The American Journal of Bioethics, 14(2): 28–37, 2014

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2013.868950

Target Article

Ethical Review of Health Systems Research in Low- and Middle-Income Countries: A Conceptual Exploration

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Given that health systems research (HSR) involves different aims, approaches, and methodologies as compared to more traditional clinical trials, the ethical issues present in HSR may be unique or particularly nuanced. This article outlines eight pertinent ethical issues that are particularly salient in HSR and argues that the ethical review process should be better tailored to ensure more efficient and appropriate oversight of HSR with adequate human protections, especially in low- and middle-income countries. The eight ethical areas we discuss include the nature of intervention, types of research subjects, units of intervention and observation, informed consent, controls and comparisons, risk assessment, inclusion of vulnerable groups, and benefits of research. HSR involving human participants is necessary to ensure health systems strengthening and quality of care and to guide public policy intelligently. Health systems researchers must carefully define their intent and goals and openly clarify the values that may influence the premises and design of protocols. As new types of population-level research activities become more commonplace, it is critical that institutional review board (IRB) and research ethics committee (REC) review processes evolve to evaluate these research protocols in ways that address the nuanced features of these studies.

Keywords: health systems, research ethics, health systems research, implementation research, ethical review, developing world

Health systems research (HSR) is a subset of public health and is defined by the World Health Organization (WHO) as "the purposeful generation of knowledge that enables societies to organize themselves to improve health outcomes and health services" (World Health Organization 2009). HSR covers a wide range of subject areas that are focused on common health systems functions, such as stewardship, financing, resource inputs, and delivery of services (World Health Organization 2009). It is not usually research that focuses on the discovery or development of new interventions to improve health; rather, research aims to understand how new interventions that are efficacious can be made more widely accessible to potential beneficiaries through policies, organizations and programs (Gilson et al. 2011). These studies may also provide data on quality and cost-effectiveness to identify more efficient strategies for health care delivery. To generate knowledge on these systems-level factors, HSR studies employ a range of experimental and quasi-experimental designs. While some adopt the traditional randomized controlled trial (RCT) model, many HSR studies are performed as nonrandomized, controlled or noncontrolled, prospective or cross-sectional assessments of new or modified health care programs and strategies (Alliance for Health Policy and Systems Research 2012a). Given the macro focus of HSR, the participants and beneficiaries are often communities, hospitals, and health care institutions, as opposed to individuals.

Since HSR has its own definitions, methods, and analytic approaches, there is an increasing realization that it may raise ethical concerns that may differ from other types of research; therefore, its ethical review should arguably be tailored to address the features and unique ethical challenges that are particularly salient (though not exclusive) to HSR. Unfortunately, many (if not most) institutions, including the WHO, use the same review criteria and process for HSR studies as for clinical trials, which can potentially create an imprecise application of criteria, confusion on the part of research teams, and unnecessary delays. The incongruity between current ethical review guidelines—which were generally developed with attention to the protection of individual subjects in clinical research—and the purpose and design of HSR raises substantive ethical concerns and

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creates practical inefficiencies. Given the nature of HSR and the limited risk these studies typically pose to human subjects, the ethical review processes of research ethics committees (RECs) and institutional review boards (IRBs) ought to be adjusted and streamlined to account for the nuances of HSR. Currently, it is not clear whether institutions are equipped to adequately address and ethically evaluate HSR in their IRBs (Hyder et al. 2012a). This is especially true for HSR in low- and middle-income countries (LMIC), where this research often plays a critical role in health systems strengthening efforts and improvement of health care delivery.

Based on the presumption that certain kinds of ethical issues may be particularly relevant to and salient in HSR, this article aims to highlight and elucidate some of these issues. We outline eight areas of ethical relevance that are particularly salient in HSR (though not unique to HSR) that may require special attention during ethics review, especially in LMIC. Each HSR issue is described and accompanied by some additional clarifications surrounding an ethical analysis of HSR studies and an example of how these ethics issues might apply to a specific HSR study.

DOMAINS OF ETHICAL RELEVANCE IN HEALTH SYSTEMS RESEARCH

This section describes eight proposed key dimensions of HSR studies that may require special ethical considerations, with a focus on LMICs; they are also listed in Table 1.

