment through the NHS.

It might be argued on the basis of the equipoise considerations above that there are ‘compelling and scientifically sound methodological reasons’ for generating further evidence by including molnupiravir in the interventions evaluated by PANORAMIC and that PANORAMIC is, therefore, compliant with the Declaration of Helsinki in the sense that it falls within the exception defined in Article 33. The compelling reason could either be the need for more evidence in general, or the need for evidence in relation to groups not included in MOVE-OUT but included in PANORAMIC, or a combination of the two. This argument seems to be undermined by the fact that the Article 33 exception only applies if patients in the non-intervention arm ‘will not be subject to additional risks of serious or irreversible harm’. In the absence of other evidence, we should accept that the MOVE-OUT estimate of efficacy applies directly to those participants in PANORAMIC who fall within the MOVE-OUT selection criteria. In addition, we should accept that for other groups included in PANORAMIC, we have little evidence to predict whether they are likely to have a higher or lower efficacy and that our best estimate is, therefore, the MOVE-OUT estimate for them as well. This entails that being randomised to the non-intervention arm (when they could access molnupiravir through the NHS) subjects the participants to an additional risk of severe COVID-19 with hospitalisation or death of, on average, three percentage points, which seems like a serious harm. This would entail that PANORAMIC contravenes the Declaration of Helsinki.

The issue identified here may be further exacerbated since there is a possible argument that a more expansive account of standard of care should be applied and that the standard of care should be defined as any intervention that has received conditional marketing authorisation by the competent national regulator. On this understanding, molnupiravir would count as the standard of care for everyone in the UK who falls within the PANORAMIC selection criteria, including those whose increased risk is only caused by having age ≥ 50 years as a risk factor.

FULLY INFORMED CONSENT

As outlined in the introduction, molnupiravir is available in England to certain patient groups on the basis of clinical indication, and these patient groups overlap substantially or, in practice, completely with the group defined by the inclusion and exclusion criteria of PANORAMIC (table 1). This raises the questions of: (1) whether potential participants in the PANORAMIC study should be informed by the investigators in the participant information sheet or reminded about the clinical availability of molnupiravir as part of the recruitment process to the trial; and (2) whether the validity of consent is affected if they are not informed or reminded.

If they consent to participation in the trial, then the patients who are both eligible for recruitment to PANORAMIC and eligible to get a clinical prescription of molnupiravir run a 50% risk of not getting molnupiravir by being allocated to the ‘Usual Care’ only arm. If they do not consent to participate, then they can access molnupiravir if either: (A) they remember that they are eligible because they have been preidentified as being in the high-risk group and contacted by the NHS or (B) their physician knows/realises that they are eligible based on their risk profile. Therefore, potential participants in this overlap group have a choice between either accessing molnupiravir through the NHS (with certainty) or participating in the trial and having a 50% risk of not receiving treatment with molnupiravir.

In terms of the 50% risk of not getting molnupiravir by being allocated to the ‘Usual Care’ only arm, it might be argued that potential participants should be allowed to make the choice and consent to trial participation because this risk is of the type and magnitude that falls below whatever threshold we set for allowable research risk. Let us accept this for the sake of argument. It still leaves the problem that participants can only make this choice and voluntarily consent to assume the risk if they have knowledge regarding the choices that are available to them. A potential participant who is not aware at the time of consent that they can access the treatment outside of the trial lacks information that one may reasonably deem to be essential for making the informed choice whether to consent or not. In order to protect and promote that patient’s best interests and autonomous decision making, or to recognise the patient as a competent deliberator of equal standing,²⁶ this also seems to be the kind of information that a physician has a professional and ethical duty to convey to a patient. Finally, it seems to be required by the first part of Article 31 of the Declaration of Helsinki (‘The physician must fully inform the patient which aspects of their care are related to the research’) as well as by the first part of Article 26:

In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, **the anticipated benefits and potential risks of the study** and the discomfort it may entail, post-study provisions and any other relevant aspects of the study²² (our emphasis).

In the literature that argues for the relaxation of research ethics regulation and principles during the COVID-19 pandemic, there are a number of authors who aim to justify the claim that potential participants should be allowed to consent to greater research-related risks than is currently the case (eg, in relation to SARS-CoV-2 challenge studies).^{8,9} We are, however, not aware of any extant arguments for allowing researchers to *not* inform potential participants about known, significant risks prior to asking for their consent to participation.

Requiring potential participants to be informed about the clinical availability of molnupiravir complicates the information and consent process, a matter that is often simplified in large, platform trials to facilitate rapid recruitment. However, as we have argued, there are strong reasons to suggest that if patients are not informed of the choices that are available to them and the research-related risks, then they are unable to, or have not provided ethically valid, informed consent.

CONCLUSION

The speeding up of research and regulatory processes that have happened during the COVID-19 pandemic is in many ways desirable. Good evidence is produced more quickly by large, well-designed trials. The evidence is processed more efficiently by regulators and health system decision makers. Therefore, patients get access to efficacious, evidence-based interventions much faster than used to be the case. However, as the analysis in this paper of the interaction between the PANORAMIC trial and the concurrent conditional marketing approval and clinical use of molnupiravir has shown, the increased speed and the contraction of research phases mean that new variants and complex versions of well-known research ethics issues may arise. These issues are not COVID-19 specific but can occur in any context where a pharmaceutical product has received conditional marketing authorisation, but where there are still reasons to conduct further clinical trials that include participants from those groups for which the product is authorised and available. These issues must be taken seriously and the interests of potential participants protected.

