

# Ethical Principles of Clinical and Translational Research



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## KEYWORDS

- Ethics • Informed consent • Confidentiality • Transparency • Artificial intelligence • Pandemic

## KEY POINTS

- Potential ethical pitfalls in research are constantly evolving.
- Emerging ethical issues in clinical and translational research include the development and increasing use of technology such as artificial intelligence, the safe management of large health databases, and managing the response to unanticipated health crises in the world.
- Navigating these issues requires consideration of the basic ethical principles of clinical research such as respect for patient autonomy and beneficence and knowledge of the latest iterations of various international guidelines.

## INTRODUCTION

Evidence-based medicine (EBM) requires researchers to manage their dual roles as clinicians and researchers while negotiating the intricacies of ethics in clinical and translational research. Increased scrutiny of potential ethical pitfalls in clinical research must be accompanied by increased vigilance. Efforts to ensure the ethical conduct of clinical research such as the European Union Clinical Trials Directive (based on the International Council for Harmonization Harmonized Guideline - Good Clinical Practice [ICH-GCP]) or the emergence of research ethics consultation services have increased the complexity and resources required in the performance of clinical trials.<sup>1</sup> Meanwhile, heterogeneity in the interpretation and implementation of such guidelines can become a source of dispute. Familiarity with relevant international guidelines, local regulatory policies, and the underlying principles of the ethical conduct of research is required to improve transparency and accountability. In this article, the authors will review potential ethical issues in research involving human subjects.

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## History

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Research on human subjects has taken place for centuries, often with no acknowledgment of the risks or ethical implications. As early as 1865, Claude Bernard<sup>2</sup> unequivocally stated that regardless of how “highly advantageous to science,” the conduct of research on human subjects that could be harmful “to any extent” would not be ethically permissible. The Nuremberg Code was issued following World War II in response to atrocities committed by Nazi physicians in the name of scientific research. Despite significant notoriety, the Nuremberg Code had no binding legal authority and had little effect on mainstream medical researchers. It was not until the 1960s that this issue was addressed.<sup>3</sup> For example, representatives in the United States blocked the requirement for informed consent in all cases and blocked a ban on research on institutionalized children and prison inmates who were used to test drugs.<sup>4</sup>

As early as the 1950s, an anesthetist called Henry Beecher<sup>5</sup> was concerned about the ethics of human experimentation. He identified issues in his own practice such as when anesthesia was prolonged to study the effects on kidney function without adequate consent. After multiple revisions, this culminated in the publication of “Ethics and Clinical Research” in the *New England Journal of Medicine* in 1966, 2 years after the publication of the Declaration of Helsinki that established ethical principles applied to clinical research involving human participants. This landmark article described a series of cases in which human subjects were subjected to participation in studies not for their benefit such as the withholding of penicillin from soldiers with streptococcal infections.<sup>6</sup> Together with the work of other researchers such as Maurice Pappworth in England, the acknowledgment of the risks and underlying ethical principles represented the transformation of bioethics and human research into what we understand and practice today.

More recently, the Declaration of Helsinki has been revised several times (last in 2013)<sup>7</sup> since its initial publication in 1964. The latest meeting of the ongoing revision was in September 2023. Other relevant international guidelines include the ICH-GCP Guideline and the Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks in 2016. The multiple revisions reflect the increasing complexity of clinical research as guidelines attempt to tackle emerging issues such as minimizing harm to the environment and the criteria to fulfill for informed consent. Amidst this changing climate, researchers must remain cognizant of the underlying ethical principles detailed later in this article to guard against potential ethical pitfalls.

## PROTECTION OF HUMAN SUBJECTS

The Declaration of Helsinki was considered the acceptable conduct of biomedical research during its inception, but ethical review for research on humans was not mandatory at that time. The onus remained with the investigator to ensure the protection of human subjects. The Belmont Report then established a framework with a set of ethical principles underlying subsequent regulation for research on humans. It remains an essential reference for institutional review boards (IRBs) reviewing proposals involving research on human subjects. It hinges on 3 ethical principles<sup>8</sup>:

1. Respect for persons: Humans are not a means to an end and their autonomy must be respected. Additional measures are required to protect vulnerable populations with diminished autonomy.
2. Beneficence: Research must be designed to maximize possible benefits and minimize possible harms. Any risks must be justified by potential benefits.
3. Justice: Ensuring the fair distribution of costs and benefits to potential research participants.

