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The Duty to Rescue and Randomized Controlled Trials Involving Serious Diseases

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Abstract

During the recent Ebola epidemic, some commentators and stakeholders argued that it would be unethical to carry out a study that withheld a potential treatment from affected individuals with such a serious, untreatable disease. As a result, the initial trials of experimental treatments did not have control arms, despite important scientific reasons for their inclusion. In this paper, we consider whether the *duty to rescue* entails that it would be unethical to withhold an experimental treatment from patient-participants with serious diseases for which there are no effective treatments, even when doing so is scientifically necessary to test the effectiveness of the treatment. We argue that the duty to rescue will rarely apply. The context of medical research also throws new light on the content of the duty to rescue, since the interests of future patients—who stand to benefit from the fruits of medical research—are relevant to whether the duty applies.

Keywords

duty to rescue – medical research – trial design – Ebola

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Introduction

Randomized controlled trials (RCTs) are widely regarded as the scientific gold standard for assessing the efficacy of new medical treatments. By randomly assigning some eligible patient-participants to the existing standard of care and others to the standard of care plus the experimental treatment, researchers can gather data about the efficacy of the experimental treatment that may not otherwise be obtainable. At the same time, randomizing some patient-participants to the existing standard of care rather than the new treatment can raise important ethical concerns. These concerns are especially acute when the patients have a serious disease for which there are no effective treatments. In this setting, patient-participants who are randomized to the experimental arm receive an intervention that might reduce or eliminate their disease; patient-participants randomized to the control arm only receive supportive care.

Debate over whether it can be ethically acceptable to withhold a potential treatment in order to answer a scientific question came to prominence in the 1980s in the context of clinical trials designed to assess experimental treatments for HIV/AIDS. The debate resurfaced recently with regard to clinical trials designed to evaluate potential treatments for Ebola virus disease (EVD) in West Africa. The lack of consensus over whether such trial designs are ethical has serious consequences. It can significantly delay the conduct and completion of clinical trials to evaluate new treatments, and can undermine institutional and public support for them. Indeed, the first trials of potential treatments for EVD were conducted without a comparator arm due to concerns that it would be unethical to withhold a potential treatment, even if unproven, from patient-participants with a serious disease.[1] As a result, it has been argued, the data collected during the Ebola epidemic are substantially less valuable than they might have otherwise been.[2] To avoid these problems in future epidemics, it is vital to work out prospectively when randomized, controlled clinical trials are ethically acceptable in the setting of serious diseases for which there are no effective treatments.

A number of commentators argue that—even when scientifically optimal—the use of a control arm providing only supportive care while testing experimental interventions for EVD is unethical because it denies access to a potential treatment to patients who face a high chance of death. Clement Adebamowo et al. write: "When conventional care means such a high probability of death,

1 Beavogui et al. Clinical research during the Ebola virus disease outbreak in Guinea: Lessons learned and ways forward. *Clin Trials.* February 2016 13: 66–72.

2 Jon Cohen and Martin Enserink. As Ebola epidemic draws to a close, a thin scientific harvest. *Science*. 2016 Jan 1; 351(6268): 12–3.

it is problematic to insist on randomising patients to it when the intervention arm holds out at least the possibility of benefit."[3] Similarly, Arthur Caplan et al. claim that:

> 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.[4]

These arguments have strong intuitive appeal when we are dealing with serious diseases—those that carry non-negligible risks of significant morbidity or mortality even with supportive care. When there are no effective treatments for such serious diseases, it does seem ethically problematic to withhold a potentially promising experimental treatment for the sake of collecting scientific data.

Perhaps the most plausible justification for this claim, which we take to be underlying the objections of Adebamowo et al. and Caplan et al., is that withholding the experimental treatment violates the *duty to rescue*—the duty to attempt to prevent serious harm to another person when the cost of attempting rescue is low.[5] If this is right, then no-treatment control arms should never be used in trials of experimental treatments for serious diseases, even if they are necessary to generate data that will benefit future patients. Researchers should not design, sponsors and research institutions should not support, and research ethics committees should not approve clinical trials that use a no-treatment control arm to evaluate new interventions for serious illnesses. Alternative methods must be identified and pursued, even if they yield significantly less information regarding the efficacy of the interventions being tested. And, if this argument is correct, it suggests that many trials currently being conducted to identify new medical treatments for a broad range of serious illnesses are unethical.

The present paper evaluates this line of argument. We focus on EVD for illustrative purposes. However, our analysis applies to any setting that involves

3 Adebamowo et al. Randomised controlled trials for Ebola: practical and ethical issues. *Lancet*. October 10, 2014.

4 Caplan, A.L., Plunkett, C., Levin, B. Selecting the Right Tool for the Job. *American Journal of Bioethics*. 2015.

5 Compare the discussion in Hawkins, J.S. Exploitation and Placebo Controls. In Hawkins, J.S. and E.J. Emanuel (eds.). *Exploitation and Developing Countries: The Ethics of Clinical Research*. Princeton & Oxford: Princeton University Press (2008): 246–285.

testing new interventions, including treatments and vaccines, for serious conditions for which no effective treatments exist and for which there is a known and non-negligible risk of substantial morbidity or mortality from supportive care alone. We argue that, despite strong intuitions to the contrary, clinical trials that rely on a no-treatment control arm to evaluate new interventions for serious conditions very rarely violate the duty to rescue.[6] Our discussion also throws new light on the content of the duty to rescue, since the interests of future patients are a vital input to the ethical analysis in this case. The interests of third parties have not received much attention in previous work on the duty to rescue.

Scientific Necessity

Medical researchers evaluate the safety and efficacy of experimental interventions by comparing patients who receive an experimental intervention to similar patients who do not receive it. When there exist effective treatments for a given condition, clinical trials to evaluate new treatments usually randomize patient-participants to either the new treatment or the existing treatment. By comparing the clinical consequences in the two cohorts, researchers can collect valuable data on whether the experimental treatment is better than the existing one. In the absence of an effective treatment, RCTs compare the outcomes in patients who receive the experimental treatment plus supportive care to the outcomes in patients who receive supportive care alone. To protect against potential bias, patient-participants in the latter arm are frequently administered a placebo that looks identical to the experimental treatment. Following standard terminology, we will refer to the arm that receives only supportive care (and possibly placebo) as the *no-treatment* control arm.[7]

6 This is not to say that such trials are necessarily ethical; one first needs to ensure that other relevant conditions are satisfied as well. These conditions include ensuring that the risks to participants as a result of not receiving the experimental treatment are minimized, that the value of the data is sufficient to justify the research risks, and so forth. See, for example: David Wendler, Ezekiel J. Emanuel, Reidar K. Lie. The Standard of Care Debate: Can Research in Developing Countries Be Both Ethical and Responsive to Those Countries' Health Needs? *Am J Public Health*. 2004 June; 94(6): 923–928.