In the preceding discussion, we proposed that, when the existence of equipoise is uncertain regarding the intervention(s) in an RCT, consideration is needed in terms of: (1) how one might reconcile a physician's duty of care with randomisation to a treatment known or thought by a bona fide expert community to be inferior to the established standard of care; and (2) the acceptability of the research-related risk. As we have attempted to demonstrate in the case of the PANORAMIC RCT, depending on the basis by which one has defined or established the standard of care, there are reasons to consider molnupiravir as the standard of care for most or all of the participants in the trial.

Where there is no longer equipoise in relation to the intervention(s) to be investigated in a trial, and where allocation to the control arm would deprive them of an authorised and available treatment, relevant patient groups must be identified prior to the initiation of recruitment. They should either be excluded from the trial, or only included if: (1) a specific judgement has been made by the research ethics committee that the research-related risk they face—if allocated to the non-treatment arm—is of a type and magnitude that patients should be allowed to consent to; and (2) they are explicitly informed about this risk and the fact that they can access the intervention outside of the trial and they consent to the risk.

Twitter Jonathan Lewis @jonlewis@84

Contributors The idea for the paper was conceived by SH and RD-R. All authors contributed to the research and drafting of the paper and approved the final version. SH is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

This article is made freely available for personal use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs

Soren Holm <http://orcid.org/0000-0002-7200-5607>

Jonathan Lewis <http://orcid.org/0000-0001-8342-1051>

Rafael Dal-Ré <http://orcid.org/0000-0002-0980-2486>

REFERENCES

- 1 Wise J, Coombes R. Covid-19: the inside story of the recovery trial. *BMJ* 2020;370.
- 2 RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384(8):693–704.
- 3 RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *Lancet Respir Med* 2021;9(12):1419–26.
- 4 RECOVERY Collaborative Group, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;383(21):2030–40.
- 5 Dawson A. Pandemic vaccine trials: expedite, but don't rush. *Res Ethics* 2020;16(3-4):1–12.
- 6 London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science* 2020;368(6490):476–7.
- 7 Solbakk JH, Bentzen HB, Holm S, et al. Back to what? the role of research ethics in pandemic times. *Med Health Care Philos* 2021;24(1):3–20.
- 8 Chappell RY, Singer P. Pandemic ethics: the case for risky research. *Research Ethics* 2020;16(3-4):1–8.
- 9 Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. *J Infect Dis* 2020;221(11):1752–6.
- 10 Nuffield Department of Primary Care Health Services. Panoramic protocol. V1.3, 2021. Available: <https://www.panoramictrial.org/for-healthcare-professionals/documents>
- 11 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386(6):509–20.
- 12 Medicines & Healthcare Products Regulatory Agency. . decision. summary of products characteristics for Lagevrio, 2021. Available: <https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio>
- 13 National Health Service. Treatments for coronavirus (COVID-19). reviewed, 2022. Available: <https://www.nhs.uk/conditions/coronavirus-covid-19/treatments-for-coronavirus/>
- 14 Lewis J. Experimental design: Ethics, integrity and the scientific method. In: Iphofen R, ed. *Handbook of research ethics and scientific integrity*. Cham: Springer, 2020: 459–47.
- 15 Alderson P. Equipoise as a means of managing uncertainty: personal, communal and proxy. *J Med Ethics* 1996;22(3):135–9.
- 16 Fried C. *Medical experimentation: personal integrity and social policy*. New York: Elsevier, 1974.
- 17 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317(3):141–5.
- 18 Veatch RM. The irrelevance of equipoise. *J Med Philos* 2007;32(2):167–83.
- 19 Freedman B, Glass KC, Weijer C. Placebo orthodoxy in clinical research. II: ethical, legal, and regulatory myths. *J Law Med Ethics* 1996;24(3):252–9.
- 20 Miller PB, Weijer C. Rehabilitating equipoise. *Kennedy Inst Ethics J* 2003;13(2):93–118.
- 21 Lilford RJ, Jackson J. Equipoise and the ethics of randomization. *J R Soc Med* 1995;88(10):552–9.
- 22 World Medical Association. WMA Declaration of Helsinki — ethical principles for medical research involving human subjects. 64th WMA General assembly, Fortaleza, Brazil, 2013. Available: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- 23 Lie RK, Emanuel E, Grady C, et al. The standard of care debate: the Declaration of Helsinki versus the International consensus opinion. *J Med Ethics* 2004;30(2):190–3.
- 24 Wendler D, Emanuel EJ, Lie RK. The standard of care debate: can research in developing countries be both ethical and responsive to those countries' health needs? *Am J Public Health* 2004;94(6):923–8.
- 25 van der Graaf R, van Delden JJM. What is the best standard for the standard of care in clinical research? *Am J Bioeth* 2009;9(3):35–43.
- 26 Walker T. Value of choice. *J Med Ethics* 2022;48(1):61–4.