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THE SOCIAL VALUE OF KNOWLEDGE AND INTERNATIONAL CLINICAL RESEARCH

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ABSTRACT
In light of the growth in the conduct of international clinical research in developing populations, this paper seeks to explore what is owed to developing world communities who host international clinical research. Although existing paradigms for assigning and assessing benefits to host communities offer valuable insight, I criticize their failure to distinguish between those benefits which can justify the conduct of research in a developing world setting and those which cannot. I argue that the justification for human subjects research is fundamentally grounded in the social value of knowledge, and that this value is context-dependent in a manner which should inform our ethical evaluation of the conduct of research in specific settings. I propose a new framework for the assessment of research benefits assigned to developing world host communities, a natural implication of which is to limit the types of research projects which may permissibly be conducted in developing world settings.

INTRODUCTION

There has recently been tremendous growth in the conduct of biomedical research in lower- and middle-income countries (LMICs). In 1991, only 10% of clinical trials were conducted in LMICs. By the mid 2000s, that proportion had increased to 40%, with Wyeth conducting 70% of its clinical research outside the US and Western Europe, and GlaxoSmithKline 50%. By 2008, spending on offshored research reached $23 billion annually.[1]

This paper seeks to explore what is owed to those LMIC communities who host externally-sponsored research. Disagreement over this topic exists not only within the bioethics literature, but also across regulatory and guidance documents of various international stakeholders. A recent review of research ethics guidelines found little consistency in the benefits expected to devolve to LMIC host communities. This inconsistency is of more than merely theoretical concern: stakeholders lack unambiguous guidance regarding their ethical obligations to host communities. And in the absence of consensus, those confronted with conflicting recommendations are likely to follow those guidelines which best suit their own interests.[2]

Although existing paradigms for assigning and assessing benefits to host communities offer valuable insight, I criticize their failure to distinguish between those benefits which can justify the conduct of research in LMICs and those which cannot. I argue that the justification for human subjects research is fundamentally grounded in the value of the knowledge sought, and that this value is context-dependent in a way which is not sufficiently appreciated by established frameworks for the assignment of research benefits. I suggest that to ensure LMIC research is conducted in an ethically supportable manner, the goals of that research must be informed by the context-dependent value of the research outputs to the host community. I go on to propose a new framework for

[1] A. Petryna. 2009. *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. Princeton: Princeton University Press: 13.

[2] G.M. Lairumbi et al. Ethics in Practice: The State of the Debate on Promoting the Social Value of Global Health Research in Resource Poor Settings Particularly Africa. *BMC Med Ethics* 2011; 12(22).

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the assessment of research benefits assigned to LMIC host communities, a natural implication of which is to limit the types of research projects which may permissibly be conducted in LMICs.

REASONABLE AVAILABILITY OF STUDIED INTERVENTIONS

Given vast disparities between developed- and developing-world access to health and wealth, there is widespread recognition of the vulnerability of LMIC populations to exploitation in medical research. International guidelines have sought to address this concern through the development of standards regarding what is owed to LMIC host communities, the most familiar of which is the 'Reasonable Availability' (RA) standard, stated in such international guidelines as CIOMS and the Declaration of Helsinki.[3]

RA demands that research sponsors and investigators ensure that any interventions successfully tested in an LMIC be made available to that population after the conclusion of the trial. If a studied intervention is not intended for local marketing, RA concludes that the trial offers insufficient benefit to the host community to ethically support its conduct. Only benefits of a specific type – post-trial access to studied interventions – are relevant to assessing the justice of trials conducted in LMICs. But limiting benefits to this type also limits the practical value of RA insofar as it fails to give clear guidance in several cases.

First, in order to supply interventions after the conclusion of a trial, sponsors and investigators must negotiate local regulatory frameworks governing the distribution and marketing of pharmaceutical products. Approval of new interventions for clinical use is complex, and often it will not be within an external sponsor's ability to ensure that a researched therapy can legally be distributed outside of the trial. There may also be logistical barriers to the safe and effective delivery of new interventions. In light of these significant challenges, it may prove implausible to expect guaranteed access to interventions after the conclusion of a trial.