7 Since there are reasons to think that supportive care (e.g. hydration) might reduce mortality, we acknowledge that it is somewhat artificial to describe it as "no-treatment." The crucial point for the purposes of this paper is that the standard of care received by both arms of the RCT—the control as well as the experimental arm—is not expected to reduce the risk of substantial morbidity or death to nearly zero, i.e. an effective treatment would be very beneficial.

Control arms are used at various stages of drug testing and development. They are used in most phase III studies, which are designed to rigorously test the efficacy of an intervention. They are often used in phase II studies, which evaluate safety and look for preliminary evidence of efficacy. And they are even sometimes used in phase I studies, which focus on identifying an appropriate dose and evaluating the toxicity of experimental interventions.

During the early HIV crisis in the United States, and the more recent Ebola epidemic in West Africa, some commentators objected to the use of no-treatment control arms on the grounds that they were not necessary to identify effective treatments.[8] These critics argued that alternative designs would answer the important scientific questions and withhold the experimental treatment from fewer or no patients. We agree that when it is possible to evaluate the clinical efficacy of new interventions for a serious disease without using a no-treatment control arm, such trial designs should be avoided. No-treatment control arms should be used only when their inclusion provides critical data that could not be collected otherwise. For instance, there is typically no need for a control arm to evaluate whether the addition of an experimental intervention is beneficial when there is systematic and reliable data on the clinical outcomes in historical controls who are relevantly similar to the study population.[9] Likewise, designs that expose fewer participants to risks, including the risks of not receiving potentially beneficial treatments, should *ceteris paribus* be preferred.[10]

8 Dan O'Connor. For immediate help, the ethics of research have to change. *The Guardian*. Saturday October 11, 2014. Available at: http://www.theguardian.com/commentisfree/2014/oct/12/ebola-drugs-medical-research-trial-placebo.

9 Thomas, R., Fleming and Susan, S., Ellenberg. Evaluating interventions for Ebola: The need for randomized trials. *Clin Trials* February 2016 13: 6–9.

10 Some study designs use no-treatment control arms in ways that increase the probability that patient-participants receive the experimental treatment. For example, Ben S. Cooper et al. simulated different treatment evaluation programs for EVD and recommend a multi-stage approach that would include a single-arm phase II trial followed by an RCT with a no-treatment arm just in case the phase II trial did not show strong evidence of benefit (Cooper, B.S., Boni, M.F., Pan-ngum, W., Day, N.P., Horby, P.W., Olliaro, P., Lang, T., White, N.J., White, L.J. and Whitehead, J., 2015. Evaluating clinical trial designs for investigational treatments of Ebola virus disease. *PLoS Med*, *12*(4), p. e1001815). Such designs may be ethically preferable to a standard RCT when they expose fewer participants to risks or get effective treatment to patients more quickly. Nevertheless, our analysis will apply to any design in which scientific necessity supports the use of a no-treatment arm, since the question of how the duty to rescue applies to patients in that arm will still arise.

Our analysis focuses on cases in which there is an important justification for including a no-treatment control arm in terms of the social value of the data to be collected.[11] For example, it is often unclear, especially in the context of a new epidemic, what percentage of patients who receive supportive care will survive. In this setting, a no-treatment control arm allows researchers to evaluate whether the fact that, say, 60% of patients who receive the experimental treatment survived indicates a dramatic treatment breakthrough or simply reflects the clinical course of the disease. The question this paper seeks to answer is: Are no-treatment control arms unethical even when their inclusion yields socially valuable data regarding the efficacy of new treatments that could not be obtained otherwise?

Ebola Virus Disease

EVD is caused by infection with one of the four Ebola virus species known to cause disease in humans. Ebola was first discovered in 1976 near the Ebola river in what is now the Democratic Republic of the Congo. Since then, outbreaks have occurred sporadically in Africa. It is believed that the virus is animal-borne and that bats are the most likely reservoir. People get Ebola through direct contact with an infected animal or contact with the body fluids of an infected person. Symptoms appear on average 8–10 days after exposure and can include fever, severe headache, pain, fatigue, diarrhea, vomiting, and bleeding. There are no known effective treatments for EVD. The chances of recovery depend on good supportive care and the patient's immune response. Many people infected with EVD die and some of those who recover develop long-term complications, such as joint and vision problems.[12]

During the recent crisis, the case fatality rate for EVD in developing countries was high—from 40–70%.[13] This is in contrast with diseases such as

11 Edward Cox, Luciana Borio, Robert Temple. Evaluating Ebola Therapies—The Case for RCTs. *N Engl J Med.* 2014; 371: 2350–2351.

12 There is limited data on the long-term health effects of EVD. However, recent work suggests substantially increased risk of ocular deficits, hearing loss, neurological abnormalities, fatigue, and other chronic health problems (Clark, D.V., Kibuuka, H., Millard, M., Wakabi, S., Lukwago, L., Taylor, A., Eller, M.A., Eller, L.A., Michael, N.L., Honko, A.N., Olinger, G.G. Jr., Schoepp, R.J., Hepburn, M.J., Hensley, L.E., Robb, M.L. Long-term sequelae after Ebola virus disease in Bundibugyo, Uganda: a retrospective cohort study. *Lancet Infect Dis*. 2015 Aug; 15(8): 905–12).

13 World Health Organization. Ebola virus disease. Available at http://www.who.int/mediacentre/factsheets/fs103/en/. Case fatality rates (CFRs) have varied between epidemics

cholera: although severe cholera also has a high case fatality rate (up to 50%), this can be reduced to under 1% with prompt treatment.[14] Moreover, despite some long-term sequelae, people who survive EVD have excellent prospects for living long, healthy lives. An effective EVD treatment would therefore be unlike many experimental cancer treatments, which, even if successful, might increase a patient's survival by only a few months.

For mild conditions, the risks of an experimental treatment can outweigh the potential benefits. For example, it is not clear whether it is better for patients with mild psoriasis to receive supportive care only or supportive care plus an experimental treatment. Given that mild psoriasis tends to be fairly well tolerated, the chance of a cure may not be sufficient to outweigh the potential for toxic side-effects. In these cases, withholding a potential new treatment in the context of a clinical trial raises few ethical concerns. In contrast, the side-effects of experimental EVD treatments are unlikely to have the same significance. From the point of view of the EVD patient, the potential for even highly toxic side-effects is likely to be outweighed by the chance that the intervention might prevent death.