Although pivotal at the time of publication, there has been growing concern that the Belmont Report may not be sufficient for the increasingly complex ethical climate of human research. For example, the Belmont Report does not address growing concerns about transparency in a field with increasing commodification of biomedicine or the rise of novel technologies that pose risks to participants' right to privacy such as the potential to identify personal information available online.<sup>9</sup> Nonetheless, it remains a milestone in the ethical conduct of human research.

### ***Balancing Risks and Benefits***

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One of the key questions during the review of proposed research with human subjects involves deciding if the benefits of a proposed project outweigh its potential risks for the participants. As early as 1907, William Osler<sup>10</sup> suggested that researchers experiment on patients only with "full consent" and if "direct benefit" is likely. The difficulty comes in deciding if the risk-benefit ratio of a proposed study permits the study to go ahead and whose responsibility it is to make this decision. It has been suggested that if the proposed study involves greater than "minimal risk," more intense scrutiny of the research is required, including its scientific validity.<sup>11</sup> True scholarly review generally requires peer review but this is logistically challenging and could result in a delay in the review and approval of the proposed research. Although researchers may feel that a review of the scientific validity of the proposal is beyond the scope of expertise of a research ethics board, the board is often qualified and diverse enough to provide a reasonable assessment. In scenarios where the risk to subjects is significant, the ethics board must also consider the scientific validity of the proposed research as part of the decision-making process.

### ***Informed Consent***

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Informed consent is the process by which a subject voluntarily confirms willingness to participate in a research study, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.<sup>12</sup> Information given to the participants or their legally acceptable representatives should be concise, use simple language, and avoid unnecessary volume and complexity. Information that should be provided to potential participants is shown in [Fig. 1](#). Important updates to the process of obtaining informed consent since the last version of ICH-GCP in 2016 include the option to obtain consent where appropriate, the concerns of the subject have been addressed, and an electronic signature is provided.

In the event of an emergency when prior consent of the participant is not feasible, the consent of the participant's legally acceptable representative should be requested. If the participant's representative is not available, the participant can still be enrolled provided measures regarding the consent requirements when the representative is not available have been described in the protocol with documented approval by the research ethics board to protect the participant's rights and well-being. The participant's representative should still be informed as soon as possible and consent should then be requested. Where possible, even if consent is provided by a legal representative of the subject, the participant should still be informed about the trial "to the extent compatible with the participant's understanding."

### ***Privacy and Confidentiality***

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The privacy of research participants should be protected and any data collected must be kept confidential by investigators. Public concerns about their privacy have been amplified by previous reports of breaches in data security and have led to extensive legislation guiding the use and storage of personal data (such as the Data Protection

<b>Informed consent</b>
Purpose of the trial
Summary of the experimental aspects of the trial
Trial's investigational products and the probability for random assignment
Trial procedures to be followed including all invasive procedures
Expected duration of trial participation and approximate number of participants
Participant's obligations and reasonably foreseeable risks to the participant (and when applicable, the participant's partner, to an embryo, foetus or nursing infant)
Reasonably expected benefits including when no intended clinical benefit
Alternative procedure or treatment that may be available and their important potential benefits and risks
Compensation and treatment available in the event of trial-related injury
Anticipated compensation and expenses to the participant for trial participation
That trial participation is voluntary and that the participant may withdraw at any time
Process by which the participant's data will be handled, including in the event of the withdrawal of participation
Allowing direct access to relevant original medical records while safeguarding the participant's confidentiality
That the participant's identity will be kept confidential and that the trial may be registered on publicly accessible and recognised databases
That the participant will be informed if information becomes available that may be relevant to the participant's willingness to continue trial participation
Relevant contact person for further information or in the event of suspected trial-related injury
Foreseeable circumstances under which the participant's trial participation may be terminated
Trial results and information on the participant's actual treatment will be made available to them should they desire it

