

Clinical Research in a Public Health Crisis: The Integrative Approach to Managing Uncertainty and Mitigating Conflict

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ABSTRACT

In order to advance science while preserving social solidarity and institutional trust, clinical research must carefully manage ethical tensions created by the two overlapping dynamics of conflict and uncertainty. One of these dynamics is inherent in the research enterprise itself and the other arises in the particular context of a public health emergency. One test for both the moral soundness and practical utility of a framework for research ethics is its ability to help stakeholders understand and manage these ethical tensions as much as possible. After clarifying the dynamics that give rise to these tensions, this paper argues that two common approaches to evaluating clinical research have significant shortcomings in this regard. This paper then sketches and defends the integrative approach to managing these tensions.

I. INTRODUCTION

Mounting an effective response to an outbreak of pandemic influenza presents a profound public health challenge. Whether we are able to meet this challenge in a way that can avoid a public health catastrophe will depend on a variety of factors, two of which are particularly important for the purpose of the present discussion. The first factor is our ability to strengthen the public health infrastructure, broadly construed, in its capacity to carry out, on a large scale, public health response measures ranging from vaccination, prevention, detection, social distancing, and treatment, to the maintenance of sanitary environmental conditions in a context in which the various systems that contribute to this end may be strained by high mortality rates and the fear of contagion. A vigorous and proactive pro-

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gram of clinical and public health research has an important role to play in strengthening the capacity of the public health infrastructure to achieve some of these goals. Undoubtedly, it is best to mount such a program before such an outbreak has been detected. But even in the midst of an outbreak, clinical research may have an important role to play.

A second critical factor in our response to an outbreak of pandemic influenza is our ability to maintain a broad sense of social solidarity, including an open relationship of trust between community members and the basic social institutions that are supposed to safeguard and advance their interests. I will use the term “social solidarity” to refer to a public sense of cohesiveness and interdependence among community members in which their awareness of a shared plight, and a shared fate, increases the likelihood of working across social divisions in order to achieve a common goal. I will use the term “institutional trust” to refer to the willingness of community members to believe the information that they receive from basic social and governmental institutions, to rely on and comply with their instructions, and to provide various forms of cooperation and support for their efforts.

Just as the presence or absence of social solidarity and institutional trust can influence the prospects for carrying out valuable clinical and public health research in an emergency context, when and how research is conducted can have an important impact on both social solidarity and institutional trust. In the discussion that follows, I assume that an acceptable framework for planning and assessing research in an emergency setting should be adequately responsive to each of these concerns. That is, an acceptable framework should ensure not only that research can generate the information that will enhance the capacity of the health infrastructure of a community to respond to a particular threat, but it should also ensure that research is carried out in a way that embodies, and communicates to the public, certain facts about the basic social and governmental institutions of the community. In particular, acting on the basis of such a framework should enable institutions to demonstrate that they appreciate the gravity of the situation that is unfolding, that they are exercising legitimate authority without bias or antipathy, and that they are using appropriate methods for the purpose of safeguarding and advancing the interests of community members.

The following discussion describes how the integrative approach to clinical research reconciles these potentially competing demands. In Part II, this Essay discusses the two interconnected dynamics of

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conflict and uncertainty that any acceptable framework for evaluating research during the course of a public health crisis must navigate and reconcile. In Part III, this Essay discusses the shortcomings of two existing frameworks for evaluating risk in clinical research and how these shortcomings may be amplified by the special features of a public health crisis. In Part IV, this Essay outlines the integrative approach and explains how it avoids the shortcomings of these other frameworks and manages the dynamics of conflict and uncertainty discussed in Part III. In Part V, this Essay provides examples of past instances of clinical trials during the course of a health crisis and discusses the relevance of the integrative approach to these examples. Part VI concludes by noting some features of the integrative approach that require further development and by emphasizing some of the unique challenges public health emergencies pose for balancing the interests of different stakeholders in the system.

II. CONFLICT AND UNCERTAINTY IN A PUBLIC HEALTH CRISIS

The central challenge facing an acceptable framework for evaluating clinical research in the context of a public health crisis is how to navigate two interlocking dynamics of conflict and uncertainty. The first dynamic is related to the research enterprise itself as a means of moving the community from a state of conflict or uncertainty about how to respond to a health threat, to one of greater certainty or coherence. In particular, there is in the research enterprise an inherent potential for conflict between the interests of current research participants and those who might benefit in the future from such increased understanding. The second dynamic is related to the special circumstances of a public health emergency. Uncertainty is likely to be pervasive in this context, and both the effects of the emergency and the means that are used to respond to it may create or exacerbate social divisions that fall along fault lines such as race, class, socio-economic status, age, and gender. It is worth saying a bit about each of these dynamics in turn.

Inherent in the research enterprise is the potential for conflict between the interests of current research participants and the interests of the future beneficiaries of that research. This potential for conflict is itself partly a function of various kinds of uncertainty that attend the research enterprise. Consider the status quo at some point in time where there is uncertainty in the expert clinical community about how best to treat a particular medical condition. Perhaps the condition is novel, and no effective interventions currently exist. Perhaps there are accepted interventions, but their relative

therapeutic, diagnostic, or prophylactic merits are unclear, or a matter of dispute. In either case, the purpose of clinical research is to pose a well-defined research question that, if answered, will either eliminate this uncertainty or make a substantial contribution to its elimination.

If we can think of the research enterprise as a kind of bridge that takes the community from a state of uncertainty to a state of greater clarity, then research participants are, in effect, the vehicles that make this possible. They bear the risks and burdens associated with purely research-related procedures, and they undergo procedures or are provided with interventions with relatively unclear merits, as part of an effort to generate the information that will ensure that future patients receive a better standard of care.

Whether this potential for conflict materializes in practice will hinge, in part, on how it is addressed. Institutional Review Boards (IRBs) are charged, among other things, with the task of ensuring that risks to participants are reasonable in light of benefits that might accrue to them, or in light of the value of the information that will be generated from the research.¹ This means that the risks to research participants can be justified by potential benefits to those participants, but they need not be.² Those risks may be justified entirely by the social value of the research.³ Moreover, as the importance of the research increases, so increases the level of risk to which research participants may be exposed permissibly.⁴

How this potential conflict has been managed in the past has also influenced the public's attitude toward the research enterprise and the uncertainties that attend it. Several commentators have noted that social attitudes toward biomedical research in the United States have vacillated at times between paradigms of protectionism and a right to access.⁵ In the protectionist paradigm, novelty is associated with risk, and the research enterprise itself is regarded as inhe-

¹ Protection of Human Subjects, 45 C.F.R. § 46.111(a)(2) (2008).

² *See id.*

³ *See id.*; see also Charles Weijer, *Thinking Clearly About Research Risks: Implications of the Work of Benjamin Freedman*, IRB: REV. HUM. SUBJECTS RES., Nov.–Dec. 1999, at 2.

⁴ *See* 45 C.F.R. § 46.111(a)(2).

