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The First- and Second-Order Ethical Reasons Approach: *The Case of Human Challenge Trials*

Davide Battisti, Emma Capulli, and Mario Picozzi

ABSTRACT At the height of the Covid pandemic, there was much discussion in the literature about using human challenge trials (HCTs) to expedite the development of effective Covid-19 vaccines. Historically, reluctance to fully accept HCTs has largely been due to potential conflicts with the principle of nonmaleficence in bioethics. Only a few commentators have explored this topic in depth. In this paper, we claim that to address ethical concerns regarding HCTs, two types of ethical reasons should be identified and investigated: first-order reasons that can be given to claim that a practice in itself is in direct conflict with the principles of bioethics; and second-order reasons that take into consideration how a practice is carried out and its consequences. We argue that understanding these ethical reasons is crucial for guiding the implementation of HCTs. We investigate a first-order reason against HCTs when the practice is in conflict with the principle of nonmaleficence, and when it is not. Following this argument and assuming there is no first-order reason based on nonmaleficence that hinders using HCTs, we argue there may be second-order reasons to guide implementation of this practice, such as difficulty in obtaining informed consent; protection of the weaker party; and trust in the scientific enterprise.

KEYWORDS human challenge trials, nonmaleficence, research ethics, harm, first- and second-order reasons approach

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Human challenge trials (HCTs) generally refer to clinical trials for a vaccine or other drug where healthy volunteers are deliberately exposed to a pathogen being studied. HCTs can accelerate the development of treatments since they allow researchers to gauge effectiveness in a much smaller population. HCTs may provide a better understanding of a specific pathogen's effect on people, and as such are not limited to the development of preventive or therapeutic treatments.

During the pandemic, there was extended discussion in the literature about using HCTs to expedite Covid-19 vaccine development. Many commentators supported the ethical appropriateness of HCTs in the emergency context and identified criteria that would reduce the risk for volunteers and to ensure the trials were conducted ethically.[1] However, some commentators were cautious about or opposed to HCTs, basing their position on the lack of effective and well-proven treatments[2] for Covid-19 and the lack of sufficient information about the virus.[3] Generally speaking, the debate on the possibility of using HCTs to deal with the Covid-19 emergency mainly focused on assessing risk and how to minimize it. The bioethical debate was not unanimous regarding the use of HCTs for Covid-19 vaccine research, and some HCTs for vaccines were conducted.[4]

The Covid-19 pandemic was not the first context in which ethical issues about HCTs have been raised. In the past, other commentators raised concerns about the principle of nonmaleficence,[5] though only a few authors

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have explored this principle in-depth.[6] In general, the literature on HCTs has primarily focused on the concept of acceptable risk in such trials: particularly minimal risk, daily risk,[7] and net risk.[8] Moreover, although there are cases in which HCTs have been carried out, for example, for vaccines against malaria and influenza,[9] there are few documents that aim to provide guidance to inform their use, and there is still debate in the literature about underlying ethical problems with HCTs.

In this article, we take advantage of recent interest in HCTs to revisit the ethical foundations that should guide their implementation. To do this, we base our analysis on a theoretical distinction, identifying two types of ethical reasons that play a pivotal role in the ethical evaluation of HCTs: first-order reasons and second-order reasons.

First-order reasons are those that can be given to claim that a practice is in direct conflict with the principles of biomedical ethics,[10] if the practice occurs in ideal conditions. By "principles of biomedical ethics," or principlism, we refer to one of the most influential approaches for bioethical issues provided by Beauchamp and Childress, who use the framework of four universal and basic bioethical principles: autonomy, nonmaleficence, beneficence, and justice. Although the principlism approach has been criticized, it has proven to have lasting staying power in bioethical analysis and debate,[11] which is why we refer to it in this article. Second-order reasons are those that take into consideration how a practice is carried out and its consequences. This involves introducing other factors we will discuss in the next section, such as difficulty in obtaining informed consent, the need to protect the weaker party, and the desire to preserve trust in science, that are external to the evaluation of the practice itself.