The Duty to Rescue and Experimental EVD Treatments

The duty to rescue (or the "duty of easy rescue") is a general duty that applies to all moral agents. In brief, moral agents have a duty to attempt to prevent serious harm to another person, when they can do so at low cost to themselves and others.[15] The duty to rescue applies most clearly when there is a nearby and

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and appear to vary based on the strain of the Ebola virus. The CFR for a particular outbreak is challenging to measure accurately, particularly given the poor healthcare infrastructure in the West African countries in which EVD originates (for some discussion see Rambaut A. Case Fatality Rate for ebolavirus. Available at: http://epidemic.bio.ed.ac.uk/ebolavirus_fatality_rate).

14 Boore, A., Iwamoto, M., Mintz, E., Yu, P (2008) Cholera and other vibrioses. In: Heymann, D.L. (ed.) *Control of Communicable Diseases Manual, 19th ed.*: American Public Health Association, Washington, DC.

15 Tom Beauchamp and James Childress state the conditions for this duty more exhaustively as follows:

> [A] person X has a determinate obligation of beneficence toward person Y if and only if each of the following conditions is satisfied (assuming X is aware of the relevant facts):
>
> 1. Y is at risk of significant loss of or damage to life or health or some other major interest.

identifiable individual who is in serious need and who can almost certainly be rescued at low cost. In the classic case used to illustrate the duty to rescue, you are walking by a shallow pond and see a child drowning. You have a moral duty to wade in and save the child, even if it means that you will mess up your clothes and be late for your meeting, and even if you are in no way responsible for the child's circumstances.[16]

We want to know whether the duty to rescue prohibits studies of new treatments for serious diseases for which there are no proven effective treatments, like EVD, with no-treatment control arms. We start with the best-case scenario for someone who believes that it does: a Phase III study. Phase III studies evaluate interventions that have been shown through earlier phase testing to be unlikely to cause serious harm and have some evidence of efficacy. As a result, the argument that the use of a no-treatment control arm violates the duty to rescue is strongest for phase III studies—the probability of harm to the patients is much lower and the probability of benefit is much higher compared to phase I and II trials.

Typically, several phase III trials are required to definitively evaluate the efficacy of an experimental treatment. As a result, the value of any individual phase III trial depends on the extent to which it provides additional evidence of efficacy, as determined by the study's power. For present purposes, we simplify matters by taking as our paradigm case a Phase III trial that is designed to definitively demonstrate the efficacy or lack of efficacy of an experimental treatment. Readers concerned by this simplification can regard our arguments as applying to the set of phase III trials needed to definitively demonstrate efficacy or lack of efficacy. Moreover, to reiterate, we are considering cases in which it would not be possible to definitively demonstrate efficacy or lack of efficacy without the use of a no-treatment control arm.

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2. X's action is needed (singly or in concert with others) to prevent this loss or damage.

3. X's action (singly or in concert with others) has a high probability of preventing it.

4. X's action would not present significant risks, costs, or burdens to X.

5. The benefit that Y can be expected to gain outweighs any harms, costs, or burdens that X is likely to incur.

(Beauchamp, T.L., Childress, J.F. *Principles of Biomedical Ethics 4ed.* New York: OUP 1994: 266.) Our later argument suggests that their characterization is incomplete because it fails to take the interests of third parties into account. It remains controversial whether "significant risks, costs, or burdens" means only low costs, or whether the duty to rescue might arise even when the costs to the agent are more substantial (see Unger P. *Living High and Letting Die: Our Illusion of Innocence*. New York: Oxford University Press (1996), especially pp. 133–157). In this paper, we assume the former.

16 Singer P. Famine, affluence and morality. *Philos Public Aff* 1972; 1: 229–43.

Suppose that the case fatality rate for patients with EVD is 60% and an effective treatment would cut this mortality in half. Experience with other investigational drugs suggests that there is approximately a 50% chance that an experimental treatment that reaches phase III testing will ultimately turn out to be efficacious.[17] Thus, providing the experimental treatment to a patient with EVD offers a 50% chance of reducing her risk of dying from the disease from 60% to 30%.

A 50% chance of reducing the probability of dying from 60% to 30% seems like a large enough benefit that a clinician who had one EVD patient would feel duty bound to offer him the experimental treatment, especially if she had data from early phase studies indicating that the treatment is likely to be safe. Assuming the patient wanted the treatment, it would be wrong for the clinician to withhold it. This suggests that *clinicians* who are in possession of experimental treatments that have successfully completed phase I and phase II testing ethically must offer them to their EVD patients. Failing to do so, absent a compelling justification, would violate the duty to rescue. This conclusion raises the question of whether *clinical researchers* in possession of an experimental treatment that has successfully completed phase I and phase II testing likewise have an obligation to offer it to EVD patients rather than randomize them to either the experimental treatment or a no-treatment control arm.

There are several differences between the case of clinicians and the case of clinical researchers that must be addressed in order to leverage the duty to rescue against the use of a no-treatment control arm. We consider them in turn. In each case, we evaluate what conditions would have to hold for the argument against a no-treatment arm to be effective.

First, in the imagined case of the clinician with one EVD patient, the treatments available are intended for clinical use. Thus, it is open to the clinician to offer them to the patient. In the setting of clinical research, the treatments belong to the sponsor of the trial who has made them available for the purpose of conducting research. To make the argument that control arms are unethical on the grounds that they violate the duty to rescue, critics must show that

17 Hay et al. analyzed success rates for investigational drugs between 2003 and 2013. Fifty percent of drugs moving into Phase III were approved for the indication being tested for (Hay, M., Thomas, D.W., Craighead, J.L., Economides, C., Rosenthal, J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014 Jan; 32(1): 40–51 at 44.). This is a low estimate for success rates: the rates of approval are higher when looking at drugs rather than individual indications and drugs for infectious diseases have higher than average success rates.

clinician-researchers have a duty to provide the experimental treatment to patient-participants, even though it belongs to the sponsor.[18]

We will not consider this challenge at length: we think it very likely that proponents of the duty to rescue-based objection to no-treatment control arms could develop a successful argument in response. Presumably, if the sponsor were itself interacting directly with the EVD patients, any duty to rescue would apply to it. Consider how we should conceptualize the situation in which the sponsor hires the researchers to conduct the trial and interact with the EVD patients instead. One way to understand what is going on is to think of the two parties as one moral agent, since they are acting jointly. In this case, the combined agent is interacting with the patients and therefore can, like the clinician, have a duty to rescue. Alternatively, we might think that the researchers are agents of the sponsor, since it employs them to act on its behalf. But in this case, it also seems plausible that the researchers will have to discharge a duty to rescue on the sponsor's behalf, as they do other things on its behalf. Either way, the mere fact that the agent who owns the experimental treatment is geographically separated from the agents who are in possession of the experimental treatment and encounter people in need does not seem sufficient to avoid the duty to rescue.[19]