⁵ *See* Anna Mastroianni & Jeffrey P. Kahn, *Swinging On the Pendulum: Shifting Views of Justice in Human Subjects Research*, HASTINGS CENTER REP., May–June 2001, at 21 (discussing the shift in federal testing policies from centering around protection of subjects to focusing upon the desire for new research).

rently dangerous.⁶ To some degree, this may reflect a collective unease about the potential for a shift in moral norms when one undertakes an activity in which participants are valued less for who they are and what they can do as individual persons or agents, than for what can be learned from the aggregate data that is collected from or about them.⁷ Undoubtedly, however, such feelings of distrust are, more concretely, grounded in and inflamed by revelations of abuse in the research context. For example, the legacy of the now infamous Tuskegee syphilis study continues to play a role in an undercurrent of distrust of public health in general and public health research in particular in African American communities.⁸

On the other hand, the access paradigm emphasizes the power of clinical research as an engine for discovery. Important discoveries not only increase our understanding of sickness and disease, but also provide the tools to intervene in order to reduce morbidity and mortality, improve quality of life, and give people the information they need to make better informed decisions. As a result, when a particular problem, condition, or population is the focus of clinical or public health research, the odds increase that members of that population who face that problem or condition in the future will benefit from this process of inquiry. Less uncertainty will surround various aspects of the prevention, diagnosis, or treatment of the condition, and medical personnel are more likely to have better alternatives for effectuating desired clinical or public health outcomes. Alternatively, when problems, conditions, or populations are not the focus of clinical or public health research, the state of the art for addressing them is unlikely to advance or change significantly. As a result, those who are excluded from research participation are likely to face greater risks

⁶ Jeffrey P. Kahn et al., *Implementing Justice in a Changing Research Environment*, in *BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH* 166, 168 (Jeffrey P. Kahn et al. eds., 1998).

⁷ Cf. Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 *DAEDALUS* 219, 219–20 (1969) (suggesting that once tests are performed on living beings, as compared to inanimate objects, “questions of conscience arise”); Alex John London, *Threats to the Common Good: Biochemical Weapons and Human Subjects Research*, *HASTINGS CENTER REP.*, Sept.–Oct. 2003, at 17 (discussing two different conceptions of the common good and their differential relation to individual rights and liberties in the face of a perceived public health threat, such as would be posed by biological and chemical terrorism).

⁸ See Vicki S. Freimuth et al., *African Americans’ Views on Research and the Tuskegee Syphilis Study*, 52 *SOC. SCI. & MED.* 797, 799 (2001); Jan M. McCallum et al., *Awareness and Knowledge of the U.S. Public Health Service Syphilis Study at Tuskegee: Implications for Biomedical Research*, 17 *J. HEALTH CARE FOR POOR & UNDERSERVED* 716, 717 (2006).

when they access the health system to the extent that less is known about their condition, or fewer options are available to treat it.⁹

An analogue to this population-level view exists at the individual level. This is the idea that clinical research often employs the best and the brightest in the medical community and uses the most rigorous methods to administer the most cutting-edge care.¹⁰ On this view, there are substantial benefits to being in clinical research, not just for those who have the condition under study, but for those who participate in individual trials.¹¹

Managing this dynamic of conflict and uncertainty under normal or non-emergency circumstances can be difficult. The revelation that research participants have been abused or treated unfairly can cause public attitudes to shift in protectionist directions, increasing wariness of research and leading to tighter oversight.¹² Over time, tighter restrictions on research may lead some to think that progress has been slowed and that in the name of protection, some groups have missed out on important social benefits.¹³ This can cause a swing back toward the paradigm of access. If social attitudes move too far in this direction, inhibitions against offering or accepting certain risks may be reduced, which, in turn, can create the potential for the abuse of research subjects.

Such difficulties are exacerbated by the special circumstances of a public health emergency.¹⁴ In part, this is because the crisis setting precipitates its own dynamic of conflict and uncertainty. In a very real sense, uncertainty is likely to precede a public health emergency as the community and relevant authorities attempt to determine the scope and severity of the emerging outbreak. Beyond this, uncertainties emerge concerning who has been infected, where it is safe to travel, who it is safe to associate with, how to protect oneself from becoming infected, and what to do once one becomes infected. There

⁹ See Rebecca Dresser, *Wanted: Single, White Male for Medical Research*, HASTINGS CENTER REP., Jan.–Feb. 1992, at 24, 26–27; Charles Weijer & Robert A. Crouch, *Why Should We Include Women and Minorities in Randomized Controlled Trials?*, 10 J. CLINICAL ETHICS, 100, 100 (1999).

¹⁰ John D. Lantos, *The “Inclusion Benefit” in Clinical Trials*, 134 J. PEDIATRICS 130, 131 (1999).

¹¹ *Id.* at 130. Explanations for the apparent benefit of participation in trials include “selection bias, placebo effects, and adherence to well-defined protocols.” *Id.*

¹² *Id.* at 131.

¹³ See Dresser, *supra* note 9, at 26–27.

¹⁴ Working Group on “Governance Dilemmas” in Bioterrorism Response, *Leading During Bioattacks and Epidemics with the Public’s Trust and Help*, 2 BIOSECURITY & BIOTERRORISM: BIODEFENSE STRATEGY PRAC. & SCI. 25, 27–29 (2004).

are also social uncertainties surrounding the basic institutions of the community. Do government and public health authorities grasp the magnitude of what is unfolding? Are public health and medical institutions responding in a way that is effective, or are they merely trying to prevent panic?

Public health emergencies are also scenes of conflict. To some degree, the mere emergence of pandemic flu will stress the social fabric of affected communities, and this, in turn, has the potential to inflame and widen existing social, racial, and economic fault lines. This problem is exacerbated by the fact that difficult decisions will have to be made about how best to deploy scarce social resources. Adding to such pressures is the special dread that accompanies public health emergencies, born of the widespread perception that ordinary social and ethical norms may not have the same force in this new context. Such worries may permeate social relations, and they have already been raised in the context of rationing scarce resources, such as flu vaccines and antivirals.¹⁵ But they are likely to have special force in the context of research where a proclivity toward utilitarian thinking is likely to be emboldened. In particular, as the threat to society increases, and research represents a credible means of stemming the tide of death and disease, the potential benefits for the many may be seen as large enough to outweigh even dramatic and certain risks to a few. Perhaps paradoxically, however, to the extent that individuals perceive that their personal interests may be unduly subordinated to or sacrificed for advances in understanding, they may refuse to participate in research. Such concerns are likely to be particularly salient in disadvantaged or otherwise marginalized communities.¹⁶

On the other hand, although eschewing the conduct of research in a public health crisis may reduce some problems of social solidarity, it poses its own challenges to institutional trust. Directly deploying non-validated interventions under the umbrella of the state's national security or public health emergency powers (as was recently enhanced by the Project BioShield Act of 2004¹⁷) does not eliminate or reduce uncertainty about the relative merits of those interventions. It therefore does not address the larger community's uncertainty about whether the methods of crisis response being deployed in the com-

¹⁵ See John D. Arras, *Rationing Vaccine During an Avian Influenza Pandemic: Why It Won't Be Easy*, 78 *YALE J. BIOLOGY & MED.* 283, 287–300 (2005).

¹⁶ See Freimuth et al., *supra* note 8, at 797–98.

¹⁷ See Stuart L. Nightingale et al., *Emergency Use Authorization (EUA) to Enable Use of Needed Products in Civilian and Military Emergencies*, *United States*, 13 *EMERGING INFECTIOUS DISEASES* 1046, 1048–49 (2007).

munity are safe and effective. This failure, in turn, may engender legitimate frustration, not only about the uncertainties that may attend exposure to an investigational intervention, but also about the inability to learn from this experience in order to reduce the uncertainties, and therefore the risks, that community members face in the future.

