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Rapid commentary: Ethical implications for clinical trialists and patients associated with COVID-19 research

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Abstract

Pandemics disrupt clinical trials worldwide, with lasting effects on research. It can severely impact clinical trialists ability to conduct safe and ethically uncompromised trials. Hence, the mounting pressure results in ethically and morally distressing decisions faced by clinical trial professionals during pandemic situations. Whilst clinical trialists attempt to think about preparedness and responses during a pandemic, the need to have an ethical framework that has real-world applicability is imperative. Pandemics are a challenging time for all, however, the safety and access to support for clinical trialists and patients within clinical trials should be at the forefront for their organisations and the government.

Key Words: COVID-19; Pandemic; Ethics; Clinical trials; Patients; Trialists

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Core Tip: This commentary provides an important facet and argues the ethical implications surrounding clinical research practices and staff during pandemic

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situations. Clinical trial professionals face ethical dilemmas whilst conducting trials safely at an unprecedented rate given the clinical urgency. This commentary highlights the detrimental impact of not having a protocol for pandemic-driven clinical research, as well the lack of an ethical framework with *real-world* applicability to support the clinical trial workforce. Unethical behaviours and practices could be introduced in the current pressurised climate in order to rapidly respond to coronavirus disease 2019 research in particular.

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INTRODUCTION

A pandemic is a time to focus on containing the clinical situation, ensuring deaths are minimised, reviewing the causation and developing treatments. However, the ethical implications surrounding clinical research practices and staff may be less considered. Ethically and morally distressing decisions may be faced by many clinical trial professionals during pandemic situations. These decisions, which could be seen as “moral injury”, may impact upon an individual’s ethical and moral code and may develop into feelings of shame and guilt^[1]. In the current coronavirus disease 2019 (COVID-19) pandemic, the wider psychosocial and psychological impact of the pandemic amongst Clinical Trialists is yet to be explored. Whilst there is an argument that there could be personal factors that may contribute to this, Clinical Trialists have had to reprioritise their work regimes to deliver research around severe acute respiratory syndrome coronavirus 2.

A useful document that has aided Clinical Trialists in particular is the World Health Organisation’s (WHO) pandemic preparedness document. Interestingly the National Institute for Health Research also provided guidance and paused non-COVID related research as of March 20, 2020. The WHO’s pandemic preparedness framework was a result of a workshop conducted in 2018 amongst the Global Health Ethics Team and the African coalition for Epidemic Research, Response and Training. The purpose of this workshop was to discuss and identify empirical processes and procedures in relation to ethics reviews and preparedness during pandemics. This included five key areas in particular; pre-review of study protocols (including multi-country reviews), coordination between national ethics committees, statistical and stakeholder considerations, data and outcome sharing, as well as transfer of samples to share knowledge and develop future proofed interventions. Another key development to come out of this workshop were standard operating procedures (SOPs) for ethical reviews, in part to protect staff and their time while conducting pandemic research. These SOPs were to provide clarity on terminology and expectations of the pre-review of protocols and to agree a specific set of standards to speed up the process. Whilst these recognised a number of complex ethical issues could be raised during pandemics, it is also imperative to consider both research and clinical staff resources. Various other aspects such as quality assurance, regulatory requirements and operational delivery of the required research, which arguably could have ethical implications due to the by-stander effect this generates, were not well discussed and reported. This should be a fundamental aspect to consider with any future pandemic preparedness documentations as well as any associated procedures. Additionally, ethical implications for specific staff groups should be considered, to ensure policy makers are able to develop relevant guidelines.

Ethical implications associated with pandemics have significantly evolved over the centuries, but developing fit for practice ethical guidelines universally applicable to policy makers, healthcare systems and clinical trial units appears to have been challenging. Furthermore, ethical implications and principles may be driven by the pandemic itself. A good example would be to consider research conducted during the H5N1 influenza endemic. A significant limitation with H5N1 research was that longitudinal data was scarce and so its wider use and applicability was constrained. In

order to aid future pandemic management plans or to better understand transmission of a virus on the scale of a pandemic, existing data could have been used as part of prediction model, to support research staff. Whilst, the infection was managed in various ways, clinical trial staff had a different set of ethical considerations that were needed to have been addressed. Currently, there is no evidence to suggest these ethical considerations for trial staff were explored and reported. The vulnerability in this situation, of course, is that addressing the needs of a pandemic alongside the need for clinical research to develop treatments and vaccines, has to sit alongside access to care and the ethical obligations of research and to our clinical research staff.

IMPACT OF PANDEMIC RESEARCH ON CLINICAL TRIALISTS

All clinical trials testing licensed or unlicensed drugs and vaccines are mainly led by clinicians and clinical academics and there are staff from many disciplines working as Clinical Trialists. Therefore, the research associated with a pandemic, resourcing levels and the mental and physical impact varies considerably. Whilst there is a wide acceptance resource issues in the NHS, this has been exacerbated during the current pandemic. As a result, there appears to have been a heavy reliance on clinical and non-trial staff to deliver some clinical trials, which could impact their mental wellbeing in the long term, although this hypothesis would require further investigation.