Second, there is an issue concerning the supply of the experimental treatment. If there are a very limited number of doses available, then the use of a control arm may not decrease the total number of patients who receive the experimental treatment. The first uses of experimental EVD treatments in patients occurred under conditions of extreme scarcity. For example, ZMapp, a combination of three monoclonal antibodies, was given to seven patients outside of any clinical trial early in the 2014 epidemic.[20] This exhausted supplies of the drug, which takes months to manufacture. We might imagine similar shortages of supplies for a phase III clinical trial, so that the researchers would have access to sufficient therapy for the participants in the experimental arm only.[21]

18 Note that we focus on the relevance of ownership here, not differences in the role obligations of clinicians versus researchers. We consider how professional duties might affect an individual's duty to rescue when we address objections at the end of the paper.

19 Compare Unger's discussion of appropriating other people's possessions to carry out rescues (Unger 1996: 62–83).

20 James Gallagher. Ebola: Experimental drug ZMapp is '100% effective' in animal trials. BBC News website. August 29, 2014. Available at: http://www.bbc.com/news/health-28980153.

21 This was part of the justification for including a no-treatment control arm in the famous 1948 RCT of streptomycin in the UK. (Crofton J. The MRC randomized trial of streptomycin and its legacy: a view from the clinical front line. *J R Soc Med.* 2006 Oct; 99(10): 531–534.)

Even if they had a duty to provide that therapy to some set of patients, this duty need not interfere with the use of a no-treatment control arm. Presumably, all the people enrolled into the treatment trial would be in desperate need of treatment and have an equal claim to receive it; supplies could then be exhausted treating (and hopefully rescuing) those who were randomized to the active treatment arm. Imagine that 1,000 infected patients have been identified and there are sufficient doses for only 250. It would be possible to conduct a single-arm study that provided the treatment to 250 patients, but left 750 not in the trial and not getting the experimental treatment. In such a case, there are no rescue-based reasons against conducting an RCT with 500 patients—250 in the active arm and 250 in a no-treatment control arm.

A scarcity of drugs is not normally the result of absolute constraints on how much can be manufactured. More often, it is the result of human decisions. In the case of ZMapp, for example, a choice had been made about the resources that would be devoted to producing the drug. Given sufficient money and a reasonable timeframe, it would have been possible to manufacture thousands of doses. Someone might therefore argue that the duty to rescue does not apply just to the provision of doses that are currently available; it also requires the sponsor to make more doses to distribute. In this case, of course, a rescuer would incur the additional costs of manufacturing and transporting new doses of the drug. If the drug is extremely expensive to manufacture, these costs might be high enough to exceed the threshold of acceptable cost for the rescuer and thereby negate the duty to rescue. For the critic of no-treatment control arms, then, it must be the case that the drug is cheap enough to manufacture that it meets the cost threshold for an easy rescue.

Note that whether the monetary cost of attempting rescue is below the threshold that triggers a duty to attempt rescue depends on the resources available to the potential rescuer. An expenditure that would entail serious sacrifices for an individual already living in poverty might have no impact on the well-being of someone who is well-off. Consequently, the poorer person might not have a duty to spend that amount of money to help someone in desperate need even though the richer person would. The resources at the disposal of the sponsor of research should be taken into account in assessing when the cost of attempting rescue negates the duty.

Third, suppose that the duty to rescue obliges the sponsor to supply the experimental drug for free up to some threshold cost of x dollars. The challenge for those who object to the use of no-treatment control arms is that it might be possible to use this amount of money to rescue a greater number of people in need who are encountered in the course of conducting an EVD trial. For example, the sponsor might provide treatment for children brought

to the research clinics who have cerebral malaria or diarrheal diseases. These treatments are cheap and have been proven to be very effective; for the same amount of money, it may be that many more rescues could be performed this way than by supplying an experimental Ebola treatment, even under the optimistic assumptions we have made about the chances that the experimental treatment is successful.[22]

A dilemma suggests itself: if the researchers (or sponsors) have a rescue-based duty to spend x dollars per patient on the experimental treatment, then they must have a duty to spend smaller amounts of money to provide urgently needed effective treatments to patients they encounter with other health conditions. In that case, the sponsor should provide the more beneficial treatments until it exhausts its duty to rescue. At that point, it may conduct the trial. Use of a control arm would therefore be inconsistent with a duty to rescue only when the cost of manufacturing the experimental treatment is sufficiently low and the cost of helping patients in other ways is sufficiently high.

Present Versus Future Patients

Let us sum up the argument so far. Our analysis suggests that researchers will have a moral obligation to provide an experimental treatment for a serious disease like EVD on the basis of the duty to rescue only if the following conditions hold:

(1) The prior probability of the treatment being effective is sufficiently high (in our hypothetical example: 50%);
(2) The expected benefit of an effective treatment is sufficiently great (in our hypothetical example: a reduction in the case fatality rate from 60% to 30%);
(3) There is sufficient supply of the treatment or sufficient supply could be manufactured in a timely way to meet existing needs;
(4) The cost of manufacturing and supplying the treatment is sufficiently low;

22 See Merritt, M. Health Researchers' Ancillary Care Obligations in Low-Resource Settings How Can We Tell What Is Morally Required? *Kennedy Inst Ethics J*. 2011 Dec; 21(4): 311–347. Rulli and MacKay point out that the duty of rescue provides no principled reason to distinguish participants from non-participants (Rulli, T. Mackay, D. The Duty to Rescue and Investigators' Obligations. *Kennedy Inst Ethics J.* 2017; 27(1): 71–105). We agree: if more harm could be prevented by providing proven therapies to *research participants or others* then there cannot be a duty of rescue to provide the experimental therapy instead.

(5) The cost of alternative ways to rescue potential participants or others who are encountered in the course of conducting a trial is not lower than the cost of providing patients with the experimental treatment.

Our first important conclusion, then, is that a duty to rescue does not arise immediately when researchers are in possession of a potential treatment for individuals with a serious disease. In some cases, these five conditions will not be satisfied, and the researchers will not have a duty to rescue. But, suppose, not implausibly, that these conditions are met for some case. Does it follow that it would be unethical to conduct an RCT which randomized some participants to a no-treatment arm?

