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Social value, clinical equipoise, and research in a public health emergency

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Abstract

The 2016 CIOMS *International ethical guidelines for health-related research involving humans* states that 'health-related research should form an integral part of disaster response' and that, 'widespread emergency use [of unproven interventions] with inadequate data collection about patient outcomes must therefore be avoided' (Guideline 20). This position is defended against two lines of criticism that emerged during the 2014 Ebola outbreak. One holds that desperately ill patients have a moral right to try unvalidated medical interventions (UMIs) and that it is therefore unethical to restrict access to UMIs to the clinical trial context. The second holds that clinical trials in contexts of high-mortality diseases are morally suspect because equipoise does not exist between a standard of care that offers little prospect of clinical benefit and a UMI that might offer some clinical advantage.

KEYWORDS

CIOMS guidelines, Ebola, equipoise, public health emergencies, research ethics, right to try

1 | INTRODUCTION

The ethics of conducting research in the context of a public health emergency became the subject of heated debate in 2014–2015 as stakeholders struggled to respond to the largest ever outbreak of Ebola in three West African countries. During this period, the 2002 Council for International Organizations of Medical Sciences (CIOMS) *International ethical guidelines for biomedical research involving human subjects* were under revision and the resulting document, the 2016 CIOMS *International ethical guidelines for health-related research involving humans*, contains two significant changes relevant to these debates. First, a new guideline (20) governing research in disasters and disease outbreaks was introduced. It states that, 'In order to identify effective ways of mitigating the health impact of disasters and disease outbreaks, health-related research should form an integral part of disaster response.'[1] It also holds that, although many people 'facing a serious, life-threatening infection … are willing to assume high risks and use unproven agents within or outside clinical trials …. widespread emergency use [of unproven interventions] with inadequate data collection about patient outcomes must therefore be avoided.'

The rationale for the position stated in Guideline 20 derives in part from a second innovation of the 2016 CIOMS Guidelines. Guideline 1 contains a strong statement that 'The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health.' The social value of research is explicated in terms of the relevance and reliability of the information a study is likely to generate. In particular, it should be relevant to the decision making of a wide range of stakeholders, since 'Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources' (Guideline 1). Because this information provides the evidence base for decisions that affect the health and welfare of people and the use of scarce resources, its social value also depends on whether it is of sufficient quality to support these decisions. In very broad outlines, the position of the 2016 CIOMS Guidelines is that research in contexts of

[1] Council for International Organizations of Medical Sciences (CIOMS). (2016). *International ethical guidelines for health-related research involving humans*. Geneva, Switzerland: CIOMS. http://www.cioms.ch.

disasters and disease outbreaks can be an important means of generating the information necessary to improve the decision making of these stakeholders and that, all else being equal, this creates a strong moral presumption in favor of conducting research rather than using unvalidated medical interventions (UMIs) on a widespread basis outside the context of a well-designed clinical trial.

The position adopted in the CIOMS Guidelines has been challenged on several grounds, two of which are addressed here. The first challenge holds that the decision to use UMIs is a deeply personal choice of the desperately ill person and that it should therefore enjoy a strong presumption against outside interference.[2] If the desperately ill have a strong claim against outside interference with their decision to use UMIs then it would be impermissible to limit access to UMIs to clinical trials on the grounds that denying a person something to which they have a prior right represents coercion and coercive offers invalidate informed consent. I argue below that this claim is mistaken: the decision to use UMIs is not solely a personal choice, and there is thus no prior right to the use of UMIs. It is a strength of the 2016 CIOMS Guidelines that it explicitly recognizes that decision making about the use of UMIs impacts a broad range of interests of numerous stakeholders and is therefore not merely a private decision between researchers and patients.

The second, and more widely held objection, claims that when people are desperately ill and the existing standard of care is of limited clinical value, equipoise cannot exist between a UMI and a control arm that includes either the standard of care or the standard of care plus a placebo control.[3] Generally speaking, 'equipoise' refers to a state of uncertainty or disagreement in the expert medical community regarding the relative merits of a set of interventions.[4] When a study is initiated in, and is designed to 'disturb' a state of equipoise, the study has a prima facie claim to social value. The reason is that resolving or reducing uncertainty or disagreement about the relative merits of the interventions in the trial helps stakeholders make better decisions about how to treat patients and make wise use of scarce resources. It is also regarded as ethically permissible to randomize patients to interventions for which equipoise obtains because the existence of uncertainty or disagreement among experts entails that no one is knowingly being given inferior care.[5] I argue below that the claim that equipoise does not exist in this context rests on numerous misunderstandings. Most importantly, I argue that this view of equipoise results in a policy position that is self-defeating in the sense that it does not advance the legitimate interests of any stakeholder—including the desperately ill—while prohibiting the generation of evidence necessary to help those stakeholders make better decisions.