RA likewise does not account for redundancy in clinical research. It generally takes years or even decades and a host of early-phase studies before an intervention progresses to phase III testing, and often several phase III trials are necessary to ground the dissemination of a new intervention into clinical practice. Moreover, a significant proportion of clinical trials fail to meet their safety and efficacy goals. As many as 40% of interventions which make it to phase III fail to demonstrate adequate efficacy, with similar or greater proportions of earlier phase trials generating negative results.[4] RA not only fails to offer guidance in this large subset of trials without confirmatory results, it also fails to address the complexity of the causal role of even successful early-phase research on the eventual marketing of interventions. Absent a clear understanding of these causal connections, RA does not inform us of what is owed to LMIC communities hosting early-phase studies. We might consider this reason not to conduct such research in LMICs, but it is likely that some early-phase research into diseases which disproportionately affect the global poor must be conducted in these contexts.

Although RA captures an important intuition regarding the need for the products of research to reach host communities, the approach fails to recognize the value of research outputs other than successful clinical interventions. In only allowing benefits of one type to legitimate the conduct of research in LMICs, RA sacrifices its practical value. To offer more useful guidance, a framework for assessing the distribution of benefits in LMIC research must be capable of allowing for benefits of more than one kind to be considered.

FAIR DISTRIBUTION OF BENEFITS

Given the significant disagreement about benefits, even among host nations, some advocate a procedural approach which leaves the distribution of benefits to host communities themselves, and the researchers they interact with. Proponents of 'Fair Benefits' (FB) argue that agreements regarding clinical research are like other transactions, in that the fairest trades are those which are beneficial and agreeable to both parties. Those in favor of this approach claim that respect for autonomy requires that 'the determination of whether the benefits are fair and worth the risks cannot be entrusted to people outside the population, no matter how well intentioned.'[5]

This emphasis on autonomy is a reaction to what has sometimes been characterized as paternalistic interference with otherwise mutually beneficial interactions, such as when, in the early 2000s, trials of Surfaxin were removed from their intended settings after American ethicists loudly objected to the use of placebos in the testing of a drug on populations in which it was not intended to

[3] Council for International Organizations of Medical Sciences (CIOMS). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS. Available at: http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm [Accessed 15 Sept 2013]; World Medical Association (WMA). 2008. *Declaration of Helsinki*. Ferney-Voltaire, France: WMA. Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf [Accessed 15 Sept 2013].

[4] D. Schroeder & E. Gefenas. Realizing Benefit Sharing – The Case of Post-Study Obligations. *Bioethics* 2012; 26: 305–314.

[5] Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Fair benefits for research in developing countries. *Science* 2002; 298: 2133–2134: 2134.

be marketed. Proponents of FB and others argue that the Surfaxin trials were an important opportunity for both the trial sponsor and host communities to benefit, and that well-meaning paternalism from outsiders ultimately undermined these communities' autonomy by denying them the opportunity to negotiate for goods they were willing to accept in return for hosting the research.[6]

But, by focusing only on individual transactions between research sponsors and host communities, FB fails to take into account the potential injustice of existing background conditions, and as a result does not address the realistic concern that bargaining disparities between international research sponsors and LMIC communities may impact the ability of host communities to 'negotiate' with industry or first world government research entities for a more fair share of the benefits derived from a clinical trial. This disparity has at least two implications.

First, FB is predicated on the value of autonomy in negotiation, but the bargaining inequality inherent to any negotiation between an LMIC community and a first-world research sponsor is likely to undermine the substantive autonomy of the community, given that they may not be in a position to refuse life-saving healthcare. Absent the constraints of vast inequities in access to healthcare, such communities may feel that their participation in research is worth far more than what research sponsors currently offer. Moreover, we might question whether the negotiations will truly reflect the interests of the host community, given that those negotiating on their behalf may be government officials with their own or broader national interests in mind.[7]

Second, there is little reason to equate the outcomes of such transactions with a substantive notion of 'fairness'. Because potential host communities are in such need of basic healthcare, they are in competition with one another to offer research subjects to sponsors for the lowest price possible, and the outcomes of negotiations reflect that.[8] Not only does this cause a 'race-to-the-bottom' with regard to trade-offs for hosting research, it also reinforces incentives for research sponsors to continue to support institutional structures which propagate inequities in healthcare access, such as the World Trade Organization's TRIPS agreement.[9]

By failing to limit the substantive content of research transactions, FB shifts all of the moral weight to the voluntary nature of the transaction, and fails as a result. That restricting the benefits of research to one specific type is erroneous does not imply that there should be no restrictions on the benefits due to LMIC communities who host research. We need an account of the benefits due to LMIC communities which is capable not only of acknowledging the moral relevance of more than one type of benefit, but also of distinguishing between those benefits which are sufficient to justify research in LMICs and those which are not.