Some of these tensions appeared in the response to the anthrax attacks on the U.S. Capitol in 2001.¹⁸ Given the uncertainty about how best to treat individuals who were at risk for inhalational anthrax, treatment recommendations changed over time. On December 21, 2001, the U.S. Department of Health and Human Services published a list of three preventative treatment options for persons at risk for inhalational anthrax, some of whom had already completed the recommended 60-day regimen of antibiotics.¹⁹ These were:

- 1) 60 days of antimicrobial prophylaxis, accompanied by monitoring for illness;
- 2) 40 additional days of antimicrobial prophylaxis (intended to provide protection against the theoretical possibility that anthrax spores might cause illness up to 100 days after exposure) accompanied by monitoring for illness or adverse reactions;
- and 3) 40 additional days of [antimicrobial] prophylaxis plus 3 doses of anthrax vaccine administered over a 4-week period.²⁰

The recommendation stated that, “[a]s an investigational new drug, the vaccine should be administered with informed consent, and vaccinated persons may participate in a follow-up evaluation measuring the effect of the vaccine when administered after exposure.”²¹

Uncertainty about the relative merits of these options created the rationale for an important prospective trial.²² Yet a failure to communicate the nature of the uncertainty and the importance of

¹⁸ For information regarding the background of the anthrax attacks and reactions to them, see Janice C. Blanchard et al., *In Their Own Words: Lessons Learned from Those Exposed to Anthrax*, 95 AM. J. PUB. HEALTH 489 (2005); Sandra Crouse Quinn et al., *The Anthrax Vaccine and Research: Reactions from Postal Workers and Public Health Professionals*, 6 BIOSECURITY & BIOTERRORISM: BIODEFENSE STRATEGY PRAC. & SCI. 321 (2008) [hereinafter Quinn et al., *Anthrax Vaccine*]; Sandra Crouse Quinn et al., *Postal Workers' Perspectives on Communication During the Anthrax Attack*, 3 BIOSECURITY & BIOTERRORISM: BIODEFENSE STRATEGY PRAC. & SCI. 207 (2005) [hereinafter Quinn et al., *Postal Workers' Perspectives*].

¹⁹ Ctrs. for Disease Control & Prevention (CDC), *Notice to Readers: Additional Options for Preventive Treatment for Persons Exposed to Inhalational Anthrax*, 50 MORBIDITY & MORTALITY WKLY. REP. 1142, 1142, 1151 (2001), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5050a5.htm>.

²⁰ *Id.*

²¹ *Id.* at 1151.

²² See Denise L. Doolan et al., *The US Capitol Bioterrorism Anthrax Exposures: Clinical Epidemiological and Immunological Characteristics*, 195 J. INFECTIOUS DISEASES 174, 175 (2007).

research to its resolution, along with differing perceptions of whether participation in the follow-up research was mandatory or optional, contributed to a perception of differential treatment between the predominantly white population of the Senate office building and the predominantly African American population of U.S. postal workers.²³ Moreover, the postal workers made explicit reference to the now infamous Tuskegee syphilis study in expressing concern that they were being subjected to experimentation that was inconsistent with their own basic health interests.²⁴

Finally, the perception on the part of at least some groups that the research enterprise itself may be particularly risky raises the prospect that some who were offered the investigational vaccine may have perceived the alternative of not participating in the research follow-up as involving less risk than participating. In actuality, if there was a difference, it is likely that not participating in the follow-up may have involved greater risk, if individuals received less frequent or careful monitoring from their personal physicians.²⁵ Additionally, reluctance to participate in research impedes the process of gathering the information necessary to improve the standard of care moving forward.

To be clear, coping with these dynamics of conflict and uncertainty requires a variety of efforts on the part of a diverse array of stakeholders. Even in the best of circumstances, it is unlikely that these issues can be eliminated entirely, and it would be nearly impossible to eliminate them simply by adopting a particular framework for assessing the ethics of research. As such, one test for the adequacy of a framework of research ethics is not whether it can eradicate these tensions, but whether it can help manage them in a way that reconciles the demands of advancing science with the goal of preserving and enhancing social solidarity and institutional trust as best as is feasible under the non-ideal conditions of an emergency situation.

III. THE NEED FOR GUIDANCE

There is currently widespread consensus about a menu of criteria that must be met in order for clinical research to be ethically acceptable.²⁶ For example, the research must be socially valuable, the

²³ Blanchard et al., *supra* note 18, at 492.

²⁴ *Id.* at 493; Quinn et al., *Anthrax Vaccine*, *supra* note 18, at 328.

²⁵ See, e.g., Franklin G. Miller & Howard Brody, *A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials*, HASTINGS CENTER REP., May–June 2003, at 17, 21–22.

²⁶ See Protection of Human Subjects, 45 C.F.R. § 46.111(a) (2008); NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, BELMONT

risks to participants should be minimized, risks that cannot be eliminated should be reasonable, the selection of subjects should be fair, the representation of various subgroups of the populations should be equitable, and where possible, participants should participate only after having given their free and informed consent.²⁷ One ambition of acceptable frameworks for research ethics is to help researchers, sponsors, IRB members, and community members assess research protocols in light of these criteria in a coherent, ethically defensible, and interpersonally justifiable manner. Unfortunately, the two most popular frameworks for guiding the ethical assessment of clinical research each suffer from significant limitations.

The first of these frameworks, what I call the “common rule approach,” adopts a sort of constrained utilitarian approach to evaluating research. Its proponents regard this as a utilitarian approach to the extent that it fundamentally involves trading risks to research participants for advances in science that will promote the welfare of future patients.²⁸ It is a constrained utilitarian approach, however, because the scope of this utilitarian calculus is limited or constrained by additional moral requirements.²⁹ For example, the requirement to respect the autonomy of research participants constrains the underlying utilitarian aspirations of the approach because advances in social welfare alone cannot justify conscripting subjects into clinical research without their free and informed consent.³⁰ Similarly, requirements of fairness prohibit research from unduly targeting vulnerable, marginalized, or disadvantaged populations.³¹

Proponents of this position have also argued that the underlying utilitarian calculus is constrained in an additional dimension. That is, they view the reasonableness of risks as a fundamentally utilitarian question about whether the expected benefits of a research initiative are sufficient to justify the various risks and burdens to participants that are not already justified by the prospect of direct benefit to those same individuals.³² But they argue that even here, these tradeoffs

REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH, 44 Fed. Reg. 23,192, 23,193–97 (Apr. 18, 1979) [hereinafter BELMONT REPORT]; Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2701–07 (2000).

²⁷ See BELMONT REPORT, *supra* note 26, at 23,195–97.

²⁸ See Miller & Brody, *supra* note 25, at 21.

²⁹ See *id.* at 23; see also sources cited *supra* note 26 (describing additional moral requirements that constrain this utilitarian approach).

³⁰ See Miller & Brody, *supra* note 25, at 23.

³¹ *Id.* at 24.

³² *Id.* at 21.

should not cross over a moral threshold, the threshold of exploitation.³³

Unfortunately, the requirement not to exploit participants appears to lack substantive content distinct from the idea of ensuring that the tradeoffs in risk and benefit are reasonable.³⁴ That is, we are told that in order for subjects to be exploited they would have to be subjected to risks that were not reasonable in light of the anticipated benefits, either to participants themselves or to the larger community.³⁵ Because the determination of whether subjects are exploited requires a determination of whether the risks to participants are outweighed by the various potential benefits of the research, this requirement does not provide an additional, independent constraint on the underlying utilitarian calculus. Rather, if anything, the touchstone for avoiding exploitation in this context appears to be simply ensuring that risks to participants can be justified on utilitarian grounds.

Furthermore, this approach provides almost no additional guidance to stakeholders about how to make such determinations in practice. Individual researchers, sponsors, IRB members, and community members more generally, are left to their own devices to provide some rough estimate of the value of individual research initiatives and how to weigh or trade that kind of value against the risks to which research participants would be exposed. Moreover, even the appeal to “utilitarianism” here obscures the fact that “utilitarianism” is the name of a fairly large family of views, some of which differ significantly in their operational content.³⁶ As a result, this approach provides woefully little practical guidance to the stakeholders that have to rely on it. Moreover, because there are myriad ways of specifying the key variables in determining when risks are reasonable, this approach provides a veneer of operational content to what will ultimately be a contest of diverse and potentially competing intuitions.