The distinction between first- and second-order reasons is different from the one between consequentialism and deontology. Both first- and second-order reasons can be either consequentialist or deontological, depending on whether they concern the violation of rules assumed to be valid or the practical consequences, assessed in terms of social utility. For instance, second-order reasons are deontological when, under certain circumstances, the implementation of an action or a practice that does not in itself constitute an infringement of moral duty or right leads to infringements of moral rights and duties. Second-order reasons are consequentialist when an action taken by itself does not produce bad consequences, but its implementation may. Moreover, nor is this distinction equivalent to the one between values that a thing, an action, or a practice has "in itself," namely intrinsic values, and values that are not good for their own sake, but for the sake of something else, i.e., extrinsic values.[12] Our approach proposes that the ethical evaluation of an action or a practice should consider two distinct dimensions, both necessary for a comprehensive investigation: a narrower observation limited to the occurrence of an action in ideal circumstances; and a broader-in-scope assessment that evaluates an action in complex circumstances where many more factors must be considered. In the first dimension, we assess the existence of first-order reasons that might lead us to consider an action undesirable; in the second dimension, we focus on second-order reasons. Analyzing and distinguishing between these types of ethical reasonings concerning HCTs is fundamental for ensuring that appropriate requirements are in place for how such trials will be conducted. Different ways of implementing HCTs might arise depending on which ethical reasons are deemed valid for limiting such trials.

Through an analysis that examines the existence of both first- and second-order reasons, it is possible to provide useful tools to guide and oversee the practice of HCTs in an ethically appropriate way.

In the first section of this article, we will analyze the first-order reason against HCTs, according to which this practice is in conflict with the principle of nonmaleficence and hence prima facie is morally wrong.[13] In the next section, we present our argument according to which HCTs do not conflict with the principle of nonmaleficence. In the following section, assuming the nonexistence of a first-order reason that hinders the use of HCTs, we argue there may be second-order reasons to limit this practice, such as difficulty in obtain-

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ing consent, protection of the weaker party, and trust in the scientific enterprise, which depend on the specific context in which HCTs are supposed to be implemented. In the final section, we present the advantages of the first- and second-order reasons approach, supported by an example based on the regulation of alcohol consumption.

FIRST-ORDER REASONS AND THE ARGUMENT AGAINST HCTS

As noted above, first-order reasons are those that can be given to claim a practice in itself is in direct conflict with one or more principles of bioethics. The principle of autonomy is met assuming that individuals will provide informed consent to participate in HCTs. The principle of justice is met assuming all healthy volunteers in a study are recruited fairly.[14] Concerns arise around the principle of nonmaleficence.

In medical ethics, the principle of nonmaleficence has often been treated as effectively identical to the maxim *primum non nocere*: "Above all [or first] do not harm."[15] In the literature on HCTs, authors usually trace the principle back to what is stated in the International Code of Medical Ethics: "A physician shall act in the patient's best interest when providing medical care";[16] in the Declaration of Geneva: "The health and well-being of my patient will be my first consideration";[17] and in the Declaration of Helsinki: "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects."[18]

Intentionally exposing someone to a pathogen may seem to be an act that is intrinsically in conflict with the nonmaleficence requirements, and is therefore morally wrong. The risk of harm from exposing someone to a pathogen is not counterbalanced with some reasonable benefit for the volunteer: we are harming someone for the good of society.

However, it's widely recognized that human subjects research does not always align with the nonmaleficence principle as strictly as clinical care does. In fact, using human subjects in research means acknowledging that researchers may take actions that might be harmful to volunteers in order to answer a question. For instance, phase I clinical trials are generally conducted on healthy volunteers to test the toxicity of drugs, which may result in harm to the human subject. In the case of phase I clinical trials, such as in the case of HCTs, the risk of harm is not counterbalanced with some reasonable benefits for the volunteers. According to this perspective, the question should not be whether HCTs harm volunteers, but how badly they harm them.

However, even if we accept the fact that some volunteers might be harmed by participating in research, the principle of nonmaleficence assumes a particular relevance in the HCT context. Let us consider again the example of phase I clinical trials. Here, researchers provide participants with drugs that are expected to be reasonably safe due to preclinical evidence. Of course, harm may occur, but it would be an expected collateral event. In the case of HCTs, exposure to certain risks or harm is the direct consequence of the action of the researcher.[19] It is not just a matter of the severity of harm but also the direct purposes of the research.