The arguments presented in the course of this analysis also explore the grounds for a reasonable skepticism about the prospect that the use of UMIs will result in clinically meaningful benefits for recipients. As a result, the arguments presented here help to clarify a range of questions that bear on the use of UMIs in a variety of contexts.

2 | UMIs AND PERSONAL LIBERTY

In the context of disaster or disease outbreaks with high mortality, stakeholders have struggled with the question of whether it is ethically permissible to restrict access to UMIs to clinical trials or to permit their provision outside of a research study in the hope of achieving a therapeutic outcome. Three positions on this issue are possible: (a) it is morally required that UMIs be delivered only in the context of a well-designed clinical trial[6]; (b) it is morally permissible (but not required) to restrict access to UMIs to the context of a well-designed clinical trial; and (c) it is morally impermissible to restrict access to UMIs to the context of a well-designed clinical trial. Only the first option prohibits the delivery of UMIs to desperately ill people outside of the context of research. The second option permits the non-research delivery of UMIs, although most proponents of this position argue that such use should be restricted so as not to interfere with the conduct of well-designed clinical trials.[7] The third position permits clinical research on UMIs only if potential study participants have access to UMIs outside a trial.

Schuklenk and Smalling defend this third positon on the ground that it is the only condition in which morally transformative informed consent is possible.[8] As they put it:

> The standard view is that an offer is not coercive whenever two conditions are met: (1) someone is offered something that could or even would make them better off than they would otherwise be, and (2) that they are not entitled to receive that something.[9]

They claim that in cases (a) and (b) above, morally transformative informed consent is not possible because desperately ill people have a right to make momentous, personal choices about their healthcare; this personal right entails a right to decide whether or not they are willing

[2] Schuklenk, U., & Smalling, R. (2017). The moral case for granting catastrophically ill patients the right to access unregistered medical interventions. *Journal of Law, Medicine & Ethics*, *45*, 382–391.

[3] Adebamowo, C., Bah-Sow, O., Binka, F., Bruzzone, R., Caplan, A., Delfraissy, J. F., … Whitehead, J. (2014). Randomised controlled trials for Ebola: Practical and ethical issues. *Lancet*, *384*, 1423–1424; Caplan, A. L., Plunkett, C., & Levin, B. (2015). Selecting the right tool for the job. *American Journal of Bioethics*, *15*(4), 4–10.

[4] Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine*, *317*(3), 141–145. doi:10.1056/nejm198707163170304.

[5] London, A. J. (2007). Clinical equipoise: Foundational requirement or fundamental error. In B. Steinbock (Ed.), *The Oxford handbook of bioethics* (pp. 571–596). Oxford, UK: Oxford University Press: p. 581.

[6] Rid and Emanuel seem to espouse this position when they argue that 'experimental' interventions 'should only be used in clinical trials, so that researchers can learn whether they work or not.' Rid, A., & Emanuel, E. J. (2014). Ethical considerations of experimental interventions in the Ebola outbreak. *Lancet*, *384*, 1896–1899.

[7] 21 U.S. Code § 360bbb—'Expanded access to unapproved therapies and diagnostics,' requires that the provision of a UMI 'not interfere with the initiation, conduct, or completion of clinical investigations.' http://uscode.house.gov/view.xhtml?req=(title:21%20section:360bbb%20edition:prelim).

[8] Consent is morally transformative when it alters the moral status of an act. For example, what would otherwise be an unwanted, and therefore impermissible act of touching is transformed in to a permissible act by the provision of informed and free consent.

[9] Schuklenk & Smalling, *op. cit.* note 2, pp. 383–384.

to try a UMI; and restricting this right therefore violates the second condition on coercion—it denies them something to which they are otherwise entitled.

On this analysis, whether desperately ill people, or their surrogates, can give morally transformative consent for research participation hinges entirely on the more fundamental question of whether restricting access to a UMI denies them something to which they are otherwise entitled. In other words, the soundness of this argument hinges on the premise that desperately ill patients have a right or an entitlement to access UMIs. Without this premise, restricting access to UMIs cannot invalidate informed consent, because the claim that such a restriction undermines the freedom of consent is based on the claim that the restriction is coercive. And the claim about coercion hinges on the restriction depriving patients of something to which they are independently entitled.

Schuklenk and Smalling correctly note that in matters of great consequence, such as questions of life and death, people ought to have broad liberty to make momentous personal decisions. But for this insight to establish a prior right to access UMIs it must be the case that the decision to access a UMI is primarily a personal decision on the part of the patient. Here, Schuklenk and Smalling articulate explicitly a view that often remains implicit and that many people may accept without question. The problem with this claim, however, is that it is false.

3 | NOT A PURELY PERSONAL DECISION

To begin with, it is worth noting that no society spends its entire budget on healthcare. As a result, just limits on healthcare have to be set and when these are enforced, some people are denied access to valuable, even lifesaving, care. Moreover, just limitations are often placed on the provision of care whose efficacy is far less speculative than UMIs. Although we may disagree with particular rationing decisions in practice, the background permissibility of limiting healthcare expenditures demonstrates that medical need alone is not sufficient to establish a just claim on social resources.