**Fig. 1.** Elements of informed consent. (*Adapted from ICH HARMONISED GUIDELINE GOOD CLINICAL PRACTICE (GCP) E6(R3)-Endorsed on 19 May 2023. Currently under Public Consultation.; 2023. Accessed December 11, 2023. [https://database.ich.org/sites/default/files/ICH\\_E6%28R3%29\\_DraftGuideline\\_2023\\_0519.pdf](https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf).*)

Act in the United Kingdom or the Privacy Rule under HIPAA [Health insurance Portability and Accountability Act]).

The expansion of data-driven clinical research and the development of health databases and biobanks have challenged research ethics, particularly regarding the confidentiality of participants' data. Anesthesia is one potential area where registries and biobanks could be strategic to advance research.<sup>13</sup> In doing so, it is critical for the investigators to protect patient-identified information from being accessed without consent. Despite ongoing discussion in the preceding years, it was only in the fifth amendment of the Declaration of Helsinki in 2000 that it was explicitly stated that research involving human subjects included research on identifiable human material or data. A further amendment in 2008 required researchers to justify the waiving of informed consent for research using identifiable human material or data obtained from biobanks. Eventually, the Declaration of Taipei was adopted in 2016 on "the collection, storage, and use of identifiable data and biological material beyond the individual care of patients." It attempts to balance the rights of individuals giving their tissue or data for research while recognizing the value of health data for increasing knowledge. Significant aspects of the Declaration of Taipei include obtaining valid

consent when data or material is collected in a database or biobank. When applied together with the Declaration of Helsinki, any research activity where there is a possibility of sharing with others of the data or material collected should also adhere to the Declaration of Taipei.

Any future plan of sharing data or material obtained should be clearly described in the study protocol and reviewed by an ethics committee. Participants should have the right to make a decision on whether to accept this secondary use of their data and their refusal should not impact their participation in the primary research. The Declaration of Helsinki has yet to be integrated with the Declaration of Taipei but with the growing development of health databases and biobanks and their potential value, the relationship between the two should be clarified.<sup>14</sup>

### ***Incentives***

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Planned compensation or benefits to study participants should be explained as part of the process of obtaining informed consent. Study benefits should account for costs, burdens, and inconveniences such as transport linked to research participation. Failure to adequately compensate study volunteers risks exploitation. However, such benefits should not result in “undue inducement” for potential participants to participate in a study.<sup>15</sup> The dilemma arises when determining what constitutes “undue inducement” which would have to be assessed in its specific context (for example developing vs developed countries). Various definitions of “undue inducement” have been proposed including fulfilling specific criteria such as a desirable offer that encourages participants to exercise poor judgment while taking on risk of serious harm.<sup>16</sup> The amount and nature of offered incentives should be reviewed by research ethics committees who should consider both the risks of exploitation and undue inducement in the proposed project’s unique context.

## **ISSUES RELATED TO THE RESEARCHER**

### ***Scientific Validity***

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Ethical research must be scientifically sound. Failure to conduct rigorous well-designed studies would not only be a waste of resources but also place human subjects at unnecessary and hence unacceptable risk. The IRB aims to safeguard participants and one of the ways it accomplishes this is to scrutinize the trial protocol to ensure the proposed study is scientifically valid. The latest iteration of the guidelines for GCP<sup>17</sup>(currently under public consultation) includes guidelines focusing on risk proportionality. In risk proportionality, risk mitigation strategies implemented for identified risk factors that threaten scientific validity should be proportionate to the risks to trial participant safety and data reliability. A periodic review of not only the study protocol but also ongoing assessment of the scientific knowledge being acquired may be required to determine whether modifications to the ongoing trial are needed. Ongoing review of findings can be performed by a subject safety committee or another group independent of the investigators. Poorly conducted studies with invalid results have potential adverse serious consequences for participants and multiple measures should be in place to uphold the validity of the proposed study.