The argument so far has only considered the costs of rescue to the rescuer. These are not the only costs that matter. We must also consider the costs to others of attempting rescue: in this case, the loss to future patients from not carrying out such a trial. For the most part, the literature on the duty to rescue has focused on the potential costs to the rescuer—the person wading into the pond in the classic case or the researcher and sponsor in the case of a clinical trial—not to other parties. In the case of the drowning child the costs to others are minimal: perhaps the other people at the meeting are somewhat inconvenienced by the delay in your arrival. Given these low costs, it is not surprising that the literature does not consider in any detail the moral relevance of costs to others. Evaluating clinical trials for serious diseases provides a context in which this factor becomes salient and thereby offers valuable insight into the scope of the duty to rescue.

The duty to rescue constrains the extent to which we are ethically permitted to pursue our own ends. In the classic case, we are not free to walk by the child, even if that is what we prefer to do. In contrast, we think that the duty to rescue places much less substantial constraints in contexts where a necessary component of an ethically important activity includes not attempting rescue. Foregoing use of a no-treatment control arm can lead to significant costs to future patients who might otherwise benefit from the results of the research. If clinical trials that can definitively demonstrate efficacy or lack of efficacy are not carried out, future patients are more likely to be given ineffective or even harmful treatments and research leading to the development of effective treatments is less likely to be carried out.[23] To characterize the classic rescue

23 Cox et al. make a similar point in their defense of RCTs against historical controls for experimental EVD treatment trials:

> If historical comparisons falsely suggest a benefit or fail to detect modest but meaningful clinical effectiveness, the investigational drug might be erroneously adopted as

case in a way that includes these costs, imagine that saving the one child in the nearby pond would prevent you from saving five children who are drowning in another pond (perhaps the children are in a pond that is over the hill and stopping for this child will leave you without sufficient time to save any of the others). It seems permissible for you not to save the child in front of you. Indeed, depending on the extent to which one believes that numbers matter morally, one might think that it would be wrong for you to save the proximate child when you know that doing so precludes you from saving the others. This does not imply that leaving the one to save the five would be psychologically easy; presumably, the urge to save the child you first encountered would be powerful (we return to this point below). Nevertheless, leaving the first child is plausibly the right thing to do.

Consider now how this modification of the classic case applies to the question of whether no-treatment control arms violate the duty to rescue. To simplify matters, assume researchers have the choice of whether to conduct a phase III RCT with a no-treatment control arm that will demonstrate definitively that the experimental treatment is effective or it is ineffective.[24] This gives us four possibilities, which we can evaluate for their likely effects on current and future EVD patients (Table 1). First, consider the case in which a phase III RCT is conducted. If the treatment is effective, the researchers will have failed to provide an effective treatment to those in the control arm, but future patients are likely to benefit from the treatment, assuming that it is manufactured and made clinically available. If the experimental treatment is shown to be ineffective, those in the control arm will not have missed out on any benefit (and will avoid any toxicity), and future patients have some increased prospect of rescue, since the trial gives the researchers useful information. At the very least, they now know to pursue alternative approaches; better, the data may suggest alternative strategies for the use of this or similar modalities.

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effective or discarded as ineffective. Possible consequences include exposure of subsequent patients to harm or to lack of effect from the mistakenly adopted treatment and failure to use a drug with a real, though modest, ability to improve survival, as well as failure to further develop an intervention that provides meaningful benefit. (Cox, E., Borio, L., Temple, R. Evaluating Ebola therapies—the case for RCTs. *N Engl J Med*. 2014 Dec 18; 371(25): 2350–1).

24 For the purposes of evaluating a phase III trial we are setting aside the possibility that the experimental treatment has serious side-effects. Limiting exposure to side-effects would give a further reason in favor of conducting an RCT, where scientifically necessary, since it would reduce the number of people exposed to the experimental treatment and help identify the side-effects before the treatment was used on future patients. We return to this point below.

TABLE 1 *Effects of a phase III RCT on control arm and future patients*

	Effective	**Ineffective**
RCT conducted	Control arm: No treatment	Control arm: No treatment
	Future patients: Effective treatment	Future patients: Higher chance of rescue through other leads than if no RCT
RCT not conducted	"Control arm": Effective treatment	"Control arm": Receive ineffective treatment
	Future patients: Some chance of effective treatment, but lower than if RCT conducted	Future patients: Lower chance of effective treatment than if RCT conducted

Second, consider the case in which no phase III RCT is conducted and all patients are simply given the experimental treatment (again: we are assuming that a no-treatment control arm would be necessary to demonstrate efficacy). If the treatment is effective, the patients who would have been in the control arm will receive it and so have a prospect of benefiting. Future patients also might receive the treatment, but this will be less likely than it would have been if efficacy had been shown, since the incentive to produce this treatment of uncertain efficacy would be limited. If the treatment is ineffective, current patients who would have been in the control arm receive an ineffective treatment, as do any future patients who are treated because the lack of efficacy is not identified. Future patients have no increased prospect of rescue because the state of EVD science has not been advanced.

What do these possibilities tell us about whether researchers have a duty to attempt to rescue current EVD patients rather than randomize some of them to a control arm without the experimental treatment? It suggests that there is a tradeoff between potential rescues of current patients and potential rescues of future patients. An RCT clearly increases the chances that future patients will benefit from an effective treatment, but, on the assumptions we have made, decreases the number of current patients who have access to experimental treatment. Ex ante, how the loss of potential benefit for future patients compares to the loss of access to the experimental treatment for patients in the no-treatment control arm will depend on:

(1) The probability that the experimental treatment is effective;
(2) The probability that an effective treatment saves the life or substantially decreases the morbidity of patients with EVD;
(3) The number of current EVD patients who do not get the experimental treatment because of the use of a no-treatment control arm; and
(4) The number of future EVD patients who do not get access to an effective treatment because a no-treatment control arm is not used.

Putting exact numbers on these values in an actual case would be challenging. But this analysis makes the tradeoffs transparent and so can still provide guidance. If the prior probability that the experimental treatment would substantially reduce mortality were over 90%, there would be little justification for carrying out an RCT with a no-treatment control arm. In this case, even absent the RCT, there is a high likelihood that the treatment would be provided to and benefit future patients. Imagine, in the modified pond scenario, that there is a 90% chance you can save the nearby child and still have time to save the other five children. It is very plausible that you should take the risk and try to save them all.