PROMOTING HUMAN DEVELOPMENT

One attempt to make such a distinction is the 'Human Development' (HD) approach, which demands that sponsors and investigators provide benefits that contribute to the capability of a host community to meet the basic needs or distinctive health priorities of that community:

> The research enterprise represents a permissible use of a community's scarce public resources and is a permissible target of social support when it functions to expand the capacity of the basic social structures of that community to better serve the fundamental interests of that community's members.[10]

Health needs are prioritized based on whether or not they can be addressed through the application of existing knowledge and resources. As a community's existing capacity to meet citizens' basic needs decreases, the sponsor's obligation to provide access to proven therapies and additional infrastructure increases.

HD grounds the obligation to increase local capacity largely in a duty of rectification, which accrues to research sponsors and investigators due to their membership in democratic states which contribute to the maintenance of a particular global institutional structure. That structure, it is argued, is imposed on LMICs in a manner which reinforces disparities in health, and members of developed societies are responsible for that imposition to the extent that they have a political voice and can refuse to support such policies. Insofar as investigators or sponsors support these structures to a greater extent than most (by exerting a heavy political influence, for example), their duty of rectification is greater than that of the average citizen, and should be discharged by assigning benefits to LMIC communities hosting their research.

Moreover, sponsors and investigators are said to owe a duty of compensation to local communities. When research is conducted in an LMIC setting, important

[6] See, for example, A. Wertheimer. 2008. Exploitation in Clinical Research. In *Exploitation and Developing Countries: The Ethics of Clinical Research*, J.S. Hawkins & E.J. Emanuel, eds. Princeton: Princeton University Press: 63–104.

[7] A.G. Mitra. Off-Shoring Clinical Research: Exploitation and the Reciprocity Constraint. *Dev World Bioeth* 2012: Epub Ahead of Print.

[8] A.J. London & K.J.S. Zollman. Research at the Auction Block: Problems for the Fair Benefits Approach to International Research. *Hastings Cent Rep* 2010; 40(4): 34–45.

[9] T. Pogge. 2008. Testing Our Drugs on the Poor Abroad. In *Exploitation and Developing Countries: The Ethics of Clinical Research*, J.S. Hawkins & E.J. Emanuel, eds. Princeton: Princeton University Press: 105–141.

[10] A.J. London. Justice and the Human Development Approach to International Research. *Hastings Cent Rep* 2005; 35(1): 24–37: 33.

human, healthcare, and infrastructural resources are diverted from other uses to which local authorities have an obligation to devote them. If this diversion of local resources occurs, those conducting the research ought to adequately compensate the community for their losses.

Finally, the ability of LMIC communities to effectively negotiate for benefits on their own behalf is impacted by both global and local socio-economic structures. To the extent that the urgency and severity of community need both undermine a community's bargaining position and systematically benefit research sponsors through the generation of willing research participants, sponsors are said to have a duty to help host communities overcome that need and, thus, their future lack of bargaining power.

It is unclear that any of the duties ascribed by HD successfully ground the claim that research sponsors and investigators must help build local infrastructure in exchange for hosting research in LMICs. Although it is arguably the case that citizens of developed nations owe duties of rectification to citizens of LMICs, if these obligations are greater for research sponsors and their employees, they cannot be cashed out in terms of benefits owed to research-hosting communities. If the added duty which devolves to investigators and sponsors by virtue of their tacit or active support of a harmfully-imposed institutional structure requires rectification to those communities in which they conduct research, the duty could be discharged simply by not conducting research in these settings. Not only would it be a strange kind of duty of rectification, if it could be met by not engaging further with the party owed, but the varying of obligation in proportion to need would actually serve to disincentivize research in those communities with the greatest need for the health benefits associated with hosting research. This seems in direct contradiction to the apparent goal of HD to ensure that those with the greatest need receive the greatest benefits.

That research sponsors divert resources away from the provision of basic services to citizens is also insufficient to ground this account of benefits. While the diversion of resources may generate a duty to compensate, it actually does not speak at all to the requirement to provide benefits to communities for hosting research. If a research team brought with them all physical, logistical, and human resources necessary for the conduct of a trial, conducted the trial, and then pulled up and took everything with them when they left, they would have incurred no duty of compensation based on resource diversion. We might nevertheless ask on what basis the sponsor was justified in using *this* population in which to conduct its experiment.

Finally, that features of both local and global institutional structures work to undermine the ability of LMICs to adequately negotiate for benefits does not establish that building capacity is sufficient to overcome these hurdles. If there exists a duty to aid citizens in LMICs to overcome existing disparities, that duty adheres to all more or less equally, and not specifically to investigators and sponsors of LMIC research.