### ***Transparency***

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Integrity in research requires transparency at all stages of a study. This involves the registration of trial protocols on publicly accessible and recognized databases such as [ClinicalTrials.gov](http://ClinicalTrials.gov) and the posting of results. Investigators must maintain trial-related records in a secure manner for a defined period of time (6 years as per HIPAA).

These records should be made readily available to authorities to enable reconstruction of the trial in order to ensure reliability of its results.

Transparency in clinical research extends to clearly delineated authorship. Authorship not only confers credit but also accountability for what is published. This is reflected in 1 of the 4 criteria for authorship developed by the International Committee of Medical Journal Editors that states that authors must be “accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.” Although these criteria are widely used amongst clinical researchers, issues persist in authorship practice such as ghost authorship (where authors who contributed are not listed to hide a conflict of interest) or guest authorship (where individuals who have not contributed are given authorship credit by virtue of their stature in their organization).<sup>18</sup> Suggestions to improve transparency in authorship practices include measures that can be adopted by both journals as well as universities and research institutions. Journals should adopt common standards for authorship and outline that the corresponding author has a responsibility to confirm that all who deserve authorship are listed.<sup>18</sup> Universities and research institutions should have clear guidelines on author roles and responsibilities and encourage discussions about authorship early. Such measures provide a common starting point for discussions regarding authorship and would discourage authorship practices that are detrimental to valid research.

### ***Dissemination of Data***

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The growth of research databases represents an increasingly important resource that can be used by researchers. However, such databases are currently underused.<sup>19</sup> An audit of research databases in the United Kingdom that have been approved by research ethics committees revealed that less than half share their data and produce publications.<sup>20</sup> If participants had given their consent for their data to be used in such databases, the underutilization of such databases is concerning. More work needs to be done to encourage the sharing of anonymized data in a transparent and equitable manner.

### ***Role of Artificial Intelligence***

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The use of artificial intelligence (AI) such as large language models in scientific article creation was uncharted territory until recent years. In particular, generative AI is able to create new data including audio, text, and images and by doing so, contribute new ideas and concepts. Although undoubtedly a useful tool, the use of AI poses several problems including a lack of transparency when AI is used, errors in the content produced, and potential breach of confidentiality if content of prompts imputed into the program is reused. Authors are encouraged to fact-check any content produced and take steps to maintain transparency and confidentiality such as describing how AI was used in sufficient detail.<sup>21</sup> Peer reviewers and editors may also use AI when reviewing submitted articles. For example, generative AI may be used in the process of peer review report generation as well as to summarize peer review reports. The risks of the use of AI such as the perpetuation of bias and breach of confidentiality are similar to that when AI is used by authors. In fact, some agencies such as the US National Institutes of Health have prohibited the use of AI in the grant peer review process due to a breach of confidentiality.<sup>21</sup> Peer reviewers and editors must be held to the same principles of accountability, confidentiality, and transparency as authors.

There are a few proposed frameworks to approach the ethical issues in the use of AI such as “GREAT PLEA” (governability, reliability, equity, accountability, traceability, privacy, lawfulness, empathy, and autonomy)<sup>22</sup> that was adapted from the military

to be used in health care. However, such frameworks may not be adequate and must continue to be refined as the technology develops and researchers find new uses for generative AI.

## THE DUAL ROLE OF CLINICIAN-RESEARCHER

The Belmont Report clearly distinguished clinical practice from clinical research. Clinical practice aims to enhance the well-being of an individual patient with a reasonable expectation of success whereas clinical research is designed to test hypotheses and contribute to generalizable knowledge.<sup>8</sup> The dichotomy between clinical practice and clinical research was echoed in the differences between the ethical requirements of providing treatment and doing research. While providing treatment, the primary duty of a clinician is to a patient's well-being whereas researchers have the competing obligation of ensuring their research generates scientifically valid data. Should their methodology not be sound, data generated would not be valid and would have placed participants at risk of needless harm. By failing to maintain the validity of research generated, researchers would also have not fulfilled their obligation to their research subjects, funding agencies, and other researchers to generate useful knowledge. Despite these differences, professional codes of ethics have made it clear that despite the researchers' other obligations, their primary duty remains to act in accordance to the participants' wishes (with respect for autonomy and need for informed consent) and best interest. There are certainly benefits to clinicians being actively involved in translational research including their clinical expertise, increased clinical relevance of research, and having researchers trusted by participants recruited. These benefits ensure the challenges of negotiating the dual role of clinician and researcher are worthwhile.