Next, it is important to recognize that access to UMIs is not primarily a question about the personal preferences of desperately ill people. Whether or not a patient wishes to try a UMI *when that is an option* is very much a personal choice. Whether to make the option of trying a UMI available to desperately ill patients is a question of policy that involves the legitimate interests of numerous stakeholders. Even if we grant that these stakeholders have a moral responsibility to give special weight to the interests of gravely ill patients, it remains the case that many of these stakeholders have important moral responsibilities that may conflict with or weigh against the provision of UMIs outside the context of well-designed clinical trials.

For example, the decision to provide UMIs has a range of consequences that impact the interests of various stakeholders. Some of these are direct costs that result from such decisions. UMIs have to be manufactured, purchased, transported under appropriate conditions, and then delivered to patients by trained medical personnel in appropriate healthcare settings. Some of these factors will be more costly or demanding than others, depending on relevant features of the UMI, such as whether it requires the maintenance of a cold-chain for transport and storage, what kind of healthcare infrastructure is required for administration, and so on.

These direct costs are borne by different parties. Production costs will likely be borne by pharmaceutical companies, but could fall to academics or government labs, depending on the nature of the UMI. Purchasing of UMIs will fall to third party payers, humanitarian organizations, governments or others, depending on the scenario being envisaged. Health systems may incur costs in creating the conditions necessary for the administration of the UMI. This is most likely to be the case when UMIs are considered in outbreak situations where they will be made available or administered to large numbers of people.

In addition to these direct costs, various stakeholders will bear opportunity costs from making UMIs available. In an emergency context, money that is spent procuring and creating the conditions to deliver UMIs will not be spent on other services. Infrastructure used to store and deliver UMIs will not be available for other purposes. The time and energy of clinicians and care givers required to deliver UMIs means that care givers are not available to provide other services. Policy makers who craft the contractual basis for the provision of UMIs will not be able to focus on other matters of disaster relief and response. One result of these direct and indirect costs is that in situations of scarcity, the decision to deliver UMIs outside of clinical trials may reduce the number of affected people who can access other health services and the quality of those services.

The decision to provide UMIs can also have consequences that affect the interests of large numbers of people in more indirect ways. In particular, it can be extremely difficult to separate the effects of a novel UMI from the background characteristics of a disease. Often the presentation of the same disease differs across patients—there is variation in which symptoms manifest, with what severity, for how long, and in how quickly patients recover or deteriorate. Inferences about the effects of a UMI on patient prognosis outside of a randomized controlled trial are prone to error and often have far-reaching impacts. Perceived negative effects of a UMI can derail a promising research program if researchers, funders, or patients perceive the UMI to be toxic or of low clinical utility.[10] Here, access to UMIs for some patients can conflict with the legitimate interests of sponsors in generating the evidence necessary to secure regulatory approval for a new intervention and community members who are likely to be future patients in having access to effective interventions for the condition in question.[11]

Similarly, perceived benefits of UMIs can lead governments, healthcare institutions, aid organizations, and patients to purchase and deliver interventions that are actually ineffective or toxic.[12] This scenario creates the potential for conflict between the financial

[10] London, A. J., Kimmelman, J., & Emborg, M. E. (2014). Beyond access vs. protection in trials of innovative therapies. *Science*, *328*(5980), 829–830.

[11] Ibid.

[12] Borio, L., Cox, E., & Lurie, N. (2015). Combating emerging threats—Accelerating the availability of medical therapies. *New England Journal of Medicine*, *373*, 993–995.

interests of the manufacturer, on the one hand, and the interests of communities in making fair and efficient use of scarce resources and of patients in being provided with care that actually advances their interests on the other.

The point of these remarks is to drive home the extent to which decisions about the provision of UMIs impact the legitimate interests of a range of stakeholders. In addition, many of these stakeholders have affirmative duties that may conflict with the provision of UMIs. Governments, insurance companies, aid agencies, and others involved in the financing of healthcare provision or disaster response and relief have obligations to make a fair and efficient use of scarce resources, recognizing that many people with the same need have equally compelling claims to assistance. Care givers faced with overwhelming needs also have a duty to prioritize their efforts in order to avoid wasted time and opportunity that could be used to more effectively minister to the needs of other patients. Drug developers have a duty to quickly and efficiently generate the evidence necessary to establish the clinical merits of interventions that advance the standard of care. This is not to diminish the plight of the desperately ill or to denigrate the urgency of their needs. It is to demonstrate that the use of UMIs in an attempt to meet those needs implicates a broader set of interests, of a wider set of stakeholders, situated within a network of ethical concerns that extend far beyond the personal plight of the desperately ill.[13]

It might be objected that although these considerations are likely to obtain in many contexts, it is possible that situations could arise in which some or all of these concerns are mitigated or can be addressed. For example, if UMIs are already available in sufficient supply in relevant locations then their use would not require new expenditures for production, transport, or administration. Does this possibility weaken the force of the objection? Two replies are in order.