Although HD does limit the kinds of benefits which justify LMIC research, it fails to sufficiently ground the constraints it imposes. An adequate framework for assigning benefits to LMIC host communities must not only make a distinction between those benefits which can fulfill moral obligations to host communities and those which cannot, it must also be able to justify its limitation by appeal to the specific duties of research sponsors and investigators, or to some other morally relevant feature of clinical research. In the rest of this paper, I propose a framework grounded in explicit appeal to the central aim of clinical research: the generation of valuable biomedical knowledge.

THE NATURE AND AIMS OF HUMAN SUBJECTS RESEARCH

Each of the frameworks discussed fails to adequately distinguish between those benefits which can justify the conduct of human subjects research in LMICs and those which cannot. In further exploring this issue, we ought to explicitly address the nature and function of clinical research – what are its aims and goals, and what feature or features of clinical research justify the intentional placing of human subjects at risk of harm? To answer these questions, we must first delineate the various types of potential benefits from clinical research, which include:

- Direct medical benefits to research subjects as a result of receiving an investigational intervention,
- Ancillary or collateral benefits to subjects as a result of participating in a trial which are not directly related to investigational interventions, such as the receipt of better follow-up care,
- Payments to subjects for participation or compensation for time spent making follow-up appointments or undergoing extra tests,
- Payments or inducements to host communities, such as increased healthcare infrastructure, and
- Benefits to science and society from the knowledge gained through the research enterprise.

Direct medical benefits to research participants are certainly relevant to the moral assessment of a clinical trial, especially when weighing risks and benefits. But benefits to participants from receiving investigational interventions cannot play the role of *justifying* clinical research, for a number of reasons. First, direct medical benefits from investigational interventions cannot be guaranteed to research participants. Clinical research is by nature an uncertain endeavor: if investigators knew in advance that

an intervention would provide a net benefit, a clinical trial would be unnecessary, and if said intervention was known to be superior to alternatives, we would consider it unethical to subject research participants to inferior treatments in the name of 'research'. This is most clearly exemplified by the case of Phase I research: if direct therapeutic benefits were necessary to justify the conduct of clinical trials, the most basic translational research – often conducted on healthy human subjects, but even that conducted on, for example, cancer patients – would be unjustifiable.

This highlights that the provision of medical benefits is not the *function* of clinical research. In fact, a large part of the informed consent process is ensuring that subjects understand this very thing: we hope they will benefit from participating, but we are not sure they will, and moreover the major orientation of the research enterprise is not towards providing treatment to subjects, but rather towards the production of knowledge which will benefit future patients.[11]

Similarly, it is not the function of clinical research to provide care to patients or to address human rights deficiencies. Although both important goals, they are not the primary aim of research and in many cases will not be priorities. Likewise, although payments or other inducements may be offered to participants or communities which host clinical trials, these payments do not function to justify the knowing subjection of humans to risks of harm, but rather to increase participation and to compensate participants for their time, effort, and in some cases, assumption of risks. When we ask *why* it is legitimate to experiment on humans, to sometimes knowingly withhold effective treatments, for example, or to subject them to unknown risks or harms, the answer is that we think the information we are going to gain from these experiments is valuable enough to warrant the risk.

Both FB and HD imply that compensation to host communities can play this important justificatory role. In each case, what is not explicitly acknowledged is that material benefits to communities are being leveraged to offset risks of harm to individual participants in a manner which eschews the function and aims of clinical research. Especially in the case of HD, there appears to be a conflation between what is due to host communities as a matter of global health justice with what benefits are necessary in order to justify the subjection of human participants to risks of harm.[12] Because neither of these approaches explicitly discusses benefits in the context of the justificatory aims of clinical research, the inappropriate nature of using human subjects research as the basis for obligations to rectify broader injustices is obscured. By focusing on benefits in the context of the justificatory aims of research, we can highlight the central importance of the epistemic benefits to society in grounding the ethical validity of conducting research on humans.

This is really a question about the value of the scientific endeavor itself, and the goals associated with that endeavor. The ultimate aim of scientific research is the production of reliable knowledge, and the decision to pursue research embodies a value judgment about its expected outputs.[13] When coupled with the risks of harm implicit to clinical research, the decision to conduct clinical trials reflects the judgment of society that the benefits of that research are valuable enough to offset the risks. And because benefits to individual participants simply cannot be guaranteed in clinical research, we must look to the epistemic benefits of such research to play that necessary justificatory role.