Stakeholders are likely to need practical guidance most in cases where intuitions conflict. At some point, even the most rigorous

³³ See *id.*

³⁴ See Alex John London, *Reasonable Risks in Clinical Research: A Critique and a Proposal for the Integrative Approach*, 25 STAT. MED. 2869, 2871–72 (2006) [hereinafter London, *Reasonable Risks*]; Alex John London, *Two Dogmas of Research Ethics and the Integrative Approach to Human-Subjects Research*, 32 J. MED. & PHIL. 99, 101–02 (2007) [hereinafter London, *Two Dogmas*].

³⁵ See London, *Reasonable Risks*, *supra* note 34, at 2871–72; London, *Two Dogmas*, *supra* note 34, at 101–02.

³⁶ For a convenient summary of possible consequentialist views, see SHELLY KAGAN, *NORMATIVE ETHICS* 25–69, 189–239 (1998).

framework for decision making must rely on the good will, common sense, and practical judgment of those who must apply it. But for the common rule approach, this point is reached sooner than it need be—as soon as intuitions conflict. Moreover, to the extent that this framework provides deliberators with relatively anemic resources for justifying their judgments to their fellow citizens, it may create the appearance, if not the reality, of a degree of arbitrariness to decision making that may undermine social trust in the institutions of clinical or public health research.

The second most popular framework attempts to remedy some of these shortcomings by introducing moral norms that can be used to determine, with greater operational clarity, when research risks are reasonable. I have referred to this as the “duty of personal care approach,” because the various proposals that fall under this heading share the foundational normative idea that, like physicians, researchers owe a duty of personal care³⁷—sometimes referred to as a therapeutic obligation³⁸ or a fiduciary duty³⁹—to each research participant. On this view, risks to participants are reasonable when they are consistent with, or do not abrogate, this duty.⁴⁰

The duty of personal care is thus supposed to provide a substantive constraint on permissible risk.⁴¹ In order to provide operational guidance to deliberators, variants of this approach agree that it is permissible for the treatment of research participants to be determined by a random process only if there is reasonable uncertainty about the relative therapeutic merits of the interventions to which participants might be allocated.⁴²

Different frameworks that fall under this heading can then be distinguished by the way that they specify key variables.⁴³ First, whose uncertainty matters? Proponents of the “uncertainty principle” argue

³⁷ CHARLES FRIED, *MEDICAL EXPERIMENTATION: PERSONAL INTEGRITY AND SOCIAL POLICY* 49–50 (1974).

³⁸ Don Marquis, *Leaving Therapy to Chance*, HASTINGS CENTER REP., Aug. 1983, at 40, 42.

³⁹ Paul B. Miller & Charles Weijer, *Rehabilitating Equipoise*, 13 KENNEDY INST. ETHICS J. 93, 95 (2003).

⁴⁰ *See id.* at 112.

⁴¹ *See id.*

⁴² *See id.* at 91; *see also* Austin Bradford Hill, *Medical Ethics and Controlled Trials*, 1 BRIT. MED. J. 1043, 1047 (1963).

⁴³ *See* Alex John London, *Clinical Equipoise: Foundational Requirement or Fundamental Error?*, in THE OXFORD HANDBOOK OF BIOETHICS 571, 573–77 (Bonnie Steinbock ed., 2007).

that it must be the individual clinician-researcher.⁴⁴ Proponents of clinical equipoise argue that it should be the medical community.⁴⁵ Proponents of community equipoise argue that it should be the broader social community, not just the medical community.⁴⁶

Second, what is the epistemic threshold for determining when uncertainty obtains and when it has been disturbed? Proponents of theoretical equipoise adopt a fragile epistemic threshold that is disturbed as soon as the various arms of the trial are no longer judged to be an equal bet in prospect. Proponents of clinical equipoise adopt a more robust threshold according to which uncertainty exists so long as the evidence about the relative merits of the interventions in question is not of sufficient weight to change clinical practice in the expert community.

This general approach has some distinct advantages and the view that I outline below incorporates several of them. Before turning to that discussion, I want to note two substantial limitations to this approach.

First, the claim that researchers owe participants a duty of personal care is often grounded on the assumption that, even in the context of research, researchers are still in some fundamental respect acting as physicians. This claim is most plausible in cases where researchers are in fact physicians; it is less plausible in cases where researchers are, for example, public health workers. Moreover, in some public health contexts, the interventions in question may be applied directly to the environments in which individuals live, rather than to individuals themselves. Such public health research may nevertheless involve human subjects and may have equally momentous implications for their health and welfare. It is not clear that the norms of the physician-patient relationship are applicable in such cases, or that they are the proper norms for regulating this kind of research, but an

⁴⁴ See Hill, *supra* note 42, at 1047; Richard Peto et al., *Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient* (pt. 1), 34 BRIT. J. CANCER 585, 606–07 (1976); Richard Peto & Colin Baigent, *Trials: The Next 50 Years*, 317 BRIT. MED. J. 1170, 1170 (1998); David L. Sackett, *Equipoise, a Term Whose Time (If It Ever Came) Has Surely Gone*, 163 CANADIAN MED. ASS'N J. 835, 836 (2000).

⁴⁵ See Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 NEW ENG. J. MED. 141, 144 (1987) [hereinafter Freedman, *Equipoise*]; see also Benjamin Freedman, *Placebo-Controlled Trials and the Logic of Clinical Purpose*, 12 IRB: REV. HUM. SUBJECTS RES. 1, 5 (1990) [hereinafter Freedman, *Placebo-Controlled Trials*].

⁴⁶ Fred Gifford, *Community-Equipoise and the Ethics of Randomized Clinical Trials*, 9 BIOETHICS 127, 128–29 (1995); Jason H. T. Karlawish & John Lantos, *Community Equipoise and the Architecture of Clinical Research*, 6 CAMBRIDGE Q. HEALTHCARE ETHICS 385, 385–86 (1997).

adequate framework for evaluating research should be broad enough in scope to apply to all research involving human subjects.

The second limitation is more subtle, but perhaps of much greater significance. To see it, consider the following dilemma. The duty of personal care sets the parameters for acceptable risk in this approach, and this duty has been traditionally understood as requiring individual clinicians “to benefit their patients ‘according to their best judgment.’”⁴⁷ How should we understand the content of this duty? One possibility is to view it as requiring researchers to advance the medical best interests of participants without reference to the broader goals and values of individual participants themselves. One advantage of this interpretation is that its application does not require an appeal to the particular valuations of individual trial participants. This makes it suited to current practice since IRBs and others must determine that the risks in any proposed study are reasonable before they may permissibly seek the informed consent of potential participants.

However, this interpretation risks being overly restrictive and paternalistic. Presumably, for instance, it would prohibit healthy volunteers from participating in most research at least to the extent that such participants are subjected to some affirmative risks in order to advance science. Moreover, this interpretation is far more rigid than the way this duty is commonly interpreted in the context of clinical medicine.⁴⁸ With the rejection of medical paternalism has come the recognition that health values are not necessarily a person’s preeminent or paramount concern and, as a result, respect for persons requires caregivers to advance the health interests of patients in a way that is responsive to the broader goals and values of such persons.⁴⁹ Given this recognition, physicians routinely assist patients in undertaking medical procedures that pose affirmative risks to the patient that are not compensated by direct medical benefits to that patient.⁵⁰ For example, living persons who donate a lobe of their liver or one of their kidneys for transplantation are exposed to the risks and burdens of the surgical procedure, the prospect of infection, and a small probability of death, all for the benefit of the organ recipient.