First, the relevance of this network of interests on the part of an array of stakeholders to the use of UMIs, and the moral significance of those interests, is sufficient to establish that the burden of proof falls to the proponent of using UMIs to show that the only interests that would be at stake in a particular case would be those of the patient.[14] In the contexts under discussion in this paper, large-scale responses to public health emergencies, it is unlikely that this would ever be the case. Public health emergencies are contexts of scarcity, and the use of UMIs will impact the provision of services, the allocation of resources, and perceived adverse events or benefits will affect stakeholder attitudes toward the interventions deployed.

Second, efforts to salvage the view that desperately ill patients have a right to access UMIs would have to establish that the interests of these individuals are so morally weighty, and the value of access to UMIs is so high that access trumps or outweighs the costs and consequences enumerated here. To make such a comparative assessment, it is not enough to establish that the interests at stake for the desperately ill are morally weighty. It must be established that the value of accessing UMIs is sufficient to outweigh the other moral concerns outlined here. Because medical interventions are tools for improving health (they are not intrinsically valuable goods), no claim of this kind could be made without reference to the probability that UMIs will actually help or harm those in need.

4 | REASONABLE EXPECTATION OF BENEFIT?

A necessary condition for any right or strong moral claim to access UMIs is that UMIs have a reasonable expectation of meaningful benefit. This position is sometimes defended with the following comparison: given the bleak prognosis of patients with conditions that lack effective medical treatments or who have exhausted the current medical options, UMIs represent their last best hope. The claim that there is no equipoise between UMIs and control arms that include the standard of care or the standard of care plus a placebo is framed in a similar way: when the prospect of benefit from interventions in the control arm are bleak, and the situation of patients is dire, a UMI that is 'potentially beneficial' is preferable to randomization to the control.[15] In both cases the structure of the argument is to portray the status quo as tantamount to relegating patients to death or severe disability with certainty and UMIs as no worse and possibly better than the status quo.

Three problems with this way of framing the issue merit special comment. First, even if we assume that a UMI is in fact a person's last best hope (not an uncontroversial assumption), establishing that access to UMIs represents the best option for a particular person does not show that the benefits of access to UMIs are sufficient to outweigh the countervailing moral concerns outlined in the previous section. In part, this is because 'x is person y's best option' is consistent with the claim that x is unlikely to provide y with a meaningful clinical benefit and may even be harmful.

Second, the duties of health professionals are bounded by the limits of established medical and public health practice, and without compelling evidence of safety and efficacy, there can be no duty on the part of health professionals to provide UMIs. If the fact that x represents y's last best hope were sufficient to generate an obligation on the part of others to make x available to y, this obligation would be unbounded. It would entail that the desperately ill have a right to any compound in academic labs or pharmaceutical company libraries for which there is even a remote theoretical rationale that it might have a desirable effect, even if the probability of success is vanishingly small.

Professionals who fail to provide established effective care may breach a moral duty because they fail to use a means of protecting a person's interests that is accepted in the relevant expert community

[13] See also London, A. J. (2012). Non-paternalistic model of research ethics and oversight: Assessing the benefits of prospective review. *Journal of Law, Medicine & Ethics*, *40*(202), 930–944.

[14] Prasad, V., & Cifu, A. (2012). Medical burden of proof: Towards a new ethic. *BioSocieties*, *7*, 72.

[15] Adebamowo et al., *op. cit.* note 3; Caplan et al., *op. cit.* note 3.

as effective for achieving that goal. Even if we grant (again, not an uncontroversial assumption) that it may be *permissible* for such professionals to assist the desperately ill in accessing interventions whose clinical merits are unknown and untested, permissibility is different from moral obligation. In the argument under consideration here, only a moral obligation to provide access to UMIs is sufficient to establish that failure to provide a UMI deprives patients of something to which they are morally entitled.

Third, whether access to some UMI actually represents a person's last best hope depends on how their prospects under the current standard of care compare to their prospects if they receive a UMI. Up to this point the arguments in this paper have granted assumptions about the safety and likely efficacy of UMIs that are deeply questionable. In particular, I will now argue that it is quite reasonable for responsible and informed medical experts to have an extremely pessimistic estimate of the likelihood that a UMI will produce a meaningful net clinical benefit in precisely those cases where access to UMIs is likely to be most pressing.

5 | A REASONABLE PESSIMISM ABOUT UMIs

On average, for every 100 drugs that enter the development pipeline, only 10 are ever approved for some indication.[16] Even at the late stages of development, roughly half of drugs in phase III trials fail. In a study of 22 trials in which promising results from phase II trials were not vindicated in subsequent phase III studies, the U.S. Food and Drug Administration (FDA) noted that the cause of the discrepancy was related to:

> … effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.[17]

Since few researchers or drug sponsors would knowingly spend hundreds of millions of dollars on what they regarded as a losing bet, these bleak figures suggest that we remain fairly unreliable at being able to anticipate which UMIs will ultimately demonstrate clinical utility and which will not.[18]

However, it would be a mistake to conclude from these figures that access to a UMI in the early stages of development entails anything like a 10% chance at a meaningful clinical benefit. The reason is that the summary statistics in the previous paragraph likely underestimate the difficulty of determining whether any particular UMI will provide a meaningful net clinical advantage to patients with a particular disease, let alone for a particular patient.