SOCIALLY VALUABLE KNOWLEDGE

A research endeavor which does not promise valuable epistemic outputs is not ethically justifiable. The very nature and justification of medical research involving human subjects resides in its ability to produce knowledge which is of value to society, and this source of justification has been appealed to consistently throughout the history of research ethics. The dictum is enunciated in the second principle of the Nuremberg Code, which states, 'The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature,'[14] and it is widely accepted that research which does not hold out the prospect of producing socially valuable knowledge should not be conducted at all.[15] It is this potential for the generation of socially valuable knowledge – knowledge which we cannot gain in another way – which provides the ethical grounding for the intentional subjection of human participants to risks of harm in scientific experiments. I will refer to this the 'SVK Principle'.

The key ethical role of the SVK Principle also serves to explain the stringent methodological standards in place

[11] P.S. Appelbaum, L.H. Roth & C.W. Lidz. The Therapeutic Misconception: Informed Consent in Psychiatric Research. *Int J Law Psychiatry* 1982; 5: 319–329; P.S. Appelbaum, C.W. Lidz & T. Grisso. Therapeutic Misconception in Clinical Research: Frequency and Risk Factors. *IRB* 2004; 26(2): 1–8.

[12] B. Pratt & B. Loff. Justice in International Clinical Research. *Dev World Bioeth* 2011; 11(2): 75–81.

[13] H.E. Douglas. 2009. *Science, Policy, and the Value-Free Ideal*. Pittsburgh, PA: University of Pittsburgh Press: 89–95.

[14] 1949. The Nuremberg Code. In *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Nuremberg, October 1946–April 1949*. Washington, DC: USGPO.

[15] S. Joffe & F.G. Miller. Bench to bedside: Mapping the moral terrain of clinical research. *Hastings Cent Rep* 2008; 38(2): 30–42; WMA, *op. cit.* note 3; C. Grady. Science in the Service of Healing. *Hastings Cent Rep* 1998; 28(6): 34–38; E.J. Emanuel, D. Wendler & C. Grady. What makes clinical research ethical? *JAMA* 2000; 283: 2701–2711.

for the conduct of clinical research. We seek to limit the impact of bias on research results because we want to ensure that the knowledge which is produced is scientific, replicable, and generalizable to larger populations and to the clinical context. In short, we want to ensure that the epistemic outputs of clinical research are *valuable*. Otherwise, we are placing human subjects at risk of harm without the prospect of a corresponding benefit: 'without validity the research cannot generate the intended knowledge, cannot produce any benefit and cannot justify exposing subjects to burdens or risks.'[16]

But the SVK Principle demands more than just methodologically sound research. The normative content of the SVK Principle is in large part filled by the value component of the dictum: the knowledge sought should be *socially valuable*. While a badly designed trial the results of which cannot be generalized to clinical practice does not produce valuable knowledge, neither does a well-designed trial investigating an irrelevant or redundant question.[17] Therefore, in order to understand how this principle ought govern the ethical conduct of research – particularly in the context of LMICs – a fuller accounting of what constitutes the social value of research-generated knowledge is necessary.

In the remainder of this paper, I provide a general sketch of how we might begin to fill out this crucial concept, highlighting some of its most important components and discussing those aspects which require further elaboration. My aim in this exposition is not to provide a full account of the social value of research-generated knowledge, but rather to motivate the need for a more formal systematization of what constitutes sufficient epistemic gain to justify the intentional subjection of human beings to risks of harm in the pursuit of biomedical progress. In sketching this account, it is my hope that the need for a fuller framework will be sufficiently compelling as to draw others into the project of its more thorough development.

A piece of knowledge can be more or less valuable. Take as an example Rawls's counter of blades of grass.[18] Without addressing whether the man truly enjoys the activity, we can acknowledge that the value of the knowledge he obtains – how many blades of grass exist in his well-trimmed lawn – is less than the value of the knowledge he might attain were he to spend that time learning how to maintain a balanced household budget: knowledge can be more or less valuable. But more than that, knowledge can be more or less valuable to different individuals or social groups. Despite what we might think about the value of the grass-counter's total sum, that sum is doubtless of more value to him – perhaps he will use it to inform the amount of fertilizer to use this spring – than it is to me, living in a small apartment halfway across the country, with (sadly) no lawn at all. The value of knowledge – much like the value of other goods – is at least in part subjective. And just as personal values will play a large role in the value one ascribes to a piece of knowledge, social values will play a large role in the value a society ascribes to a piece of knowledge.