Nature of Interventions in HSR

HSR is fundamentally about translating efficacious interventions into effective practice at the population level. As a result, the interventions under investigation in HSR can vary greatly, as can their methods of delivery, resulting in ethical issues quite specific to a given study. These interventions might be health messages, incentives, measurement tools, performance guides, intervention packages, financial subsidies, or delivery systems. Typical interventions in HSR involve new methods of delivery or dissemination of existing or proven interventions, novel approaches for creating demand for efficacious interventions, new packaging of two or more interventions for enhanced program effectiveness, or knowledge generation on costs or cost-effectiveness for policy impact. This diversity in the intensity, invasiveness, and duration of implementation requires a very good understanding of the intervention in each HSR study in order to define relevant ethical issues.

HSR also blurs the distinction between research and nonresearch processes. It is important to make the distinction between quality improvement (QI) projects, which are meant to improve service deliverance and process performance, and research, which is meant to produce generalizable or transferable knowledge. Though the former is typically exempt from ethical review, pertinent issues may overlap for both QI and HSR, regardless of what may be legally required vis-à-vis regulations. From a practical standpoint, this range and variability can pose difficulties for RECs in gaining experience reviewing certain kinds of HSR and applying recommendations consistently. As compared to clinical trials, which often share common features and have more clearly identified areas for ethical consideration established in the literature, HSR may present unique challenges for review committees with each new protocol. This is specially the case when HSR refers to areas wherein the REC does not have much experience, which can impact the quality of the review and further strain the limited capacity of RECs to assess study proposals in a thorough and efficient manner.

Ethical challenges that are intervention specific in HSR vary from concerns around scientific rationale to distribution of benefits to sustainability issues. For example, in the case of HSR testing new delivery methods (e.g., for child health), one could question whether there is appropriate evidence to support the testing of a new approach or challenge the need for innovation over continuing with existing delivery systems (e.g., community health workers versus facility based delivery). Where there is not much

Table 1. Proposed ethics considerations of special relevance in health systems research in low- and middle-income countries

Ethics issue	*Application to health systems research in low- and middle-income countries*
Nature of interventions	System based such as delivery systems, financing, human resources, or policies
Type of subjects	Groups of people or communities
Units of intervention and observation	Often different such that intervention distributed to one group and measurement based on another
Informed consent	Group consent and permissions needed (in addition to individual consent)
Comparison groups	Comparators often receive different interventions or observed in real world
Risk assessment	Broad range and different types of minimal risk—social, communal
Inclusion of vulnerable groups	The focus of HSR and proposed beneficiaries
Benefits assessment	Expanded definition including training, infrastructure, health systems strengthening

prior evidence on an approach, are theory and hypothesis enough to justify testing the intervention, or is there some population-level experience that should be required to demonstrate proof-of-concept prior to a larger scale trial of the new method (e.g., use of the "kangaroo" methods for neonatal child health)? This is of particular concern in LMICs, since their need for novel interventions to deliver services efficiently makes them arguably ideal candidates for testing health systems innovations, and if there is meager evidence supporting the effectiveness of interventions, these resource-constrained settings may bear a disproportionate burden in the generation of global health systems innovations. Implicit in this concern are (1) the obligation of researchers to not impose undue harm upon populations, which may occur in the absence of sufficient evidence (e.g., distortion of a local health market), and (2) issues of distributive justice, in which disadvantaged communities assume the risks of research on interventions that will ultimately benefit more advantaged populations, an increasing concern as more high-income nations adopt innovative models from developing country settings (Fry et al. 2011).

Another type of ethical concern that is particularly unique to HSR relates to determining the potential for harm with new health delivery methods and associated safety. The kinds of harms resulting from HSR tend to be more obscure, downstream, and harder to quantify than those typically associated with a clinical study. In order for RECs to adequately assess the potential harms associated with certain types of HSR, they will have to rely on the existing evidence base of the approach, with a good understanding of the history of a particular delivery method and its success or failure with similar types of health interventions. However, for many novel approaches, there might be scant prior evidence available to inform the ethical review process.