Assume, therefore, that we understand the duty of personal care as a duty to advance the medical best interests of subjects in a way

⁴⁷ BELMONT REPORT, *supra* note 26, at 23,194.

⁴⁸ *Id.*

⁴⁹ ALAN H. GOLDMAN, THE MORAL FOUNDATIONS OF PROFESSIONAL ETHICS 185–86 (1980).

⁵⁰ BELMONT REPORT, *supra* note 26, at 23,193 n.* (first footnote).

that is informed by the broader goals and values of those persons. Now rigidity and paternalism are eliminated, but at the cost of the determinacy or operational content of the standard. In part, this is because this standard must be applied before it is permissible to offer participation in the study to participants. It therefore faces a kind of catch-22: the parameters for acceptable risk are set by the physician's duty to advance the medical best interests of individual patients, consistent with that individual's broader goals and values, but this standard must be used by an IRB to assess the acceptability of risks in a clinical trial before participation can be offered to any particular individual. That is, IRBs must apply this test before they have any information about the values of potential trial participants. Moreover, if the duty of personal care permits assisting patients in advancing their project of helping others through living organ donation, then it may also be permissible to ask research participants to forgo significant health benefits, or to bear significant risks and burdens, for the purpose of advancing science. While this may indeed be permissible, it becomes questionable whether the physician's duty of personal care now provides an independent constraint on the reasonableness of risks.

These problems are only exacerbated when considering research that might be carried out in the midst of a public health emergency. On the one hand, community members should be able to view research as a viable means of serving the common good, and it seems reasonable that they should be permitted to bear some affirmative risks to themselves in order to help their compatriots. At the same time, it seems reasonable to think that members of a pluralistic community will disagree about the nature and extent of the risks that social institutions can offer to community members, even in the service of noble ends. Additionally, the strains on institutional trust and social solidarity will likely only be exacerbated if disagreement about the latter issue erupts in the context of a public health emergency.

IV. AN OUTLINE OF THE INTEGRATIVE APPROACH

Forging social solidarity within liberal democratic communities poses a challenge even under non-emergency situations because such communities are characterized by, and often explicitly committed to fostering, social pluralism. That is, individual community members may disagree about fundamental questions of value, including the value of various life plans, the importance of various social goals or objectives, and the means that are appropriate for advancing or attaining these. This disagreement, in turn, creates a challenge for se-

curing institutional trust, insofar as some may regard important social institutions as offering undue assistance or support to some segments of the community while neglecting or frustrating the projects or plans of others.

In order to preserve or foster institutional trust in the context of a public health emergency, social institutions, such as the institutions responsible for emergency response and conducting clinical and public health research, require a social standpoint that the members of such communities can recognize as appropriate for making important social decisions. Moreover, if this standpoint is sufficiently compelling to secure the allegiance of community members, it may provide a lever for preserving or enhancing social solidarity.

A. *The Theoretical Underpinning of the Integrative Approach*

The integrative approach constructs the required standpoint by adapting a distinction first enunciated by John Rawls.⁵¹ Rawls notes that members of liberal democratic communities may differ radically in what I call their “personal interests.”⁵² These “personal interests” are interests that agents have in their personal conception of the good and the distinctive projects and plans that they adopt as a means of pursuing this conception.⁵³ Differences in and disagreements about personal interests are a common source of conflict in social decision making and public policy. But, Rawls argues, this first-order conflict over values and ends is predicated on a shared, higher-order interest in the ability of each individual to advance his or her first-order interests effectively without unwarranted outside interference.⁵⁴

Within the integrative approach, this shared higher-order interest in being free to advance one’s personal interests provides the basis for distinguishing and giving evaluative priority to what I call “basic interests.” Basic interests are interests that agents have in being able to cultivate and to exercise those fundamental human capacities that are constitutive of what Rawls refers to as our two moral powers: the capacity to formulate and to pursue a life plan based on a conception of the good and the capacity to regulate our conduct with others on the basis of principles of right.⁵⁵ Such basic interests in-

⁵¹ See John Rawls, *Social Unity and Primary Goods*, in *UTILITARIANISM AND BEYOND* 159, 159–85 (Amartya Sen & Bernard Williams eds., 1982).

⁵² *Id.* at 160–61.

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.* at 164–65.

clude developing and exercising one's capacities for reflective thought and practical decision making, developing and cultivating one's basic affective or emotional capacities, and having the effective freedom to exercise those capacities in the pursuit of particular projects and meaningful social relationships.⁵⁶

The integrative approach uses this shared higher-order interest to define a social position of common ground from which decisions can be made about how basic social institutions should be regulated and to define the "space of equality," the domain over which all community members have a just claim to equal treatment. Although individuals may adopt particular life plans that have little in common or that conflict or diverge in fundamental ways, all can recognize that each requires the ability to cultivate and to exercise certain basic physical, intellectual, emotional, and social capacities to be able to pursue a life plan. Moreover, despite differences in dress, demeanor, or aspiration, each person can recognize every other person as a moral and political equal because each person's ability to pursue a distinctive and meaningful life plan is predicated on his or her ability to safeguard and to advance these basic interests.

I refer to this as an "integrative" approach because it tries to find ways of resolving social conflicts that safeguard and advance the underlying basic interests of the relevant parties. To this end, it holds that the basic institutions of a society treat individuals as political equals, not by striving to advance the personal ends of any set of individuals, but by safeguarding and advancing, *for each individual*, those basic interests that make possible the pursuit of a reasonable life plan from among a rich array of possible alternatives. That is, these basic institutions operate in a fair way by working to ensure that every individual can function effectively in those rudimentary ways that are necessary in order to be able to pursue some distinctive life plan. In this regard, the integrative approach seeks to be responsive to the idea that each individual is a source of value in his or her own right.⁵⁷ Unlike consequentialist theories that view individuals as repositories for some more fundamental value, such as pleasure or welfare, the integrative approach seeks to respect the status of each community member as the political equal of every other without summing the interests of community members together.⁵⁸ It does this in several ways.

⁵⁶ *Id.* at 165–66.

⁵⁷ JOHN RAWLS, A THEORY OF JUSTICE 29 (1971).

⁵⁸ *Id.* at 32.

First, on this view, when the basic interests of some individuals are threatened, endangered, or inadequately protected, the importance of those interests to the individuals' ability to advance their first-order interests provides the normative ground for a claim to assistance from their compatriots. In the face of a public health emergency, for example, each community member whose basic interests are threatened has an equal claim on the basic institutions of their society to use the best practices available to safeguard and to advance their basic health interests.

Second, the imperative to meet these claims as effectively and efficiently as possible provides the justification for creating a social division of labor in which some community members are empowered to advance the basic interests of others in a particular sphere or domain. The institutions of clinical and public health research are one element within this larger social division of labor. Their special role, what might be called their moral mission, is to bridge gaps between the basic health needs of community members and the capacity of the community's health-related institutions to meet those needs.⁵⁹ Members of a pluralistic, liberal, democratic community have a compelling interest to support the research enterprise insofar as it serves as an engine for improving the capacity of public health care institutions to fulfill their social role more effectively, either now or in the future.⁶⁰

Finally, in order to clarify some of the moral constraints on the way that permissible research may be carried out, the integrative approach focuses on two aspects of the link between the basic interests of community members and the network of social institutions that are necessary to preserve and advance them. First, as one element within the larger social division of labor, research should empower those who are willing to take on, as part of their particular life plan, the project of preserving the basic health interests of community members. This means that research participants should be able to dedicate their time and energy, and to accept some personal risk, in order to advance science for the common good. Second, although those whose basic interests are threatened or endangered can make a legitimate demand on their compatriots to provide them with aid or relief, no party can claim that the preservation or advancement of his or her basic interests is more important than the basic interests of

⁵⁹ See Alex John London, *Justice and the Human Development Approach to International Research*, HASTINGS CENTER REP., Jan.-Feb. 2005, at 24, 24-25.