If HCTs result in a violation of the principle of nonmaleficence—in a way that does not occur in other studies—there would be a first-order reason to limit the use of them. This line of thought could lead to asserting the necessity to conduct HCTs with forethought, caution, oversight,[20] and in the presence of robust informed consent.[21]

An important clarification is in order: usually, authors who argue that HCTs are in conflict with the principle of nonmaleficence do not advocate an absolute ban on this practice. Unless we're assuming a strong monist deontology perspective, according to which every action against the principle of nonmaleficence should be avoided, such moral reasoning should be connected to other moral reasoning at stake. Recognizing the conflict with the principle of nonmaleficence will produce a justified use of HCTs only in rare circumstances. For example, the use of HCTs in dramatic pandemic-type contexts such as smallpox, influenza, and cholera[22] would be acceptable. In such cases, in fact, HCTs can be interpreted as a sort of lesser evil: exposing a selected group of volunteers to risk in order to save many lives in the future. This approach can be justified both from a utilitarian perspective, and from a pluralist deontological perspective, which suggests that there is a plurality of prima facie duties determining what is right, all things considered.

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In summary, according to the argument presented in this section, HCTs are in conflict with the principle of nonmaleficence since they involve deliberately harming volunteers; this reason may justify their use only in emergency conditions with limited risk levels. As stated above, HCTs do not produce a certain direct benefit to volunteers. Moreover, in the case of HCTs, exposure to certain risks or harm is the direct consequence of the action of the researcher, as opposed to other medical interventions (such as surgery, drug prescription, or during an experimental trial that benefits volunteers) where the harm caused is not intended, but only an expected collateral event that may or may not occur.[23]

CHALLENGING THE ARGUMENT: THE DEFINITION OF HARM

The claim that HCTs are morally wrong in light of the conflict with the principle of nonmaleficence is contentious. For instance, Hope and McMillan challenge this viewpoint by questioning the alleged distinction between intention and foresight, a key aspect of their critique.[24] We will now explore another line of thought that further challenges this claim. In this effort, we question the very definition of harm implicitly used up until now. Research ethics guidelines often refer to "psychophysical" harm, which could be defined as an impairment, to some extent, of the normal functioning of human beings.[25] However, from a liberal philosophical perspective, in which the autonomy of the individual assumes decisive importance, it should be noted that the definition of harm cannot be reduced to "psychophysical" impairment. In a pluralist context, such as the one protected by the liberal paradigm in which our reflection is embedded, harm can be understood as a shifting concept, i.e., something that changes according to the preferences and interests of the individual.

Following this idea, one of the most debated definitions of harm, proposed by Joel Feinberg, states that a person is harmed only if their interests, and not mere psychophysical integrity, change their status from a better to a worse condition.[26] People generally have an interest in maintaining optimal health, which is why regulatory codes presuppose and protect this. However, this may not always be true; for example, in the emblematic case of living organ transplantation in its Samaritan meaning,[27] where an individual opts for organ removal in order to donate the organ to an unknown third person. The donor decides to partially sacrifice their health by making this choice. Note that this sacrifice is carried out not only in the interest of those who will receive the organ, but also in the donor's own interest to satisfy an altruistic need that the donor considers characterizing their existence and their system of values. Given those premises, can we argue that the donor has been harmed? Presumably not, at least according to the argument presented, because donating an organ was a free, autonomous act, aligned with the donor's personal values and interests. Since people generally share an interest in health and life, undermining them may constitute a strong indicator of harm, although nondefinitive. That interest may not always be aligned with others' interests in leading self-defined, self-discovered, and self-directed lives.[28]

Using this alignment, we could argue that HCT volunteers agreeing to take a risk for altruistic purposes are doing so by expressing a preference to contribute to society at the expense of their own health. HCTs would thus not be intrinsically harmful, if the volunteer decides that running the risk of worsening their mental and physical health is in their own interest. Consequently, HCTs would only be harmful when they are no longer in the participant's interest.[29]

Someone might reply that an altruistic kidney donor is still surely harmed by donating a kidney (e.g., from being cut with a scalpel, or by enduring surgical complications), just as the HCT participant is harmed by participation (in most cases), even if this voluntary participation is indeed consistent with their interests. The supporters of this view can contend that if there were other less demanding ways to donate or participate from a psychophysical perspective—such as ensuring that a given recipient received a kidney (or had their disease cured) or contributing to society to an equal degree by participating in an HCT—the volunteer involved would surely choose the option causing less psychophysical distress.