Contrast this with a case in which there is a 50% chance that the experimental treatment is effective and a 50% chance that it is not effective. Further suppose that, as is typically the case, the future cohort of patients who would benefit from an effective treatment is orders of magnitude larger than the number of patients in the no-treatment control arm of the RCT. In this case, the use of a no-treatment control arm seems consistent with the duty to rescue. The chance that the much larger group of future patients would miss out on a potentially life-saving treatment would be too high. This, we suspect, is the more likely scenario, even under the optimistic assumptions we have so far granted to the proponent of the duty to rescue-based objection to the use of a no-treatment control arm. For most serious diseases for which we lack effective treatments, including EVD, the number of future patients who are expected to develop the disease will be many times more than the number who would be in the control arm of a phase III RCT. We therefore think it unlikely that there will be actual cases in which researchers both need a no-treatment arm to establish efficacy *and* are prohibited from withholding the experimental treatment from the control group by the duty to rescue.

Other EVD Trials

Our argument so far has focused on Phase III treatment trials. However, these are not the only studies that are relevant to developing new interventions for

serious diseases. Would the analysis be any different for phase I or phase II treatment trials or for studies of preventive interventions? The likelihood that any particular experimental drug going into phase I will ultimately be shown effective and approved for marketing is substantially lower than for drugs going into phase III trials—around 10%.[25] As the probability of benefit from receiving the drug drops, the relative importance of the costs to others will increase and so it becomes less plausible that there is a duty to provide the experimental therapy. Moreover, in a phase I study, there is significantly less data on the safety of the experimental intervention. This requires us to take into account a further possible cost to researchers.

Attempting rescue involves one agent interfering in the life of an otherwise independent individual. In standard duty to rescue cases, the costs to the rescuer tend to be very low: the burdens of rescue (e.g. soiled clothing) as well as some minor opportunity costs of carrying it out (e.g. missed meeting). The costs to the potential rescuee of attempting rescue are minimal or nonexistent. In brief, there is essentially no way that attempting to rescue the drowning child in the pond might make the child worse off. Moving from phase III studies to phase I introduces an additional type of possible cost to the rescuer. Even when the expected benefits of treatment outweigh the costs to patients, providing experimental treatments in phase I studies that have not been shown to be safe introduces the possibility that the clinicians will harm some patients who otherwise would have recovered. We think that causing harms to others constitutes a cost to the clinician, even if her patients request treatment and are reasonable to do so.

Suppose that a researcher gives the experimental treatment to a patient who then has an anaphylactic reaction and dies. Of course, it is possible that the patient would have died from the natural course of his condition. But the researcher won't know whether this is the case. Moreover, in this case, the researcher will be directly involved in her patient's death. Patients may be indifferent as to whether they die as the result of their condition or as the result of the researcher's actions. The researcher is almost certainly not going to be indifferent between these two possibilities. At a minimum, researchers may experience significant psychological burdens as a result of attempting rescue but causing death. Moreover, it seems plausible that killing their patients is contrary to the interests of researchers, even if it is done while attempting to assist them. For clinicians, a better career and to that extent a better overall life is characterized in part by fewer rather than more instances of killing one's

25 Hay et al. *op. cit.*

patients. Other things being equal, killing a patient represents a setback to the clinician's interests.[26]

These potential costs are obscured in standard rescue cases because we assume that the efforts of the rescuer will save the child and without these efforts the child will drown. The rescuer does not run the risk of possibly drowning a child who would otherwise have floated to shore. For present purposes, the point is this: to the extent that being the cause of a patient's serious harm or death counts as a cost to the clinician, these costs must be considered in determining whether there is a duty to rescue in the first place. When these costs are sufficiently high, they will obviate a duty to rescue.

To summarize, for Phase I and II trials, it is even less likely that the conditions identified above will be met and so even less likely that a scientifically necessary no-treatment control arm would be impermissible because of a conflict with the duty to rescue. In these trials, the expected costs to researchers and patient-participants are higher and the prospects for benefit are lower. With respect to vaccine trials and studies of other prevention measures, the potential benefits would be even lower. These trials are conducted with individuals who do not have the disease in question, but are only at risk of acquiring it.

Objections

1 *Proximity*

There is some debate over whether physical proximity to and identifiability of the victim are necessary conditions for having a duty to rescue.[27] Someone

26 For readers who are skeptical of the relevance to someone's interests of the causal impact she has on others, consider two possible lives. The first involves a good and decent life. The second involves precisely the same life, with the following exception. At the age of three, the individual comes across a shiny new object and reaches out to grab it. The object turns out to be a loaded pistol and the individual's reaching out presses the trigger and discharges a bullet which strikes and kills a nearby friend. Thinking only about your own interests, consider whether you would be indifferent between these two lives. If you would prefer the former life, this suggests that the causal impact we have on others can affect our interests, even when we do not act maliciously and are not at fault for what happens. For more discussion of this possibility and its implications see Wendler, D. *The Ethics of Pediatric Research*. Oxford: Oxford University Press. 2010.

27 Kamm, F.M. Does Distance Matter Morally to the Duty to Rescue? *Law and Philosophy* 19 (2000): 655–681. Peter Singer argues against the relevance of these considerations in Singer P. Famine, affluence and morality. *Philos Public Aff*. 1972; 1: 229–43. See also Unger 1996: 33–36.

who thinks proximity is morally relevant might argue that our duties to rescue are greatly attenuated when the people in need are distant in space *or in time*. Consequently, future patients—who cannot yet be identified and are yet to become infected—do not have the same claim on researchers as do people dying in front of them.

Two points may be made in response. First, although the psychological urge to help is often much stronger with respect to people nearby—it is much harder to turn a blind eye to someone who is dying in front of you than to ignore reports describing people dying in a distant famine—it has proven challenging to provide a principled justification for the claim that the duty to rescue tracks this urge. Moreover, even if some defense of the importance of proximity could be made, it seems implausible that there is *no* duty to rescue people at a distance. Suppose that I can see, through a conveniently directed webcam, that a child is drowning in a pond in another country. For the cost of a long-distance call and the inconvenience of placing it, I can wake the lifeguard and save the child. In this case, it seems clear that I have a duty to do so, suggesting that there is a duty to rescue those at a distance in some cases.