To begin with, statistics about the rates of drug approval focus on 'drugs' as the unit of translation. This is a sensible choice for an investor who cares only about the likelihood that a novel product in a firm's pipeline will eventually make it to market. But whether a drug is helpful or harmful depends on numerous features of its use.[19] One of these is indication—the population in which the drug is likely to have a beneficial effect. The fact that one in 10 drugs is approved for *some* indication tells us nothing about how many indications were investigated for each drug, whether ultimately approved or not. In many cases, however, drugs that are ultimately approved for one indication (e.g., a particular tumor type) have been tried in numerous phase I and phase II trials of different indications.[20] And as our knowledge about disease mechanism changes, drugs initially tried in one area (e.g., diabetes) are investigated in new indications (e.g., dementia).

In addition to indication, the effect of a drug depends on the dosage used, the schedule on which it is given, whether it requires co-interventions to promote a therapeutic effect or to mitigate adverse reactions, and how it interacts with other interventions the patient has received. Each of these factors—drug, indication, dose, schedule, co-interventions—is a component of what Kimmelman and London call an 'intervention ensemble.'[21] At the beginning of clinical translation, few of the factors necessary to produce an effective intervention ensemble have even been explored, let alone explored to the point where clinicians can be confident they are approximating values that promote desired effects without being ineffective or positively harmful.

In the course of translation, a particular drug may be tried not just in numerous indications, but at different doses or schedules, with different co-interventions and diagnostic criteria. In effect, developers have to explore numerous intervention ensembles featuring the same drug in order to identify an ensemble that warrants testing in a large, confirmatory trial designed to establish efficacy. For any successful translation trajectory, dozens or even hundreds of different intervention ensembles have been explored. The vast majority of these show no benefit or even harm patients. The same is true for many drugs that never feature in an approved intervention ensemble or that are approved for some indication but trialed in new indications. These exploratory activities are also not reflected in the denominator of the above statistics.

[16] Hay, M., Thomas, D. W., Craighead, J. L., Economides, C., & Rosenthal, J. (2014). Clinical development success rates for investigational drugs. *Nature Biotechnology*, *32*, 40–51.

[17] U.S. Food and Drug Administration. (2017). 22 case studies where phase 2 and phase 3 trials had divergent results. Retrieved from https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm535541.htm

[18] Kimmelman, J., & London, A. J. (2011). Predicting harms and benefits in translational trials: Ethics, evidence, and uncertainty. *PLoS Medicine*, *8*(3), e1001010.

[19] Kimmelman, J., & London, A. J. (2015). The structure of clinical translation: Efficiency, information, and ethics. *The Hastings Center Report*, *45*(2), 27–39.

[20] Ibid., pp. 33–37; see also Carlisle, B., Demko, N., Freeman, G., Hakala, A., MacKinnon, N., Ramsay T., … Kimmelman, J. (2015). Benefit, risk and outcomes in drug development: A systematic review of sunitinib. *Journal of the National Cancer Institute*, *108*(1), djv29.

[21] Kimmelman & London, *op. cit.* note 19.

For clinicians and patients trying to use base rates of success to inform their estimate of the likely benefits and harms of taking a UMI, the proper denominator is not the number of drugs that enter the pipeline, or even the number of indications investigated, but the number of intervention ensembles tested. This figure is undoubtedly larger (perhaps by several orders of magnitude) than the number of drugs that enter the pipeline.

To assess the prospects that a UMI will actually benefit a particular patient, the decision maker has to estimate the probability that there exists a dosage and a schedule on which the drug in question can provide clinical benefit to patients with this disease, the probability that the drug will be given in the proper dose (not one that is ineffective or toxic), on the proper schedule, that no additional interventions are necessary to promote a therapeutic effect, that there are no adverse reactions with other interventions the patient is receiving, and that this patient does not fall into a subcategory for which the drug is contraindicated.

Additionally, statistics that average over development efforts in different diseases can mask difficulties in precisely those areas where access to UMIs is likely to be most attractive, namely, conditions for which drug development has proven most difficult. For example, Cummings and colleagues report that in the 10 years between 2002 and 2012, 244 interventions for Alzheimer's disease were assessed in 413 trials with an overall failure rate of 99.6%.[22] When patients have a condition for which there are few effective treatments or they are part of a subgroup for whom existing treatments do not work, the probability of benefit from a UMI may be far lower than average.