A further example can help to illustrate this point. While attending a conference, three physicians who run an urban charity clinic in Chicago learn of a new compound which can cheaply and effectively treat sleeping sickness. They learn how it works, at what dosage it is most effective, and how to administer it so as to maximize its efficacy. To their community in Chicago, where sleeping sickness does not occur, this knowledge is of little value. But when those same physicians decide to spend two years doing aid work in sub-Saharan Africa, this knowledge is suddenly of enormous social value – to the population within which they now find themselves.

The example shows that when we talk about the *social* value of knowledge, we are referring to instrumental value. This is not to deny that there is or can be inherent value to knowledge, only that for knowledge to have social value, that value must include an instrumental component. This is true particularly in regards to research-generated knowledge: knowledge of a specialized nature which only certain members of society will be in a position to understand and make use of. For that knowledge to be of value to society, therefore, the use to which it is or can be put must be the locus of the value ascribed.[19] And the *usefulness* of certain pieces of knowledge will vary widely on the basis of contextual features of a society – features such as disease prevalence, public health resources, and local infrastructure, for example.

The SVK Principle states that the epistemic value of the outputs of clinical research is essential to the moral validity of that research. If the moral legitimacy of clinical research is grounded in the social value of the knowledge to be generated, and the social value of the knowledge to be generated is context-dependent, then the moral legitimacy of clinical research is context-dependent. In other words: if the value of knowledge is relative to social context, then there is at least *prima facie* reason to think that the epistemic value of the outputs of human subjects research to a given community is

[16] E.J. Emanuel et al., ibid: 2704.

[17] I am thinking here of placebo-controlled trials which do not evaluate comparative effectiveness, for example, or the proliferation of research into so-called 'me-too' drugs.

[18] J. Rawls. 1971. *A Theory of Justice*. Cambridge, MA: Harvard University Press: 432.

[19] The instrumental social value of research-generated knowledge should not be conflated with economic value: knowledge can simultaneously hold great social value and little economic value. For example, knowledge of a cheap and effective method of malaria prevention would be of enormous social value to many populations, but likely of little economic value given low per capita funding available for healthcare in such populations.

essential to the moral validity of conducting that research *within that community*. This contextual nature of the value of knowledge syncs well with the discomfort many express regarding the conduct of research in LMICs. Intuitively, it seems like what is ethically troubling about some cases is that all of the epistemic value produced accrues to populations who do not share the same social context as those undertaking risk for the sake of its generation.

The SVK Principle as currently laid out seems predicated on the value of the actual outputs of research. But the research enterprise is essentially an uncertain one, and it cannot be the case that we reserve judgment on the ethical justification for a clinical trial until after the trial has been conducted. Rather, the SVK Principle has to operate on the basis of the *expected* or *intended* epistemic outputs of a clinical trial, and the value which can be ascribed to the knowledge anticipated. Although we do not have access in advance to the actual knowledge to be gained through research, we are able to assess what kind of knowledge it will be and how robust the findings, what diseases or conditions are addressed, and how and whether the results – positive or negative – will be relevant to specific populations.

It is this appeal to *intention* which provides the morally relevant difference between the epistemic gains of a phase I trial conducted in an LMIC – whose practical benefits may not be realized until many years down the road – and the long-run trickle-down benefits of late-phase research conducted in an LMIC on an intervention intended for initial marketing only in the developed world. Assuming positive findings, in each case the host community is likely to benefit fifteen or twenty years from now: in the first case, when an effective intervention is finally developed and marketed locally, and in the latter case, when the intervention comes off patent and can be manufactured inexpensively by generic producers. But we can point to the difference in the primary intended beneficiaries of the epistemic gains sought. As the targeted SVK from clinical research plays the foundational justificatory role for the use of human subjects in experiments from which they are not guaranteed to benefit directly, the primary epistemic aim of the trial should be to produce knowledge which will be of value to the community of those subjects. This requirement speaks to the *aims* of the research endeavor, and not just its side effects. In other words, it is not sufficient justification for the conduct of a trial within a given context to accidentally or unintentionally produce knowledge of local benefit. The SVK Principle operates at the front end of the research enterprise, and the knowledge which is sought should be appropriately relevant to the host community in order for the research to be ethically conducted in the first place. Locally valuable knowledge must be the primary epistemic aim in order to *justify* the use of members of a given community in research. And although we do not always have direct insight into the aims of individual studies or their various stakeholders, there are good surrogate indicators available, such as study hypotheses, approval and marketing plans, plans for the continuation of a line of research, or the costs involved in the manufacture of a pharmaceutical entity in relation to the healthcare resources available within a community.