⁶⁰ *Id.* at 34.

their compatriots. As a result, although the institutions that divide social labor for the purpose of advancing the basic interests of community members may empower individuals to advance the common good, the same concern must be shown for the basic interests of those who make this mission possible as for those that the institutions seek to benefit. In other words, the justification for including clinical and public health research in a division of social labor aimed at advancing the basic interests of community members does not permit showing a lesser regard for the basic interests of research participants or otherwise compromising their status as political equals of their compatriots in the process.

B. Equality and the Integrative Approach

It is within this general context that the integrative approach understands a general principle that I refer to as the Principle of Equality. The principle holds that *as a necessary condition for ethical permissibility, research with human subjects must be designed and carried out so as not to undermine the standing of research participants as the moral and political equals of their compatriots, by either knowingly compromising their basic interests or showing unequal concern for their basic interests and the interests of the people the research is intended to serve.* The integrative approach uses two operational criteria to specify the terms on which important research can be advanced without compromising the status of research participants as the moral and political equals of their compatriots.

1. The First Operational Criterion for Preserving Equality

The first operational criterion for preserving equality consists of two necessary conditions for ethically acceptable research in the context of a public health emergency. These conditions are that (1) *the risks to subjects should be reduced to those that are necessary to address an important public health question, and (2) when research participants' basic interests are threatened by sickness, injury, or disease, they must receive a level of care and protection for their basic interests that does not fall below what at least a reasonable minority of the expert clinical or public health community would regard as the most appropriate method of response available.*

Condition (1) entails the position that it is never acceptable to expose research participants to risks that are gratuitous or more significant than is necessary. Under this condition, research should take place in the context of a public health emergency only if it could not feasibly take place in another context. This requirement also covers more than risks to basic interests since the personal interests of re-

search participants may not be widely shared but may nevertheless be of profound importance to the particular individual.

Condition (2) articulates the mechanism that determines the level of care and protection that must be provided to research participants whose basic interests are threatened by sickness, injury, or disease in order to ensure that they are respected as the moral equals of their compatriots. It does this by allowing participants to be allocated only to trial arms that provide a level of care or protection that does not fall below what at least a reasonable minority of the expert clinical or public health community would recommend as the method with the best overall prospect of safeguarding or advancing their basic interests. The focus here on not falling below this standard is meant to capture the idea that even when there is significant uncertainty or widespread disagreement about what constitutes the best response to a particular problem, it is often possible to identify interventions that would not be regarded as such by even a reasonable minority of the relevant expert community.

Before turning to the second operational criterion, I want to note that condition (2) articulates the parameters for what kind of *offers* researchers can make to potential research participants. The focus on basic interests in this condition reflects the idea that community members owe one another a social division of labor that preserves and protects the rudimentary building blocks that individuals need in order to be free to pursue a distinctive life plan. It is not permissible to offer to potential participants research studies providing a lower level of care and protection for the participants' basic interests. However, community members can ask one another to risk, sacrifice, alter, or limit ends or goals that are part of their individual life plan in an effort to secure for others the freedom to pursue and revise such a life plan of their own. In this view, properly functioning IRBs should permit public health researchers to ask participants to endure unpleasant experiences, inconveniences, or to bear other burdens that do not compromise their basic interests, so long as such risks or burdens are necessary for the conduct of sound science and have been reduced as much as possible. It is then up to individuals, via the process of informed consent, to evaluate these offers and to decide whether those particular burdens are reasonable in light of the goals of the research.

The guidance in the first operational criterion may need to be augmented for two reasons. First, it may be desirable to carry out research in the context of a public health emergency that does not evaluate methods of crisis intervention and response. Such research may

involve, for example, the evaluation of diagnostic tests or studies that increase our understanding of conditions of sickness and disease that arise in a public health emergency.

Second, even when research studies interventions for public health emergency response, the application of these interventions in the context of research may differ from their application in a non-research context. In particular, additional testing or procedures may be required in order to advance research goals that would not be required in another context. Often, the most immediate effects of such purely research-related elements of a study implicate only the personal interests of participants, as their risks are limited to some degree of bodily intrusion or discomfort. But even in this case, such procedures nevertheless pose some additional, incremental risk to the basic interests of study participants. As a result, additional guidance is necessary to determine when such incremental risks to the basic interests of participants are consistent with an equal regard for the basic interests of participants and nonparticipants.

2. The Second Operational Criterion for Preserving Equality

The integrative approach uses a second operational criterion to apply the principle of equality to risks that arise from purely research-related elements of clinical and public health research. The second operational criterion requires that in all cases, *the cumulative incremental risks to the basic interests of individuals that are derived from research activities and not offset by the prospect of direct benefit to the individual must not be greater than the risks to the basic interests of individuals permitted in the context of other socially sanctioned activities that are similar in structure to the research enterprise.*

The second operational criterion recognizes that respect for the moral equality of individuals cannot require that they be prohibited from voluntarily assuming some degree of risk to their basic interests, in part because such a standard simply could not be achieved. Even routine activities involve some incremental risk to a person's basic interests and in liberal, democratic communities, individuals routinely participate in activities posing some degree of additional risk to their basic interests.

The challenge, therefore, is to establish when incremental risks to the basic interests of individuals violate the underlying commitment to moral equality. The second operational criterion represents a proposal for how these comparisons might be effectuated in practice.

C. *Establishing Tests for Meeting the Operational Criteria*

In order to ascertain when these operational criteria are satisfied in practice, stakeholders require practical tests with well-defined operational content. The remainder of this essay is limited to discussing research aimed at developing methods or interventions for public health emergency response. This class of research has special importance because of its direct relevance to the capacity of public health institutions to fulfill their social role more effectively in the future. It also provides fertile ground for elaborating the content of the practical test for the first operational criterion articulated above. I will conclude with some remarks about how a similar test for the second operational criterion might be developed.

The integrative approach uses the following test to apply the first operational criterion to research aimed at developing or evaluating methods of interventions of public health emergency response: *When evaluating one or more methods or interventions for public health emergency response, individuals must be allocated only to methods or interventions where there is conflict or uncertainty in the expert public health community about whether the provision of methods other than those under study could more adequately safeguard or advance the basic health interests of individuals.*

This test ensures that two important objectives are met. First, as I will discuss in greater detail in the next section, it promotes research that has significant social value. In particular, research that satisfies this test is designed to resolve substantive conflicts about best practices and advance the capacity of important social institutions to provide more effective emergency response in the future.

Second, this test articulates the conditions that decision makers can use to determine whether participants in a particular trial receive a level of care or relief that does not fall below what would be recommended by at least a reasonable minority of experts in public health as the most appropriate method for providing emergency response.⁶¹ It does this by permitting individuals to be allocated to interventions on the condition of either uncertainty or conflict about the relative merits of those interventions or methods for the basic interests of individuals in the particular case.

I use the term “uncertainty” to refer to a state in which relevant public health experts have not formed a settled opinion about whether one mode of crisis response is superior to another. This is not a state of indifference, since I take the latter to refer to a belief

⁶¹ See BAYESIAN METHODS AND ETHICS IN A CLINICAL TRIAL DESIGN (Joseph B. Kadane ed., 1996).

that the methods in question are of equivalent value. By contrast, uncertainty represents a situation where the evidence supporting the relative merits of candidate interventions is not of sufficient quantity or quality to ground the conclusion that it is better than the relevant comparator. The determination of the relevant comparator will depend on the state of knowledge in the relevant expert community. If, for instance, there is no known effective intervention for a condition, then a no-treatment or placebo arm may be an appropriate comparator. If there are several known effective interventions, then one or more of these may be the appropriate comparator. In all cases, the role of research is to generate the information that will allow experts to clarify the relative merits of the various options in an effort to narrow the zone of uncertainty or conflict and to forge a social consensus on the appropriate standard of care.