Now, if the duty to rescue those close by were stronger than the duty to rescue those at a distance then, by analogy, it might be thought that the claim to access of patient-participants in the control arm of a trial is stronger than the claim of future patients to have the experimental treatment evaluated. We concede that this might affect our conclusions if the numbers in each group were similar. If there were 250 controls and a similar number who might contract the illness in the future, then it is plausible that the researchers should just provide the experimental treatment to the present patients. One might even argue that proximity and identifiability weight the claims of the present patients such that the duty to rescue 250 present patients outweighs the claims of some slightly larger number of future patients. However, it seems implausible that proximity and identifiability are so important that they can outweigh the interests of 10 or 100 times as many future patients. The history of EVD provides good reason to believe that that there will be very many people affected in the future and that if a treatment is proven effective there is a reasonable prospect that it could be provided to many of them. Thus, if it is correct to predict multiple future outbreaks of similar severity to the 2013–16 epidemic, the duty to rescue future patients will be sufficient to outweigh the duty to rescue current patients.

Second, suppose for the sake of argument that the duty to rescue applied *only* to identifiable and proximate individuals. What would follow? As noted previously, costs to third parties are still capable of overriding the duty to rescue. This point applies even if there is no duty to rescue these other parties. If the costs to future patients are sufficiently high, there will not be a duty to

rescue present patients who would be in the control arm. If the number of future patients is several orders of magnitude greater than the number of patients who would be in the control arm, these are surely substantial enough costs to negate any duty to rescue the present patients. At the very least, a proponent of this view needs to provide some argument for why we should think that future need is so greatly discounted.

2 *Professional Duties*

Professionals tend to have greater duties to rescue those within their professional domain than do non-professionals. The lifeguard, at least while on duty, has stronger duties to rescue drowning children than do bystanders.[28] Since individuals conducting clinical trials are typically clinicians who are expert in the disease under study it might be argued that they have a stronger duty to rescue which precludes the use of control arms in clinical trials.[29]

The first thing to note in response is that if this objection were correct, it would at most shift the thresholds for when attempting rescue would be ethically required. It would require rescue attempts when the chance of success is lower and when the cost to the rescuer is higher. Second, in order to affect our overall analysis, a distinction would have to be drawn between clinician-researchers' special duties to EVD patients enrolled in their trials and their duties to future EVD patients. Given that the central goal of clinical research is the generation of knowledge to help future patients, justifying a greater duty to rescue current patient-participants would be particularly tricky. It looks like the role moralities of clinicians and researchers might directly conflict in this case.

Moreover, even if the argument that clinician-researchers have special duties to rescue present patients that they do not have to future patients were convincingly made, it would have to be shown that they have a greater duty to rescue individuals who are enrolled in their trials than other current patients who are in need. Compare, for example, the need of those in the control arm to patients who are screened out as ineligible for the study, or patients that the researcher passes on the ward, or in the street. Unless one argues that the duty to rescue them is lower, it is not clear why the researchers need to give the experimental treatment to patients in the control arm rather than to these others. One might try to argue that researchers have greater obligations to rescue patient-participants in the control arm because it is these individuals with

28 Rulli, T., Millum, J. Rescuing the duty to rescue. *J Med Ethics*. 2016 Apr; 42(4): 260–4, at 262–3.

29 For discussion, see Rulli and MacKay 2017.

whom the researchers have a professional relationship. However, if researchers have a greater obligation to rescue those with whom they are involved, this most likely traces to their status as clinicians, not their status as researchers. Hence, it seems that this obligation will be as strong for the individuals the researchers evaluate and find ineligible for the study as it is for individuals that the researchers evaluate and find eligible.

3 *Rescue and Respect*

When she discusses the situation of physicians who have only experimental treatments to offer their EVD patients, Sarah Edwards writes:

> … where there is no alternative active therapy, placebo or ineffective treatment controls are indeed controversial. The problem stems from the possibility of a doctor denying a dying patient the last chance of benefit, which seems too cruel for physicians to countenance even when they are also scientists.[30]

One way to interpret the underlying ethical issue that Edwards has identified is to view rescue attempts as a way of showing respect for those in need. When faced with someone in crisis, it seems callous not to at least attempt rescue, even if the prospect of success is very low. Making an attempt shows that the individual matters and that one cares. Following this line of reasoning it might be thought that randomizing patients with a serious condition to a no-treatment control arm would, symbolically, be akin to abandonment.

The idea that even actions that have very low chances of success might have normative significance because of what they express—"you matter and we care"—would make sense of our general preference for action over inaction. We see this, for example, in the phenomenon of physicians continuing to propose interventions for very sick patients even when, objectively, there is a very low chance of success. The relevance of respect to caregiving actions is an important but under-analyzed issue in applied ethics. However, we think it unlikely that the expressive function of offering experimental treatment will be important enough to affect our conclusions in this paper.

First, it is important to remember that being randomized to the no-treatment control arm means that individuals do not receive the experimental treatment; it does not mean that they receive no care whatsoever. Frequently, patients in a no-treatment arm are provided with state-of-the-art supportive

30 Sarah, J.L. Edwards. Ethics of Clinical Science in a Public Health Emergency: Drug Discovery at the Bedside. *American Journal of Bioethics* (2013)13: 9, 3–14.

care, as well as ancillary care for conditions not associated with the illness under investigation. Second, the value of showing respect by offering experimental treatment would have to be substantial enough to outweigh the considerations in favor of not providing the experimental treatment to all patients. In particular, it would have to trump the interests of future patients who will be in equally desperate need. Third, there are multiple ways in which to show someone respect. Soliciting patients' opinions, obtaining informed consent to research participation, considering patients' psychological needs, respecting their privacy, responsiveness to cultural and religious requests, calling patients by the appropriate name, and many other actions express respect. In the present context, acknowledging that patient-participants, including those in the no-treatment control arm, are vital contributors to a clinical trial that has the potential to help many thousands of future patients is an important way to respect them. Offering an experimental treatment, if it has this expressive function, would certainly add to this list, but its absence does not imply that researchers are treating patient-participants as though they don't matter.

4 *The Urge to Help*

Our discussion began with the widely held intuition that it would be wrong to deny experimental treatment to participants in a control arm when they have an illness as dangerous as EVD and there are no existing effective treatments. But our analysis suggests that the conditions under which the use of a no-treatment control arm both is necessary to test the efficacy of an experimental treatment and violates the duty to rescue are rarely met. This conclusion prompts the question of why the pull of providing treatment is so powerful. Why do so many informed and well-intentioned observers believe that it is unethical to use a no-treatment control arm in these circumstances?

One possible explanation is that people tend to conceptualize the situation in terms of the case of a single drowning child in a shallow pond. When we think about individual cases, we see only the need of the individual in front of us; we lose sight of the needs of less proximate and future victims.[31] This is often the right response for an individual clinician faced with an individual patient. Much of the time she should focus on the needs of her patient and not attempt to weigh his interests against the interests of others.