Success in drug development is also more complex than it may at first appear. That a drug is ultimately approved for an indication is consistent with wide variability in the clinical significance of its effects and the probability that any particular patient will experience benefit. For example, some drugs have been established as effective for a particular condition, but nevertheless have only a marginal benefit, or a relatively small probability of conferring benefit. Among healthy people, for example, daily aspirin is effective at preventing heart attacks and strokes, but in the course of one year it is likely that these benefits will accrue to one in 2,000 and 10,000 patients respectively.[23] In oncology, new drugs have been approved that offer only marginal survival advantage over their comparators.[24] From the standpoint of patients and clinicians, the relevant question is not the probability they will see an effect that would win approval from a regulatory body, but whether the deployed intervention ensemble is more likely to help than to harm them, and whether the net benefit will be clinically meaningful.[25]

In light of these reflections, anticipating the likely effects of a UMI is a situation of radical uncertainty in which reasonable people, confronted with all of the relevant information, can have radically different prior beliefs. Prior beliefs to the effect that a UMI is unlikely to be better than the current standard of care for particular patients seem both reasonable and warranted. There are also strong reasons for judging that a UMI in the earliest stages of development is unlikely to help a desperately ill patient and may simply worsen their condition and hasten death or disability.

6 | UMIs AND CLINICAL EQUIPOISE

We are now in position to evaluate the claim that if x is the last best option for y, then there cannot be equipoise in a study that would randomize y to x or to a control group that includes the standard of care, or the standard of care plus a placebo. To be clear, the question of equipoise is relevant because it purports to provide independent reason to believe that desperately ill patients have a right to receive a UMI. That is, if there is no equipoise because the UMI is regarded as medically obligatory, then requiring patients to take the chance of being randomized to something other than a UMI would force them to accept the risk of being allocated to a control condition that is ethically impermissible.

As one group argued:

> Equipoise, however, breaks down when available conventional care offers little benefit, some agents appear promising and safe, and mortality is extremely high. This is the case with Ebola in West Africa. Mortality rates where experimental drugs and agents are and will be tested are estimated to be as high as 70% (Hunt 2014). When available conventional care means a high probability of death and a novel intervention holds some possibility of benefit due to promising prior if limited use in humans, animal studies, or simply theoretical plausibility, it is morally problematic to insist on randomizing patients to a control arm in the context of an ineffective standard of care.[26]

The rationale for the position articulated here is not immediately clear. It seems to be a form of dominance reasoning: if a UMI is believed to be safe and there is even a theoretical possibility that it offers some positive probability of benefit, then it must be preferable to allocation to a standard of care that includes a high probability of death.

[22] Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimer's Research & Therapy*, *6*, 37.

[23] http://www.thennt.com/nnt/aspirin-to-prevent-a-first-heart-attack-or-stroke/.

[24] Rupp, T., & Zuckerman, D. (2017). Quality of life, overall survival, and costs of cancer drugs approved based on surrogate endpoints. *JAMA Internal Medicine*, *177*(2), 276–277; Kim, C., & Prasad, V. (2015). Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. *JAMA Internal Medicine*, *175*(12), 1992–1994; Kumar, H., Fojo T., & Mailankody, S. (2016). An appraisal of clinically meaningful outcomes guidelines for oncology clinical trials. *JAMA Oncology*, *2*(9), 1238–1240; Fojo, T., Mailankody S., & Lo, A. (2014). Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity. *JAMA Otolaryngology – Head & Neck Surgery*, *140*(12), 1225–1236.

[25] On the gap in perception about the meaning of FDA approval and clinical realities, see Schwartz, L. W., & Woloshin, S. (2011). Communicating uncertainties about prescription drugs to the Public: A national randomized trial. *Archives of Internal Medicine*, *171*(16), 1463–1468.

[26] Caplan et al., *op. cit.* note 3, p. 6. A very similar passage appears in Adebamowo et al., *op. cit.* note 3, p. 1423.

This position rests on several faulty assumptions. First, the quoted position glosses over the degree of uncertainty that surrounds each of its key claims. As a recent report from the U.S. National Academies of Sciences, Engineering, and Medicine states:

> In retrospect it is clear that initial assumptions about mortality rates and the shape of the epidemic were incorrect. As the response to Ebola improved, the overall mortality rate in the three high-impact countries progressively dropped over the course of the epidemic, from 61.5 percent in July 2014 to 40.7 percent in July 2015; the mortality rate also differed among the three countries, from a high of 66.6 percent in Guinea to 45.1 percent in Liberia and 30.0 percent in Sierra Leone.[27]

The morality rate for patients who received fluid replacement therapy was uncertain, and appears to have dropped significantly over the course of the outbreak. The claim that such treatments were ineffective assumes a position that was highly questionable at the time and was likely false. At best, this shows only that experts disagreed about the likely clinical merits of fluid replacement therapy for Ebola. The claim that UMIs under consideration were known to be safe is also dubious as many had never been tested in humans, or in humans in as fragile a medical state as patients with Ebola. The comments of the previous section underscore the realities that most novel intervention ensembles do not work or are positively harmful.