Even if we assume the reasonableness of this argument, we can still claim that the volunteer acting according to their interests experiences "no net harm," even though their volunteering may cause them some psychophysical consequences that they would have preferred to avoid if they were given another option to

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satisfy their interests. By "net harm" we mean balance between all interests at stake in our choices, both negative and positive. If a person has (generally) an interest in not suffering psychophysical distress, such distress might be acceptable if it is the only way to achieve a certain personal goal. From this perspective, the volunteer might experience greater harm by not being able to suffer these psychophysical consequences to follow their interests, such as donating an organ or helping society. Everything considered, according to this thesis, it is problematic to argue that HCTs are inherently morally ambiguous because of considerations related to harm. This is because we are applying a general model of individual preferences and implicitly assuming a specific definition of harm that cannot be valid for all individuals and in all circumstances as it conflicts with pluralism. Considering this, a strict application of the principle of nonmaleficence would lead to relative disregard of the concept of patient harm linked to the idea of pluralism of values protected in the liberal horizon assumed in this article. Even if we consider the principle of nonmaleficence as a valid one in the clinical setting linked to the doctor-patient relationship, it cannot be considered a reason for rejecting HCTs. In fact, in a pluralist context, different concepts of harm will lead to different personal choices when it comes to one's own health. Such a conclusion may provide the practical implication indicating that we should have a regulatory regime permissible for all kinds of research, and rarely prohibit certain kinds of research per se. However, as we will discuss, an assessment of the first-order reasons relating to the principle of nonmaleficence is not sufficient to provide an all-things-considered judgment of this type.

SECOND-ORDER REASONS

Asserting that there are no first-order reasons linked to the principle of nonmaleficence for limiting the use of HCTs does not mean that this practice can always be implemented without any limitation. We need to consider second-order reasons, as they may offer elements for limiting the use of HCTs. Three second-order reasons will be addressed here: difficulty in obtaining consent; protection of the weaker party; and trust in research and the scientific enterprise. We note that these reasons appear applicable to other research topics and have been explored in detail.[30] We claim that some of these reasons, or potential problems, may appear more evident in the context of HCTs compared to other research types. For instance, the implementation of risky HCTs could undermine trust in science more than the implementation of other equally risky ordinary trials. This is due to their potentially controversial impact on public perception.

Difficulty in obtaining informed consent. We argued that HCTs would theoretically not be problematic if the volunteer autonomously agrees to receive the pathogen. However, the process of obtaining informed consent can pose some challenges. The informed consent process requires a description of the research and the purposes of the expected risks or harms, plus other relevant information.[31] It may be difficult to assess when a signature on an informed consent form indicates that an individual fully understands the purpose of the research and the potential risks to participants. Participants may misunderstand the trial's purpose, leading to misconceptions. Furthermore, especially concerning very risky HCTs, some participants may not be fully aware of the burdens and risks associated with the experimental practice to which they will be subjected. Potential confusion and misinterpretation could emerge, and this would undermine the ability of the participants to make autonomous choices. The aforementioned guidelines[32] highlight the potential greater danger of HCTs when used with diseases, like COVID-19, with a poorly understood pathogenesis, and no specific treatment available, that can cause death. It is utterly important to ensure that in risky trials the experimentation is accompanied by a rigorous informed consent, as also stated by the World Health Organization.[33] Thus, we argue that informed consent, especially in the context of very risky HCTs, should be carefully verified, to exclude individuals who are unable to choose independently whether the study is in their own interest.