Previously, we considered a scenario in which an individual can save either a single child in a nearby pond or a greater number of children who are in a

31 This urge to attempt to rescue identifiable victims, even at great cost, is sometimes described as the "rule of rescue" (Rulli and Millum 2014, at 261).

pond over a hill. In that scenario, we claimed that there is no duty to save the first child. However, in an important sense, this scenario does not capture the challenge of conducting a clinical trial. To conduct a trial, one has to interact, perhaps for an extended period of time, with the people in the trial, including those in the no-treatment arm. A more apt analogy for these circumstances might be a case in which the potential rescuer first has to watch to see whether the first child drowns or floats to shore before she can go and rescue the children over the hill. In this situation, one would understandably have an urge to help the first drowning child. It seems callous to stand by and watch to see whether the first child drowns without doing anything to help.

This inclination may be even stronger if we add an additional feature to tighten the analogy. It is not only that one has to observe the first child's fate before proceeding to rescue the children in the next pond. This would suggest that what happens in the two ponds is essentially independent. In the context of clinical trials, the benefits that are available to future patients depend on observing what happens to present research participants. For example, to show that the experimental treatment is efficacious, researchers must collect data to show that those in the no-treatment control arm did significantly worse than those in the treatment arm. In effect, one group did worse precisely because the investigator did not attempt to rescue them. To make the cases analogous, then, we have to stipulate that, in the process of observing what happens to the first child, the passerby collects information that is crucial to saving the other children.

Close interaction with patients in need understandably arouses a strong urge to attempt to rescue them. From the first-person perspective, the urge to help may feel no different than the duty to rescue. This is important. It suggests that RCTs of experimental treatments for serious diseases with no-treatment arms may feel unethical to those who conduct them and, possibly, to those who witness them. We suspect that this phenomenon may lead some commentators and researchers to judge that it is ethically inappropriate for clinician-researchers not to offer the experimental treatment to individuals in the control arm. But, before they draw normative conclusions and set policy based on these judgments, stakeholders in clinical research need to acknowledge the larger context and the implications of their actions for the wider patient population. What looks to be an opportunity to rescue is in fact just a chance at rescue (and a small chance for early phase trials). What looks like an individual callously standing by and watching to see if a child drowns is in fact someone who is doing what is necessary to be in a position to effectively rescue significantly more children and who is trying not to make the children she tries to rescue worse off.

Even if we are right that trials with no-treatment arms are ethically acceptable when scientifically necessary, the powerful pull of the urge to help in individual cases has important consequences. First, it might be difficult for clinicians to conduct RCTs, since they will be interacting with patients in the control arm. Even if a clinician is blinded to which patients are receiving the active treatment such interactions may be psychologically challenging for her. Moreover, there may be pressure to identify those who are not receiving the experimental treatment in order to provide it clandestinely.

Second, the apparent callousness of using a no-treatment control arm might undermine public trust in research and support for the trial. This problem has to do largely with the relative transparency of the reasons for and against using a no-treatment control arm. The reasons to provide an experimental treatment to a person who has a potentially deadly disease for which no other treatments exist are obvious. In contrast, the scientific reasons to include a no-treatment control arm in order to evaluate the efficacy of experimental treatments are complicated. Even for those who understand these reasons, it is often not immediately obvious whether they apply in a given case. Thus, to the casual observer, including community members, it may seem that the researchers are declining to help people who are very sick without good reason.

The primary challenge that the use of no-treatment control arms leaves us with, then, is how to address these practical concerns. Presumably, we do not want to discourage in researchers and clinicians the urge to help those who are in desperate circumstances. One option might be to invest more in the education of staff and the community about the science of Ebola and trial design.[32] For example, researchers might engage trusted community representatives early on in the design of a trial. This would allow the researchers to make the reasons for including a no-treatment control arm transparent to community members and explain the reasons to think that the importance of doing so outweighs the value of providing experimental treatment to current patients. Obtaining the endorsement of individuals who understand these reasons may offer one way to try to increase the trust of community members in general. In particular, it will be important to show these individuals that the trial design is not chosen to earn profit for a pharmaceutical company or benefit rich patients, but to benefit the community in the long run. The scientific need to not provide experimental treatment to some participants arises precisely when it

32 Kennedy, S.B., Neaton, J.D., Lane, H.C., Kieh, M.W., Massaquoi, M.B., Touchette, N.A., Nason, M.C., Follmann, D.A., Boley, F.K., Johnson, M.P. and Larson, G., 2016. Implementation of an Ebola virus disease vaccine clinical trial during the Ebola epidemic in Liberia: Design, procedures, and challenges. *Clinical Trials.* 2016; 13: 49–56.

is not known whether the treatment is effective. If it was known to be effective, the patient would have a strong interest in receiving it, and the investigator would have no reason to withhold it. Although limited, there is some evidence that education regarding the importance of a control arm has successfully reduced the extent to which people thought that they were unethical.[33] In any case, if our arguments are sound, the urge to help does not indicate that there is an underlying duty to rescue.

Conclusion

Faced with patient-participants in desperate need, the urge to help is understandably strong and arises from laudable motives. The classic child in the pond case establishes that when we know how to save those in crisis, and we can do so at very low cost to ourselves, we have an obligation to do so. However, the setting of a clinical trial of an experimental treatment for a serious disease is an imperfect analog to the drowning child.

We have argued that the use of a no-treatment control arm in a clinical trial would only violate the duty to rescue in very limited circumstances. The duty to rescue implies that researchers have a moral obligation to provide an experimental treatment to patients with a serious disease only under the following conditions: (1) the prior probability of the treatment being effective is sufficiently high; (2) the expected benefit of an effective treatment is sufficiently great; (3) there is sufficient supply of the treatment or sufficient supply could be manufactured in a timely way to meet existing needs; (4) the cost of manufacturing the experimental treatment is sufficiently low; (5) the opportunity cost of rescuing potential participants or others in different ways is higher than the cost of the experimental treatment; and (6) the loss to future patients does not outweigh the expected benefits to potential participants who would be assigned to the control arm. These conditions—particularly the last—will very rarely be met. Consequently, the duty to rescue will very rarely require the provision of experimental treatment.

Our analysis has also revealed an important constraint on the scope of the duty to rescue that has been under-appreciated. The duty is not only limited by costs to the rescuer, but also by costs that a rescue is expected to impose on others. Where the costs to third parties are sufficiently high—as we have argued they likely would be in the context of clinical trials for EVD treatments—there will be no duty to attempt to rescue one party at the expense of these others.

33 Beavogui et al. 2016.

Biographical Note

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