Second, and most importantly, the quoted passage enforces a self-defeating moral position.[28] It permits clinicians who favor the provision of UMIs to provide them to patients and it permits clinicians who favor standard treatment to provide that, but it *prohibits* research that would allocate patients to a UMI or the standard of care in a way that would generate the evidence necessary to establish the relative merits of those practices. But, if it is permissible for a patient to be treated by clinicians from these conflicting schools of practice, then it must also be permissible for such a patient to be part of a study in which they are randomized to the interventions that would be recommended for them by clinicians from these same groups.[29] In both scenarios, some desperately ill patients receive a UMI while others do not. But prohibiting the trial prohibits allocating those interventions in a way that grounds valid inferences about their relative clinical merits. It advances the interests of no stakeholder while frustrating the generation of information that a wide range of stakeholders require to make 'decisions that impact individual and public health, welfare, and the use of limited resources' (CIOMS 2016 Guideline 1).

Finally, the position in the quoted passage is self-defeating because it misconstrues the nature of the equipoise requirement. Clinical equipoise is a state of conflict or uncertainty within the relevant expert community.[30] There is credible uncertainty in the expert medical community when there is not sufficient medical evidence to ground a professional duty to provide one intervention over the others. There is conflict or disagreement in the expert medical community when some fully informed experts regard one intervention to be best while other, equally well-informed experts judge a different intervention to be best.[31] Uncertainty and conflict can co-exist, since the presence of conflicting expert judgments may lead some experts to believe that the available evidence is insufficient to ground a considered medical preference for one intervention over the others. Allocating study participants to interventions that are the subject of such conflict or uncertainty via a mechanism that supports reliable inference (such as randomization) does not knowingly disadvantage any participant.

The logic of the argument in the previous paragraph can be generalized in two ways. Call the first the Argument from Permissibility. I argued above that without credible evidence of efficacy in patients with the disease in question, there can be no duty to provide a UMI to patients. In the presence of uncertainty about the benefits of the best available medical alternative, it may be permissible to provide a UMI. But it would also permissible not to do so. If it is permissible to offer patients access to UMIs and permissible not to do so, then it must also be permissible to allow patients to be randomized to a UMI or to the standard of care. Allowing patients to be allocated to interventions by randomization facilitates the generation of socially valuable knowledge without depriving anyone of a level of care to which they are entitled by a duty of care.

The Argument from Permissibility is relevant to cases such as the one reported by Fedson et al., who describe the use of statins and angiotensin receptor blockers to treat 'approximately 100 patients with laboratory-confirmed Ebola virus disease' in Sierra Leone.[32] In this 'study' 100 patients were treated with this investigational regimen while many others were not. So these clinicians regarded it as

[27] US National Academies of Sciences, Engineering, and Medicine. Committee on Clinical Trials During the 2014–2015 Ebola Outbreak. (2017). *Integrating clinical research into epidemic response: The Ebola experience*. Washington, DC: The National Academies Press. Retrieved from https://www.nap.edu/catalog/24739/ integrating-clinical-research-into-epidemic-response-the-ebola-experience. p. 2–22. The passage quoted cites Johnston, W. R. (2015). *Statistics on the 2014–2015 West Africa Ebola outbreak*. Retrieved January 20, 2017, from http://www.johnstonsarchive.net/policy/westafrica-ebola.html.

[28] London, *op. cit.* note 5, p. 581.

[29] More precisely, if clinician A would recommend intervention i1 for patient P, and clinician B would recommend i2 for P, then both i1 and i2 are admissible options for P. A trial in which P is randomized to i1 or i2 ensures that P receives a level of care that does not fall below what would be recommended by at least a reasonable minority of medical experts. See London, A. J. (2007). Two dogmas of research ethics and the integrative approach to human-subjects research. *Journal of Medicine & Philosophy*, *32*(2), 99–116; see also London, *op. cit.* note 5.

[30] Freedman, *op. cit.* note 4; London, A. J. (2017). Equipoise in research. *Journal of the American Medical Association*, *317*(5), 525; London, A. J. (2006). Reasonable risks in clinical research: A critique and a proposal for the integrative approach. *Statistics in Medicine*, *25*(17), 2869–2885. Miller, P. B., & Weijer, C. (2003). Rehabilitating equipoise. *Kennedy Institute of Ethics Journal*, *13*(2), 93–118.

[31] It should be noted that some commentators proposed adaptive trial designs as a more ethical alternative to traditional randomized controlled trials (Caplan et al., *op. cit.* note 3 and Adebamowo et al., *op. cit.* note 3). That the view defended here applies equally well to adaptive trial designs is demonstrated in London, A. J. (2018). Learning health systems, clinical equipoise and the ethics of response adaptive randomisation. *Journal of Medical Ethics*, *44*, 409–415.