We note that assuming the previous argument is reasonable does not necessarily imply a ban on the use of HCTs or a strong limitation of its use exclusively to emergency conditions. Although there are some categories of people for which it is difficult to obtain fully informed consent, this is not true for others. For example, health care workers such as physicians and researchers may have the conceptual and experiential tools to

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understand the risks and burdens associated with very risky HCTs. Nonetheless, during the consent process for high-risk HCTs, it may be necessary to implement a stringent procedure to verify that volunteers understand the information presented to them. This article does not intend to detail the methodologies for defining such a procedure. We limit ourselves to suggesting that the "teach-back" method could be particularly suitable in this regard.[34] Volunteers should have a greater and more detailed understanding of potentially risky trials versus those with a relatively low risk of harm.[35]

At this juncture in our analysis, a potential objection arises in situations where HCTs proposed involve new and not yet well-studied pathogens. In these situations, some may argue that, because of the great uncertainty around the effects of a given disease on the human body and the unpredictable consequences of the infection, it is impossible to obtain valid informed consent even from those who are deemed fit to participate in risky trials. This argument was used in the debate regarding the use of HCTs for a Covid-19 vaccine. For instance, as Bowman noted, "You have consent, but is it really well-informed? Do people fully understand? Because if we don't understand the virus itself, I wonder about the quality of informed consent that you can ask of people."[36] In response to Bowman's concerns, Steel and colleagues argued that high uncertainty among experts is reasonably compatible with valid informed consent,[37] which means that informed consent can remain valid even when researchers' understanding is incomplete or false. According to these authors, if we consider plausible that informed consent is possible only in cases with low or no uncertainty, then many older studies would have to be considered problematic. Those studies would have failed to obtain valid informed consent, on both ethical and legal levels, and therefore are to be deemed ethically questionable, given the prevailing ignorance at the time they were conducted. However, these a posteriori implications seem quite implausible. It is more reasonable to support a conception of consent that requires researchers to communicate their best concurrent understanding of relevant features of a study to volunteers. Uncertainty is itself another thing that must be responsibly communicated,[38] rather than an impediment making informed consent impossible.

From another perspective, Keren and Lev maintain that providing false information can invalidate the consent, even though they agree on the fact that uncertainty does not necessarily dismiss the possibility of informed consent. In fact, if we consider the concepts of incompleteness and falseness, it appears that they may have conspicuously different effects on the validity of consent. While volunteers may suffer from incomplete understanding, they can take that sense of incomplete understanding into account in their decisions and deliberations. On the other hand, when they suffer from a false belief, they cannot take that fact into their deliberations. According to Keren and Lev, decision-making based on a false belief undermines autonomous authorization, and thus can render one's consent invalid.[39]

We contend that an investigation of the right conditions for informed consent is necessary for assessing the permissibility of HCTs, since having a well-informed and autonomous will to undergo experimental trials is a necessary condition if we want to consider HCTs ethically acceptable.

Protection of the weaker party. A further second-order reason we want to discuss involves the moral obligation to protect the weaker party and the structural imbalance existing in the relationship between the scientific enterprise and research participants. In this context, we do not refer to categories of prospective participants who may be considered vulnerable, i.e., people who are partially or completely unable to protect their interests such as individuals subjected to a hierarchical relationship, residents in nursing homes, prisoners, minors, and incapacitated adults.[40] Instead, we refer to a concept borrowed from regulatory systems, in particular from contract and labor law.[41] The moral obligation to protect the weaker party becomes relevant when there is an asymmetry with respect to intellectual control, availability of information, or the socio-economic position of two subjects. In these cases, a regulatory intervention that can assess the balance of power and ensure a correct exercise of autonomy by the parties is needed.

For healthy volunteers, the ethical analysis for HCTs centers on circumstances in which a participant acts with the intent of promoting a benefit for society and not solely in their own personal interest. The obligation to protect the weaker party in clinical research is consid-

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ered relevant, since, in addition to the healthy volunteer and their interest in solidarity, some other subjects and interests may come into play; for instance, researchers' main interests lie in generating scientifc knowledge and in obtaining economic profits. Of note, all the guidelines on experimentation on human beings refer not only to volunteers, but also to researchers, funders, and sponsors, whose primary aims are to obtain greater results from research and economic profit.