In addition, although generally uncontested when first presented, the boundaries between clinical practice and research may not be as clear as when originally described. Clinical research has been described as applied patient-oriented research (APOR) that involves "direct contact with patients in which the investigator prospectively conducts controlled observations of a legitimate, yet incompletely tested, rival candidate for the optimal management of a disease in order to develop clinically relevant knowledge."<sup>23</sup> With this definition in mind, it has been argued that it is impossible to perform APOR without the context of clinical practice or actual disease management.<sup>24</sup> This inevitably blurs the lines between clinical practice and research. The growing emphasis on EBM and medicine-based evidence accompanied the development of translational research where aims encompassed quality improvement and better routine patient care in practice. Translational research has been described as emphasizing the link between clinical research and medical care and "showing how both need to be grounded in the ethics of a doctor-patient relationship."<sup>25</sup> Eventually, this contributes to the development of the "learning health care system" where knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the health care delivery process and leads to continual improvement in care (as defined by the Institute of Medicine). At the same time, translational research poses unique bioethical challenges such as in the difficulty of applying common bioethics principles to other issues that might impact study design and implementation such as politics<sup>26</sup> or the impact of community engagement.<sup>27</sup>

Nonetheless, negotiating the dual roles of researcher and clinician can remain challenging. Potential ways in which tension between the dual roles may arise were reviewed in a systematic review of 36 studies. Themes that emerged included<sup>28</sup>

1. Negotiating patients-participants' and third party (such as referring clinician) agendas such as a request from the referring clinician for an update on the participant that could risk research confidentiality
2. Difficulty participants have in distinguishing a clinician-patient relationship from the researcher-participant relationship, especially if the participant expects the research to be therapeutically beneficial (therapeutic misconception)
3. Overidentification with the patient-participant or with their clinical self
4. Therapeutic misdirection as the researcher has used their clinical expertise to direct the research process in an attempt to provide therapeutic benefit
5. Fear whether researchers were exploiting the participant or situation to their advantage and if the motives underlying their behavior involved any abuse of power in the clinician-patient relationship

Considering the benefits of the dual roles of researcher and clinician, various measures have been suggested to anticipate and overcome tension between the 2 roles. While research ethics committees have their role to play in negotiating the tenuous balance between the 2 roles, the insight and understanding of the clinician-researcher is required to produce research that is both rigorous and ethical. Proposed measures include particular attention during recruitment and process of obtaining informed consent such as using a model of continuous consent.<sup>29</sup> Other suggestions include regular review and discussion in research team meetings and with others from different backgrounds to improve awareness of potential challenges of the dual role. Questions to keep in mind when planning research with patients-participants and during subsequent regular review include how the team plans to manage incidentally detected clinical issues during the course of the study, signs that the patient-participant may feel coerced into the study for researchers to actively look out for, and what happens if the clinician-researcher meets the patient again after the study but as a clinician and patient instead of a researcher and participant.<sup>28</sup> While it is unlikely that all potential issues can be anticipated, heightened awareness of potential conflict between the 2 roles will enhance outcomes.

### **ETHICAL CONSIDERATIONS FOR RESEARCH IN A PANDEMIC**

The World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic in March 2020. The pandemic posed a unique challenge to the practice of clinical research and presented several new barriers, including regulatory and ethical challenges.