[32] Fedson, D. S., Jacobson, J. R., Rordam O. M., & Opal, S. M. (2015). Treating the host response to Ebola virus disease with generic statins and angiotensin receptor blockers. *mBio*, *6*(3), 1–4.

permissible to provide this investigational regimen to some patients but not to others. Yet, they chose to allocate patients to this UMI in a way that did not promote reliable medical inferences. Nor were patients informed that they were being provided with an investigational medical intervention: 'The agreement did not stipulate that signed informed consent be obtained from each patient because it was assumed that physicians and the government would be acting in the best interests of their patients.'[33]

Fedson and colleagues claim that 'reports indicate that rapid clinical improvement was seen in almost all patients' but no data or corroborating evidence are available to substantiate this claim.[34] This situation is strictly morally worse than one in which the provision of this UMI was carried out within the confines of a well-designed and properly controlled clinical trial. In the latter case, some patients would receive the UMI, while others would not (exactly as happened in this case). But the probability that the study would support reliable inferences about the relative merits of this UMI and the best medical alternative would have been far higher. Furthermore, the requirement of informed consent for research participation ensures that patients or their representatives are not subjected to a UMI without their knowledge or consent.

Call the second approach the Argument from Informed Conservative Practice. This position holds that fully informed experts in the medical community, confronted with the same information, may reasonably have different estimates of the likely clinical value of a UMI. Clinical equipoise obtains between the UMI and the best medical alternative(s) as long as an informed but conservative expert community would continue to recommend the best medical alternative(s) as a permissible intervention for patients with the condition in question. In light of the reasoning in the previous section, it is quite reasonable for at least a minority of responsible and informed medical experts to have a pessimistic estimate of the likelihood that a UMI will produce a meaningful net clinical benefit in precisely those cases where access to UMIs is likely to be most pressing. When some informed, expert clinicians recommend the use of a UMI but other, more conservative, but equally informed and expert clinicians do not, then it does not show a lack of concern for the welfare or health interests of the desperately ill to allocate them to such interventions by a mechanism that permits reliable scientific inferences about the relative clinical merits of the interventions in question. Each patient is guaranteed to receive a level of care that would be recommended for them by at least a reasonable minority of experts.[35]

Together, these arguments rebut the claim that there can be no equipoise between a standard of care control arm and a UMI in cases where the medical merits of the standard of care are uncertain and a disease has high fatality rates. In doing so, these arguments undermine an independent route to the claim that patients have a right to access UMIs in such contexts.

It might be objected that the arguments in this section do not establish the permissibility of restricting access to UMIs to the context of clinical trials. Strictly speaking, this is correct. However, the arguments of previous sections undermine the claim that the decision to utilize a UMI legitimately falls to the sole discretion of the patient, such that limitations on that decision represent illegitimate interference with personal liberty. As a result, limiting access to UMIs to participation in clinical trials does not make the desperately ill worse off in the sense of denying them access to something to which they are otherwise entitled. The upshot of this analysis is thus that it is not impermissible to limit the use of UMIs to the context of well-designed and properly controlled clinical trials and that doing so often represents an ethically sound strategy for reconciling respect for the desperately ill with the goal of generating socially valuable information.[36] This weaker claim is all that is needed to support the position articulated in the 2016 CIOMS Guidelines.

As the 2016 CIOMS Guidelines note, how and when clinical research is carried out impacts the interests of a broad range of stakeholders because 'Patients, health professionals, researchers, policy-makers, public health officials, pharmaceutical companies and others rely on the results of research for activities and decisions that impact individual and public health, welfare, and the use of limited resources' (Guideline 1). Limiting access to UMIs to well-designed and properly controlled clinical trials generates the evidence that these stakeholders need to discharge important social responsibilities. In the presence of clinical equipoise, this limitation does not disadvantage study participants either by consigning them to care that is known to be inferior or by denying them access to something to which they have a just prior claim.

In this regard, the new CIOMS Guidelines are well situated to prevent self-defeating approaches to emotionally charged medical situations, while ensuring that study participants are protected from abuse, neglect, and other moral wrongs. As such, the position in the 2016 CIOMS Guidelines that 'health-related research should form an integral part of disaster response' represents ethically sound guidance for generating evidence-based responses to public health emergencies.

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CONFLICT OF INTEREST

I have no conflicts of interest to disclose, but it should be noted that I was a member of the working group that revised the CIOMS Guidelines.

[33] Ibid., p. 2.

[34] Richardson, T., Johnston, A. M., & Draper, H. (2017). A systematic review of Ebola treatment trials to assess the extent to which they adhere to ethical guidelines. *PLoS One*, *12*(1), e0168975.

[35] Kadane, J. B. (1996). *Bayesian methods and ethics in a clinical trial design*. New York, NY: John Wiley & Sons Ltd; London 2006, *op. cit.* note 30.

[36] London, A. J. (2009). Clinical research in a public health crisis: The integrative approach to managing uncertainty and mitigating conflict. *Seton Hall Law Review*, *39*(4), 1173–1202.

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