Researchers directly expose volunteers in HCTs to varying degrees of risk. As Hermansson and Hansson[42] and Rózynska[43] report, the relationship between researchers and volunteers is characterized by a strong intrinsic imbalance. This imbalance concerns several situations that can occur during HCTs, the first of which relates to the different distribution of information and control over the procedure. Researchers master the entire research project and convey how information is shared with volunteers. As we have seen, the very nature of informed consent is meant to address this lack of balance, because the one who possesses the information and skills is generally the researcher. A significant imbalance also exists concerning the distribution of psychophysical risks, which solely affect the volunteer. In a situation of this kind, not only do volunteers accept risks without always having a direct benefit in terms of health, but it is the researchers who have control over and make decisions about the evolution of the risks and damages that are possibly produced.[44]

Trust in science. The third second-order reason to consider in the ethical evaluation of HCTs lies in the relationship between society and science. Trust in the scientific enterprise is crucial to ensure that citizens heed scientific guidelines, both in ordinary and emergency conditions.[45] Societal confidence in scientific research influences decisions, for instance, when parents choose to vaccinate their children, thereby preventing potential, unwarranted risks. Moreover, this trust encourages better compliance with policies or rules founded on solid scientific evidence, such as when citizens adhered to the lockdown or social distancing measures during the Covid-19 pandemic.

The relationship of trust between research and society is delicate. While some authors argue that this trust is currently in deep crisis,[46] empirical studies suggest that trust in science generally remains robust. However, the same studies highlight that the public's actions, choices, and preferences often reveal skepticism toward policies based on scientific evidence.[47] The fact that nonexpert citizens are constantly bombarded by pseudoscientific news that questions the scientific and medical evidence at hand plays a fundamental role in undermining this already fragile relationship.[48] Historically, scientific research has not had a good reputation due to several ethically unacceptable experiments such as the tragic example of the Tuskegee study of untreated syphilis in Black males conducted by the U.S. Public Health Service[49] and, of course, notorious Nazi experiments during World War II.

Scientific research should take very seriously its duty to minimize risk for volunteers and to promote rigorous ethical and scientific control of trials.[50] This implies that riskier HCTs should be limited and a maximum risk threshold should be defined. Defining a threshold will be influenced by several social and cultural factors,[51] which can be assessed to some extent using both qualitative and quantitative research techniques. For example, such a definition of a maximum risk threshold will partly depend on what the public deems acceptable, which is fundamentally an empirical question.[52] Surveys that ask respondents about their attitudes toward certain practices such as HCTs or who assess trust in the research enterprise in a given population can at least inform discussions about the level of risk that can be considered acceptable by the public. Through these tools, we could observe if levels of trust in science are higher in some countries than in others or if HCTs are more acceptable in some communities than in others. This information could inform different context-dependent policies where, in accordance with strict ethical and scientific oversight of trials, different risk thresholds for HCTs could be set. We believe the idea of an empirically measurable threshold should be further developed and considered as it appears to have more advantages than identifying a risk threshold based only on theoretical reflection.

What may these second-order reasons entail? In this article, we do not intend to focus on how specifically the second-order reasons discussed above may determine the regulation of HCTs. We discussed a few second-order reasons that might be particularly relevant for guiding the ethical implementation of HCTs, since

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they highlight some of the problematic issues in the implementation of these trials. It is beyond the scope of this paper to provide a comprehensive guidance framework regarding the implementation of HCTs, a matter to be left to further research. Through the approach of first- and second-order reasons we have proposed, we aim to show that ethically driven analyses of the kinds of reasons underlying the permissibility of HCTs is crucial for appropriately guiding their implementation.

Nevertheless, we can propose some hypotheses derived from the discussed second-order reasons. For instance, considering concerns about informed consent, we suggest limiting access to HCTs only to volunteers expected to fully comprehend the associated high risks. The greater the severity of the expected psychophysical consequences for the volunteers, the more carefully the researchers should verify the consent.

Similar considerations apply to protecting the weaker party. We emphasize the importance of ensuring continuous information for volunteers and the option to withdraw from the trial at any time. True adherence to informed consent by volunteers also necessitates a closer examination of their relationship with researchers. Moreover, it should be noted that the imbalance between the parties participating in HCTs can become glaringly evident when the practice is implemented in countries with low levels of health care and education.