The process of obtaining informed consent had to be altered during the pandemic. While traditionally taken face-to-face, the pandemic interfered with this by preventing direct contact. Novel ways to obtain informed consent (such as e-consent) had to be developed together with support services to ensure the consent remained valid. In addition, informed consent for studies had to include information about the risk of study-related spread of COVID-19.<sup>30</sup>

The study of the use of new drugs or the “off-label” use of drugs during the pandemic also posed an ethical dilemma. Arguments in favor of the use of repurposed drugs included the need to identify whether the drugs might have value in treating patients with COVID-19 at a time when there was a significant lack of effective therapies as the death toll rose, a “right to try” in order to mitigate suffering and enhance self-preservation,<sup>31</sup> as well as the ethical trap that whatever intervention being proposed was better than nothing. Similarly, while the use of a placebo arm or best supportive care is accepted as a way to improve validity of results, physicians found this difficult in the context of a pandemic and there are reports of physicians

requesting the open-label use of an unproven study drug.<sup>30</sup> The dual roles of clinician and researcher came into direct conflict here and led to hesitancy to discuss or recruit patients for clinical trials during the pandemic. In addition, the use of such therapies outside of a well-designed clinical trial affects the validity of any information obtained about the potential benefits and risks of these therapies. This has downstream effects of hindering future research about their effective use<sup>32</sup> as seen by the failure to generate useful information about therapeutics during the 2014 to 2016 Ebola epidemic. At a time where misinformation regarding the pandemic and proposed therapies was rampant, scientific validity of research was paramount. Failure to safeguard validity of results published could result in erroneous prescription of therapeutics and shortage of these drugs for other approved indications such as when there was growing concern about shortage of hydroxychloroquine during the pandemic.<sup>33</sup> Ethical principles to guide the design for trials of experimental treatments (Fig. 2) can help maintain the ethical conduct of clinical research in the context of a pandemic.<sup>34</sup>

## DISCUSSION

Managing potential ethical pitfalls in clinical and translational research is an issue that has been discussed for many years. One does not need to look far back in history to identify instances where research was conducted at the expense of human subjects in the name of scientific progress. Guidelines such as the Declaration of Helsinki and the requirement for ethical board approval all attempt to regulate and ensure ethical conduct of clinical and translational research. Although core principles such as respect for autonomy and beneficence should remain the cornerstone of ethical research, technological progress such as the establishment of large health databases or the use of AI adds complexity to current ethical review. Ethical principles and guidelines in the scientific community must be dynamic and continuously updated to respond to the changing climate that could range from new technology, such as AI, to new crises such as the COVID-19 pandemic. Clinical researchers have a responsibility to remain vigilant for potential ethical pitfalls as complacency in this area could bring harm to patients and erode trust in the scientific community.

<b>Ethical principles for trials of experimental treatments in a pandemic</b>
<p><b>Patient population</b></p> <ul style="list-style-type: none"> <li>- Involve local communities to create a collaborative partnership</li> <li>- Disseminate knowledge to improve its social value</li> <li>- Fair and transparent selection of study population, taking care to avoid prioritisation of well-connected individuals</li> <li>- Ensure informed consent, especially in the social and cultural context</li> <li>- Maintain respect for study communities by protecting their confidentiality and keeping them informed of the results</li> </ul>
<p><b>Researcher</b></p> <ul style="list-style-type: none"> <li>- Ensure scientific validity of data</li> <li>- Favourable risk-benefit ratio</li> <li>- Continuous independent review to ensure public accountability</li> </ul>

**Fig. 2.** Ethical principles for trials of experimental treatments in a pandemic. (Adapted from Rid A, Emanuel EJ. Ethical considerations of experimental interventions in the Ebola outbreak. *Lancet*. 2014;384(9957):1896-1899. doi:10.1016/S0140-6736(14)61315-5.)

## SUMMARY

The ethical principles of clinical and translational research are complex. Potential issues that can arise relate to both the subject and the researcher. Maintaining the ethical conduct of research requires management of the dual role of clinician and scientist while integrating the principles described earlier into their practice.

## CLINICS CARE POINTS

- International guidelines such as the Declaration of Helsinki and the Declaration of Taipei outline ethical principles in research.
- Principles described in the Belmont Report such as respect for autonomy and beneficence should remain the foundation of the ethical conduct of research.
- Technological developments and unanticipated health crises present new challenges. Guidelines and ethical review boards should remain dynamic to respond appropriately.

## DISCLOSURE

The author has nothing to disclose.

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