One might object that an appeal to the instrumental value of research-generated knowledge leaves little to distinguish this account from reasonable availability, and that therefore it is open to the same kinds of objections, but this objection would be misplaced. The complaint with regard to RA is not merely that it is a difficult standard with which to comply due to practical and regulatory hurdles. The deeper complaint is that RA can be construed in one of two ways: It might be interpreted as a post hoc standard, which establishes the requirement that *if* a trial generates confirmatory results, *then* the proven effective intervention should be made reasonably available to the local population. If this is the intended meaning of the standard, then it fails to generate any positive duties for sponsors and investigators in the very large proportion of trials which fail to establish safety and efficacy of new interventions. On the other hand, if we interpret RA to place an *a priori* restriction on the conduct of trials, it would seem to imply that we must conduct only that research which we know in advance will produce something which can later be made available to the local population. But this rules out the vast majority, if not all, of clinical research, given the uncertainty inherent to the endeavor, in addition to the logistical hurdles canvassed above.

Although RA offers valuable insight into the appropriate goals of LMIC research, it nevertheless fails to account for many of the ways in which research-generated knowledge might be instrumentally socially valuable, and this is why it fails to plausibly govern the ethical conduct of research in LMICs. In contrast, the SVK standard is capable of recognizing that the production of an effective intervention is not the only valuable epistemic output of a clinical trial. Knowledge which leads to the development of new lines of research or which feeds back into the scientific process, for example, also contributes to social utility.[20] Because the SVK standard is focused on the ethical justification of the research enterprise itself, and is applied at the formative stage of a clinical trial, it is capable not only of accounting for disconfirmatory trials, but also of distinguishing between those epistemic aims which can function to legitimate the research in the first place and those which

[20] J. Kimmelman. 2010. *Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation*. Cambridge, MA: Cambridge University Press: 92–97.

cannot, as well as distinguishing those trials of greater and lesser merit on the basis of their trial design and the likelihood of a given trial generating useful knowledge – whether confirmatory or not.

One might ask why it is the case that a transaction between a research sponsor and a host community should be treated differently from any other interaction. That is, why is it not the case that if all parties have agreed to the interaction and all parties leave the interaction in a better position than they were prior to that interaction, that this suffices to ethically ground the transaction? First, the existence of Pareto-superior, or win-win, transactions which are nevertheless *unfair* in a substantive moral sense is not only plausible, but largely acceded to even by those who insist that we ought not interfere with such transactions.[21] The fact that both parties to an interaction benefit relative to some pre-transaction baseline is not, of itself, sufficient to establish the ethical *bona fides* of that interaction. But regarding the defense of the SVK Principle, I would distinguish between two importantly different claims. One claim I might make is that the intended production of socially valuable knowledge is a necessary condition for the ethical conduct of research. Another is that some regulatory or oversight body ought to intervene to prevent the conduct of research which does not meet the criteria set out by the SVK Principle. Although I believe a case can be made for the latter claim, it is a more difficult case to make, especially with regard to trials involving a low risk profile. I defend this claim elsewhere, but do not make or seek to defend it here.[22] The claim I defend here is the more conservative: that in order for a clinical trial to have sufficient ethical justification to be undertaken within a given population, its epistemic aims should be of local social value to the community hosting the research.

It is also important to note that the SVK Principle is intended to function as a necessary, but not a sufficient, condition for the ethical conduct of research. It is but one of many ethical constraints operating on the use of human subjects in experimentation. Therefore it is consistent with the SVK Principle that there exist additional requirements regarding benefits which must accrue to individual subjects participating in clinical research, such as ongoing access to proven or investigational therapies, although the SVK Principle itself does not require such. The SVK Principle merely highlights that *direct therapeutic benefits* from research participation cannot be an ethical requirement due to the uncertainty necessary in the research enterprise, and that moreover the expected *epistemic benefits to society* function as a minimal criterion for the justification of human subjects research. The SVK Principle is also consistent with, but silent regarding, more demanding ethical criteria regarding respect for human rights and, potentially, positive obligations of justice towards those in LMICs.

I have, throughout this discussion, bracketed the important question of how to designate the relevant community for determinations of SVK. This is actually two, distinct, questions: First, who comprises the relevant community – that is, to what group of individuals ought research-generated knowledge be of value? And second, who ought to make the determination regarding whether a particular epistemic aim is of social value? While related, these questions require separate treatment.