In contrast to uncertainty, “conflict” refers to the state of affairs in which at least a reasonable minority of experts champion one method as superior to some other method while at least a reasonable minority of other experts champions another method as superior. In this case, each side has a determinate conviction about what is best for members of the affected population, but those convictions are in conflict.⁶² The integrative approach permits individuals to be allocated—at random or by some other proper method—to any intervention that would be recommended for them by at least a reasonable minority of clinical or public health experts.⁶³

When the condition of conflict exists, it may not be the case that any individual expert is uncertain. Versions of the equipoise requirement that require individual experts to be uncertain would not permit research to go forward under such conditions. But requiring individual uncertainty and prohibiting research from moving forward in the face of conflict between reasonable experts does not settle the substantive conflict over the relative merits of the competing interventions. It merely consigns the affected populations to receiving a particular intervention—perhaps as a result of the contingent fact of who gets to make the relevant decision—without using the research

⁶² ISAAC LEVI, *HARD CHOICES: DECISION MAKING UNDER UNRESOLVED CONFLICT* 28–35 (1986).

⁶³ The approach that I argue for here thus captures what is most appealing about approaches that rely on clinical equipoise, but in a way that is much more general. For further discussion of clinical equipoise, see generally Freedman, *Equipoise*, *supra* note 45; Freedman, *Placebo Controlled Trials*, *supra* note 45; London, *supra* note 43. For an analysis of the respect in which the integrative approach is more general in scope, see London, *Two Dogmas*, *supra* note 34, at 99–116.

methods necessary to settle the substantive issue about whether one of the alternatives is better than the others.⁶⁴

Undoubtedly, our ability to apply this framework in practice will be enhanced by having a clear account of how to distinguish what I am calling basic interests from non-basic interests.⁶⁵ Even without such clarification, however, this framework still provides substantive guidance to decision makers. In particular, if there is uncertainty about how to classify the interest in question, then the appropriate default requirement for research in this context is to treat it as basic and to apply the above stated practical test.

V. APPLICATIONS AND EXAMPLES: SARS, HIV/AIDS, AND PANDEMIC INFLUENZA

At this point, some examples provide helpful guidance. During the initial phases of the SARS outbreak, Muller and his colleagues noted that caregivers in different locations adopted different strategies for treating SARS victims.⁶⁶ In the United States, for example, clinicians chose to provide only supportive care.⁶⁷ In other areas, clinicians were more aggressive in providing therapeutic interventions to cover a wide range of bacterial and viral pathogens.⁶⁸ In some of these locations, ribavirin was identified as a promising therapeutic agent, although considerable uncertainty remained about the relative balance of risks and benefits associated with this treatment.⁶⁹ The existence of this uncertainty led Muller and his colleagues to attempt to design a clinical trial to evaluate the efficacy of ribavirin.⁷⁰

As they note, however, increasing reports of toxicity associated with high-dose ribavirin therapy led to a preference for lower dose regimens in Toronto.⁷¹ Such reports, along with the isolation of SARS-CoV and subsequent in vitro susceptibility studies, were sufficient to bring personnel in Toronto to discontinue ribavirin as a treatment for SARS.⁷²

⁶⁴ See Emily L. Evans & Alex John London, *Equipose and the Criteria for Reasonable Action*, 34 J.L. MED. & ETHICS 441, 444-448 (2006); London, *supra* note 43, at 577-84.

⁶⁵ See generally London, *supra* note 7 (discussing this distinction and its significance for larger debates about interpersonal tradeoffs in research ethics).

⁶⁶ See Matthew P. Muller et al., *Clinical Trials and Novel Pathogens: Lessons Learned from SARS*, 10 EMERGING INFECTIOUS DISEASES 389, 389 (2004).

⁶⁷ *Id.* at 391.

⁶⁸ *Id.* at 389.

⁶⁹ *Id.* at 389-94.

⁷⁰ *Id.* at 389-91.

⁷¹ *Id.* at 390-91.

⁷² Muller et al., *supra* note 66, at 389.

Currently, no consensus exists on the best practice for treating SARS.⁷³ However, if new animal and in vitro studies and an increased understanding of SARS-CoV were to lead some experts to favor one set of interventions while other experts favor a different set, then the expert clinical community would move from a state of uncertainty into a state of conflict. The expert community may remain in conflict about whether the relative net therapeutic advantage of one or more of these options dominates or is clearly superior to supportive care alone. If, on the other hand, some experts still believe, for example, that the side effects of candidate agents are severe and their therapeutic merits sufficiently uncertain, then it may remain permissible to randomize some participants to supportive care and others to promising candidate interventions.

This highlights the second important feature of the practical test. Namely, it promotes research with significant social value. This social value emanates from the fact that research meeting this test is designed to resolve substantive conflicts about best practices and thereby advance the capacity of important social institutions to provide more effective emergency response in the future.

Similarly, we are currently in the midst of a global HIV-AIDS pandemic. A variety of preventative strategies have been tested in clinical trials, ranging from vaccines⁷⁴ to microbicides⁷⁵ to male circumcision.⁷⁶ In each of these cases, some investigational intervention has been compared with a placebo or a no-treatment arm.⁷⁷ The use

⁷³ See Lauren J. Stockman, Richard Bellamy & Paul Garner, *SARS: Systematic Review of Treatment Effects*, 3 PLOS MED. 1525 (2006).

⁷⁴ Margaret I. Johnston & Anthony S. Fauci, *An HIV Vaccine—Challenges and Prospects*, 359 NEW ENG. J. MED. 888, 888–90 (2008).

⁷⁵ Janneke H.H.M. van de Wijgert & Robin J. Shattock, *Vaginal Microbicides: Moving Ahead After an Unexpected Setback*, 21 AIDS 2369, 2369 (2007).

⁷⁶ See Bertran Auvert et al., *Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial*, 2 PLOS MED. 1112, 1112 (2005); Robert C. Bailey et al., *Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial*, 369 LANCET 643, 643 (2007); Ronald H. Gray et al., *Male Circumcision for HIV Prevention in Men in Rakai, Uganda: A Randomized Trial*, 369 LANCET 657, 657 (2007).

⁷⁷ This statement is potentially misleading if it is taken to imply that participants in these trials were provided with no care or preventative measures other than either the investigational intervention or a placebo substitute. In actuality participants in these trials are provided with a basket of care that is aimed at reducing their susceptibility to contracting HIV. This usually consists of the provision of counseling and other social services, access to condoms, and even treatment for additional sexually transmitted diseases. For example, Auvert and colleagues randomized participants to immediate circumcision or to circumcision at a later date. See Auvert et al., *supra* note 76 at 1113–14. Individuals in the latter arm could thus serve as a control for the former group during the time they remained uncircumcised. Nevertheless, all sub-

of such designs is permissible in many of these trials because the distinctive immunological challenges posed by the HIV virus have resulted in an inability to replicate the successes that have been achieved against more common viral agents.⁷⁸ As a result, considerable uncertainty remains about whether a novel vaccine or microbicide will result in a net benefit to recipients. This is underscored by evidence that in some instances, microbicides⁷⁹ or vaccine candidates⁸⁰ may have increased the susceptibility of some recipients to seroconversion.