Finally, establishing a relationship of trust between scientific research and the lay public can provide reasons for setting a maximum risk threshold for HCTs. This threshold, however, depends—among other factors—on empirical evidence regarding the population's attitudes toward this practice.

ADVANTAGES OF THE FIRST- AND SECOND-ORDER REASONS APPROACH

We argued that, through an analysis that examines the existence of both first- and second-order reasons, it is possible to provide useful tools to guide and oversee the practice of HCTs in an ethically appropriate way. If this practice is considered an intrinsic violation of the principle of nonmaleficence, the aim should be to explore the rare circumstances under which HCTs can be considered a viable option as a lesser evil (as previously discussed). Instead, if we recognize that there are no first-order reasons for limiting HCTs, then our focus should shift to the issues arising from the implementation of HCTs, and to the identification of ways to solve or contain such issues. The first- and second-order reasons approach to defining whether a practice is ethically acceptable or not is crucial in the context of HCTs, but not limited to them.

Such first- and second-order reasoning approaches could also be applied to other ethical and social issues, even to ones that are not related to research ethics. Perhaps our strategy can be clarified by the following example: consider the regulation of alcohol consumption. In Western societies, there are no first-order reasons to consider consuming alcohol problematic per se or ethically controversial. From a regulatory perspective, we tend to consider such consumption as a matter of private choice. However, alcohol consumption is not entirely up to free will. In fact, it is under strict control: for instance, in many countries, selling alcohol to minors or driving a car with a high blood alcohol level is forbidden. These regulations are in place not because the alcohol consumption is intrinsically wrong, but due to the consequences that drinking alcohol may have in some specific circumstances, such as running over someone because a driver's reflexes are compromised by excessive alcohol consumption. In Western societies, alcohol use is regulated only by second-order reasons. On the contrary, in a few other countries, drinking alcohol is considered intrinsically problematic; hence, along with second-order reasons, those countries also consider first-order reasons to regulate alcohol consumption. In Muslim theocracies such as Iran where legislation is also based on religion, producing, selling, and drinking alcohol is a punishable crime[53] because these practices are perceived to be in contrast with Islam. This example shows that, according to the different kinds of reasoning we may consider at a certain time, a different regulation of the practices in question may arise. We believe this point is relevant for HCTs. Until now, as we have argued, HCTs have been generally addressed by presupposing a conflict with a first-order reason such that a practice would conflict with the principle of nonmaleficence. However, understanding HCTs as a practice whose implementation should be guided only by second-order reasons may lead to a clearer identification of the associated problems and, consequently, to a different and well-informed regulation.

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CONCLUSION

In this article, we did not aim to provide a comprehensive picture regarding the ethics of HCTs nor to propose guidelines that specifically inform this type of trial. For instance, we did not address the problem of compensation to participants of HCTs. Nor did we discuss how consent to participate in HCTs can be obtained or how reasonable risk thresholds can be formulated. Instead, what is central in this article is our effort to analyze, question, and rethink the current structure of the ethical-normative principles underlying the permissibility of HCTs. Our primary contention is that in a philosophical liberal context, the principle of nonmaleficence cannot be invoked as a first-order reason for limiting the use of HCTs, since the harmfulness of the practice is determined by the structure of the values and interests of the volunteer. We discussed the second-order reasoning for the limitation of HCTs, delving into the need to implement a stringent and differentiated process to verify information held by the volunteer according to the specificity of the trial, as well as the need to oversee the relationship between researchers and volunteers because of their differences in mastery of information and control over the procedure. We stressed the importance of promoting empirical studies and surveys to the public, which would be aimed at contributing to assessing the maximum level of acceptable risk that volunteers might take to minimize the public's potential loss of trust in scientific research. It's important to note that none of these reasons necessarily suggest a ban on HCTs or limit their use strictly to emergency situations, as has seemed to be the case until now. ♦

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14. This doesn't mean that there are no reasons connected with autonomy or justice for limiting the practice; for example, as we will argue later, some difficulties in obtaining informed consent or concerns about fairness in recruitments could emerge. However, this is relevant if we consider the second-order reasons, namely considerations arising from the evaluation of the practice in complex circumstances that are not directly dependent on the HCTs in itself.

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