Regarding the first question, while it is the case that communities are often largely geographically defined, physical location may be less important than how individuals identify themselves. Socioeconomic status, for example, might impact how a community is defined: different socioeconomic groups within and across states are likely to have different health needs. A fully elaborated account of SVK must delineate how the determination of the relevant 'society' is related to the physical location of a trial, its actual participants, and the broader communities to which those individuals belong. In the interim, we can nevertheless identify clear instances of the SVK Principle's violation based on our current loose understanding of the relevant population. Vaccines tested in developing communities which are meant to be distributed only to developed world servicemen are not likely to produce knowledge of local social value,[23] nor is the testing of a new drug to treat sepsis in intensive care units going to produce much value for communities battling under-nutrition and water-born parasites in rural India.[24]

The second question is potentially less tractable. There is ongoing debate regarding the proper locus of motivation for scientific priorities, even in developed nations – whether such determinations of value ought to lie with expert scientists, or are better addressed through more inclusive or democratic procedures.[25] In the case of clinical research, the question is more complex given the numerous stakeholders involved in setting the research agenda and their varying, and often competing, motivations. However, I want to be careful to emphasize the following distinction: contemporary debates regarding the intersection of science and social values ask who ought to determine how research resources are distributed, whereas the SVK Principle is intended to operate as

[21] A. Wertheimer. 2011. *Rethinking the ethics of clinical research: Widening the lens*. Oxford, England: Oxford University Press: 213–223.
[22] Under preparation.
[23] J. Andrews. Research in the Ranks: Vulnerable Subjects, Coercible Collaboration, and the Hepatitis E Vaccine Trial in Nepal. *Perspect Biol Med* 2006; 49: 35–51.
[24] E. Abraham et al. Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death. *N Engl J Med* 2005; 353(13): 1332–1341.
[25] See, for example, P. Kitcher. Scientific Research – Who Should Govern? *NanoEthics* 2007; 1: 177–184.

a constraint on the ethical conduct of research. A fully developed conceptual framework for determining whether knowledge is valuable within a specific social context should be capable of delineating between that research which it is ethically legitimate to conduct in a given population and that which it is not. While stakeholders may be tasked with the application – and therefore the interpretation – of such a standard, this speaks to the practical implementation of such a limitation, and not to the content of the ethical principle itself. Any adequate account of SVK needs to be unambiguous enough as to provide concrete guidance to such stakeholders, and thereby minimize the opportunities for misapplication by those with vested interests in the continued proliferation of lower-cost, global experimentation.

CONCLUSION

The debate regarding the distribution of benefits to LMIC communities hosting externally-funded research has in many ways failed to appropriately distinguish between those types of benefits which can legitimate the conduct of clinical research and those which cannot. Although this is not the stated purpose of such accounts, I have used the valuable insight contributed by each of the received theories regarding benefits sharing in order to highlight that an important justificatory component of research has been overlooked in discussions regarding the benefits due to host populations. Specifically, I have argued that the central aims and justification of clinical research, as embodied by the SVK Principle, should be brought to bear in assessing the ethical appropriateness of the conduct of specific research projects within specific populations, and that while additional benefits may be warranted, locally relevant epistemic goals are a minimal necessary criterion of ethical research conducted within an LMIC.

The account that I have offered establishes that the social value of research-generated knowledge is context-dependent, and that in order to play the justificatory role necessary to ground the ethical conduct of research, the expected epistemic gains from a research endeavor must be primarily intended to benefit the community(ies) in which that research is conducted. This preliminary defense of the centrality of SVK leaves incomplete the crucial development of this concept, which demands a fuller accounting. In order for the SVK Principle to govern our ethical assessment of clinical trials, an analysis of the extent to which various metrics of social value can be applied to research-generated knowledge is required, as are a better-defined understanding of the relevant community and the development of a mechanism for the prospective evaluation of the expected epistemic benefits of clinical trials.

Although I have not answered these questions, I hope to have demonstrated the need to address them, and to have motivated further efforts towards our understanding of the value of research-generated knowledge and the justificatory role that value plays in the ethical use of human subjects in research. I also hope that further development of this concept will shed light on additional topics of relevance to global health, such as the validity of intellectual property laws governing pharmaceutical interventions and appropriate clinical trial design.

Biography

Danielle M. Wenner is the Andrew W. Mellon Postdoctoral Fellow in the Humanities at Carnegie Mellon University. She earned her PhD in philosophy from Rice University in 2011, and completed a clinical ethics fellowship at the Cleveland Clinic in 2013. Her research interests include clinical research ethics, justice and exploitation in healthcare and other market contexts, and the impact of cognitive and deliberative pathologies on social and political interactions.