In contrast to HIV, we have a much better understanding of the major immunological properties of the influenza virus. This is not to say that our knowledge is perfect or that the influenza virus is not constantly changing. It is to say, rather, that knowledge regularly used to create vaccines for nonpandemic flu strains is being applied fruitfully to the creation of vaccines for potential pandemic strains. Several H5N1 vaccines have been developed; one has been licensed in Europe, and another received FDA approval in 2007.⁸¹ Important work is also underway to develop a cell-based vaccine, rather than the traditional egg-based vaccine, and to develop adjuvant agents that may reduce the dose necessary to produce an immune response in recipients while also potentially broadening cross-clade immunity.⁸²

These vaccines do not appear to be as efficacious as vaccinations for nonpandemic strains, but their true efficacy could only be ascertained in the face of an influenza outbreak. Although it is likely that the clinical community may be uncertain or in conflict over the relative prophylactic merits of these various vaccine candidates, there does not appear to be credible uncertainty about the relative merits of at least some of these agents in comparison to comfort care or non-vaccination.⁸³ As a result, it would not be permissible to include a placebo-only arm in an eventual trial of these various agents. This is because the health consequences of contracting a pandemic flu strain

jects received counseling, condoms, and ancillary care for opportunistic infections. *See id.* at 1114. For a general discussion of the importance of distinguishing the provision of placebo as a substitute for some element of standard therapy or prophylaxis from the addition of placebo to standard therapeutic or prophylactic strategies, see Stephen Senn, *Placebo Misconceptions*, AM. J. BIOETHICS, Sept. 2009, at 53.

⁷⁸ Johnston & Fauci, *supra* note 74, at 889–90.

⁷⁹ *See* van de Wijgert & Shattock, *supra* note 75, at 2369.

⁸⁰ Johnston & Fauci, *supra* note 74, at 889.

⁸¹ Isabel Leroux-Roels et al., *Broad Clade 2 Cross-Reactive Immunity Induced by an Adjuvanted Clade 1 rH5N1 Pandemic Influenza Vaccine*, 3 PLOS ONE 1, 3, 5 n.25 (2008).

⁸² *Id.* at 1–2.

⁸³ *Id.*

are likely to be dire, and because the strong grounds for the belief that the current FDA approved vaccine will provide recipients with a significant degree of protection means that the option of a no-treatment or placebo-only arm falls outside of the zone of uncertainty or conflict within the relevant expert communities.

As the number of prophylactic or therapeutic candidates increases, it becomes more likely that there will be either uncertainty or conflict in the expert clinical or public health communities about how best to prevent or treat the particular pandemic strain that eventually does emerge. If this is the case, there may be significant utility to designing head-to-head trials of the relevant interventions in order to ascertain the best practices for prevention and treatment. But one should not underestimate the potential difficulties associated with designing and conducting such a trial in the context of a public health emergency. Among other things, careful consideration will have to be paid to ensuring that a study hypothesis can be formulated in real-time that captures the relevant uncertainty or conflict in the expert communities. This is likely to be particularly difficult in a context where information is scarce or rapidly changing.

Bringing well-designed clinical trials to fruition in the fluid and often uncertain context of a public health emergency poses thorny logistical challenges. Such trials are also likely to be resource-intensive at a time when health-related resources are scarce and must be shepherded with care. This means that the decision to initiate research in this context must be made with care. Nevertheless, it is of paramount importance to enact research programs when there is compelling reason to think that addressing the study hypothesis represents one of, if not the best means of generating the information, interventions, practices, methods, or policies that are needed to bridge significant gaps between the basic health interests of community members and the capacity of the community's health-related structures to safeguard or advance those interests.

VI. CONCLUSION

Whether social solidarity and institutional trust can be secured or maintained when the common good is threatened by an actual pandemic will hinge on a variety of factors, many of which involve community planning, preparedness, and communication. The point of the above analysis is not to claim that the integrative approach can address all of these factors. It is, rather, to argue that it provides a better foundation than the two most prominent alternatives for creating an institutional framework for clinical and public health research

that would *merit* such trust and could provide an anchor for such solidarity, within a limited domain, if the community in which it were implemented were fully aware of the terms on which it functions.

In particular, I have sketched an operational test that the integrative approach uses to provide greater practical guidance to stakeholders than is available from the common rule approach. This practical guidance is also grounded in higher-level moral commitments that, I argue, should have broader normative scope than the relatively parochial norms of the duty of personal care approach. This approach is also more flexible and less paternalistic than the duty of personal care approach in that it provides a justification for an institutional design where it is permissible to offer some individuals the opportunity to accept increased personal risks and bear greater personal burdens with the goal of advancing science that will serve the common interest. At the same time, this approach recognizes that the willingness of individuals to contribute to such endeavors may be compromised by an institutional setup equating such a willingness with a broad permission to disregard or to be indifferent to the basic interests of research participants. Unlike the common rule approach, therefore, the integrative approach helps to eliminate uncertainty about the moral norms that structure the research process. Further, it expresses a clear moral and practical commitment to fostering research that advances the common interest without compromising the moral and political equality of research participants in the process.

Every framework of research ethics must provide stakeholders with guidance on how to evaluate risks associated with purely research-related elements of clinical trials. Every framework must therefore strike a balance between restricting the liberty of community members to freely accept some incremental risks to their basic interests and preserving public trust in the institutions of research as adequately responsive to the rights and welfare of research participants.

The second operational criterion for preserving equality represents a proposal for assessing clinical trial risks in a more transparent and systematic fashion. In order to generate a practical test for this criterion, stakeholders will have to identify comparison classes of activities that are sufficiently similar in structure to clinical research that they can be used to calibrate assessments of incremental, research-related risks. I have argued elsewhere that structurally simi-

lar activities should have certain features.⁸⁴ For instance, the incremental risks to the basic interests of individuals who engage in these activities should result from efforts to benefit others or to advance the common good. Similarly, the risks associated with such activities should be viewed as necessary evils and not as desirable in their own right, as is often the case with dangerous pursuits such as rock climbing or motorcycle riding. To the extent possible, such activities should also be the subject of social oversight or review so that there is some reason to view their associated risks as socially acceptable.

I have proposed using the activities of public service professions, such as paramedics or firefighters, as possible reference classes.⁸⁵ It may be useful to consider other public service professions as well, such as social workers and even public health officials. The point of this selection process is to construct comparison classes that can be used to ensure that the incremental risks to the basic interests of research participants that are associated with purely research-related elements of an investigation are not greater than the incremental risks to the basic interests of others in the community who work on a routine basis to advance the common good.

A public health emergency, however, is a unique situation. Elements of the larger infrastructure that supports a range of rights and abilities of community members may be inoperative or compromised. As recent experience with Hurricanes Katrina and Rita powerfully illustrated, public health crises can exacerbate preexisting social inequalities, exacting the harshest toll on marginalized, poor, or otherwise vulnerable groups. Special care must be taken, therefore, not to place significant additional burdens on the basic interests of disaster victims. Additionally, special care must be taken to ensure that the burdens of such research are not disproportionately borne by persons who are already socially, economically, or politically disadvantaged and that special protections are in place to ensure that the risks to individuals from such groups are minimized.

It will be important, therefore, to ensure that a wide range of stakeholders are involved in the process of determining the content of the practical test for the second operational criterion. It is also important to ensure that this process is completed prior to the onset of a major public health crisis.

Undoubtedly, many of the points made here will strike some readers as controversial and in need of further philosophical defense,

⁸⁴ See London, *Reasonable Risks*, *supra* note 34, at 2881–83.

⁸⁵ *Id.*

refinement, or explication. I hope, however, that the outline provided here will persuade the charitable reader that it is worth undertaking this process of refinement and defense in earnest.