Interestingly, Alperovitch and colleagues^[2] stipulated whilst there is a need for research to be conducted during a pandemic, the major implications are in respect to managing the ethical principles pertaining to the studies themselves, research participants and Clinical Trialists. A key issue to consider is the informed consent aspect. Some studies have had deferred and/or waived consent models when conducting clinical trials during previous pandemics^[2]. Whilst participants, clinicians and researchers often agree emergency research consent could be waived in some urgent situations, this method isn't suitable and acceptable for all. Clinical Trialist based research requires informed consent, and recognition that an electronic method of conducting a trial could be an efficient way to gather insightful data to further evaluate this is often missed. For example, the European Medicines Agency has provided clarity that informed consent must be taken before enrolling any patients into COVID-19 clinical trials taking place in Europe. Gobat and colleagues^[3] discussed this issue further in their systematic review, and highlighted that patients accept clinicians acting as surrogate arbitrators. However, research regulators were more judicious if studies had substitute consenting procedures. Also, while further recommendations around study setup and protocol design need to be fit for purpose for any pandemic-driven clinical research such research should comply with both research and practice ethics. Alternative consent models could also have major psychological impact on Clinical Trialists and research to this effect remains limited.

Balancing clinical care and research to manage pandemic preparedness

Another common ethical argument presented during pandemics is that clinical care for current patients outweighs clinical research around non-pandemic issues. This may impact both patients and ongoing clinical care in a multitude of ways. Currently there are clinical trials taking place to test the use of Lopinavir, Ritonavir or Dexamethasone for COVID-19 (*via* the RECOVERY Trial); all of which are licenced treatments for other diseases. As there is clinical and adverse effect data already available for these drugs, there are minimal risks and ethical and moral implications for staff conducting these trials, when compared with COVID-19 vaccine studies or first in human trials. However, there could be unlicensed drugs that may also be suited to combating a new infection or a modified strain of a known infection such as COVID-19.

Another facet to pandemic preparedness is whether countries have ample research capacity to ensure an efficient and effective response in terms of research. The requirement for ethical principles and merit of incorporating these into research and clinical practices using specific guidelines could be endorsed during public health emergencies and it is widely recognised this could be a cost effective way to further operational capacity for Clinical Trialists in particular. As such, policy makers, clinicians, researchers and stakeholders need to identify time and resources to provide immediate treatment and maintain other activities, inclusive of an integrated approach for research as part of a pandemic response. In situations such as the COVID-19 pandemic, developing research and clinical practice "ethics preparedness" can help provide an efficacious response.

Challenges with implementation

Whilst ethical preparedness has the potential to cover an array of factors, a key challenge is the applicability of ethical standards between the “individual” and “group”. There may be conundrums around duty to act to preserve lives of patients and the general public, *vs* the personal risks of those providing clinical care. It is clear that those in frontline clinical positions put themselves at risk in order to save lives and that this is morally acceptable. However, there may be others who may feel, as a healthcare professional, their right to conduct their role in a safe manner is compromised due to the very obligations of the role they play during a pandemic.

Identifying specific risks for staff

COVID-19 has a unique aspect, that is, the infection having particular effects on the black, Asian and minority ethnic (BAME) population based on the current data reported specifically within the United Kingdom. 44% of the NHS workforce belongs to the BAME population and to date, several reports state approximately 62%-75% of the 181 healthcare worker deaths were of BAME descent^[4-6]. Ethnicity has the potential to influence the disease transmission through societal, cultural and behavioural differences^[7]. The Francis report^[8] found the frontline doctors who are of ethnic minorities may feel more vulnerable to raising concerns at work, thus BAME staff may not have vocalised concerns around their health risks and lack of access to personal protective equipment (PPE) during the pandemic. Minimal or lack of PPE has been found to correlate with increased anxiety levels in healthcare professionals^[1]. As the causation of the ethnic bias in COVID-19 is yet to be understood, this introduces ethical implications for those serving in the frontline and in COVID-19 related research and potentially needs further investigation before this impacts other frontline BAME staffing groups.

RISKS OF PREDICTION MODELS

Historically, the rate of deaths during a pandemic depends on the number of those infected, the virulence of the infection and the efficiency and effectiveness of the preventative measures^[9]. In addition, accurate mortality rates can be challenging to establish. However, this may be because the use of Artificial intelligence (AI) methods, coupled with data science and its influence on healthcare, has been minimal until now. Therefore, another facet to complicate ethical implications for staff could be that prediction models for COVID-19 are AI instead of traditional statistics. Whilst, AI methods and statistics have their own strengths and weakness, the rapid reviews being conducted to develop these prediction models could lack quality and perhaps be poorly reported, which would contribute to increasing bias. This was highlighted in a recent systematic review conducted by Wynants and colleagues^[10]. Therefore, there is an argument that unethical behaviours and practices could be introduced in the current pressurised climate due to the rapid response-based research conducted. Whilst conducting “rapid reviews” is very much appropriate and is a time sensitive matter, academia maybe overloading the journals with a large number of papers in a bid to put their views across and to support healthcare practitioners. This could raise more confusion within frontline services than anything else. In fact, this counter productivity itself could be deemed unethical. Furthermore, an already overstretched healthcare system may feel overwhelmed and may also have very limited time to use this evidence in a meaningful manner.

CONCLUSION

It is anticipated that national research ethics committees, research consortia, funding agencies, healthcare organisations and policy makers will work towards promoting better recommendations and for conducting effective research during a pandemic, whilst still protecting our clinical trial workforce. A key factor that must remain at the forefront as we think about preparedness and responses during a pandemic, is that, despite theoretical and conceptual debates, the real-world applicability of any ethical frameworks is imperative. This is vital to keep in mind when decisions are made with regard to research and supportive strategies for clinical research staff working during pandemics.

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