Finally, in LMIC where a lack of access to health interventions exists, ethical concerns around future availability become salient (also see later section on benefits). Will the community involved in the trial continue to have access to beneficial services provided as part of the study, if the intervention is not adopted and taken to scale? While the issue of posttrial access is not unique to HSR and has been widely discussed in research ethics literature, this issue is of particular import for HSR given the well-documented lag in, or absence of, research-to-policy translation (Grady 2005; Lavery 2004). What impact might the temporary change in health delivery mechanisms or available services have on the community, and could this disruption in the status quo have net negative consequences for the population? At the systems level, decisions to adopt new approaches for providing health to the population often weigh costs and benefits at the aggregate level, so even interventions that show improvements for those involved in the pilot may not be taken up in the end if they do not prove cost-effective. These concerns must play a role in how local and national health sectors analyze and respond to the results of a HSR study and raise questions about what obligations exist for research institutions and funders conducting such work.

Type of Research Subjects in HSR

The "research subjects" in HSR studies can either be humans or nonhumans, each with their own respective ethical challenges. Nonhuman "subjects" in HSR may include units of allocation, such as hospitals or schools involved in a study of cost containment budgetary strategies; or units of interventions, such as motorcycles equipped with safety features in a vehicle crash reduction study. When reviewing study protocols with these kinds of nonhuman subjects, it may be challenging for RECs to assess what role various actors should play in the authorization and implementation of the study. For instance, when schools or hospitals are the unit of allocation, how should the employees of these institutions factor into the ethical analysis? When the intervention involves safety features for products, how should RECs weigh the interests of the manufacturers as well as consumers of these products? For HSR studies, the level of impact goes far beyond individuals, and even research with nonhuman "subjects" requires consideration of a wide range of stakeholders who may be affected by the investigation. As of yet, there is no standard universal guidance on how to assess and balance the interests of these various parties in HSR studies.

When considering HSR with human subjects, the study may target individuals as units of allocation or intervention, though more commonly they are directed at groups of people, as in population-level or cluster-based studies. The emphasis on groups of people as research subjects introduces the ethical challenge of defining the moral status of a group or community as opposed to individual persons. Identifying appropriate representatives or leaders of these groups may also be trying, especially when assessing their legitimacy and source of authority. The principle for respect for communities has been proposed as a means of defining moral worth and protecting the interests of a given community (Weijer and Emanuel 2000). This principle understands the community as a source of values, a social structure that sustains its members and makes decisions for its members. Therefore, RECs concerned with respect will have to think far beyond the typical construction of respect for persons, concerned with individuals (and often focused on consent—see later discussion), and instead adopt the broader interpretation of respect for communities to determine what is required. Their review of such an HSR study will have to take stock of study community priorities and norms, and determine appropriate levels of engagement with local leadership, which presents further challenges, particularly in pluralistic communities embodying a range of diverse interests. This extension of "respect" from an individual to a population requires further exploration for global health research (Wallwork 2008).

HSR studies involving large populations or groups of people also require a broader interpretation of burdens and benefits that may be involved, as well as an acknowledgment that the associated benefits and burdens may be differentially distributed across various subset of the study population, raising distributive justice issues. Similarly,

concerns around potential harms need to be reviewed, such as a group reputation potentially affecting individuals—for example, a hospital that is perceived to provide low-quality care, and this reputation affects the flow and type of individual patients who visit it. Wallwork describes this concept of *group harm* by which "members suffer it *by virtue* of their identification with or participation in the group" and discusses the difficulty in identifying and quantifying group harms that impact belief systems and institutions (Wallwork 2008). This presents complications for RECs in assessing cost–benefit ratios at the community level. The current norm for reviewing research focuses on the individual, but this narrow application of principles at the individual level is not well suited for assessing HSR, in which group-level interventions and impacts require a much broader lens.

Units of Intervention and Observation in HSR

Unlike typical clinical research, in which interventions are often administered to individuals who are then observed for potential effects, HSR often targets a unit of intervention at a more macro level and then assesses its impact at a more micro unit of observation. In other words, the units of intervention and observation are often not the same. For example, imagine an HSR study that provided local taxi drivers (unit of intervention) with incentive payments to transport pregnant women to the clinic for antenatal care and delivery; although the intervention is administered to the taxi drivers, the outcomes data would be collected on mothers and infants (unit of data collection/observation) within the intervention community. Another example would be hospitals introducing quality assessment activities for infection control by teams of health providers (unit of intervention), but where outcome data is collected on hospital-acquired infections among patients (unit of observation) admitted to those hospitals.

The use of different units for intervention and observation creates a new set of challenges for ethical review. One issue is in terms of defining and assessing risks and benefits for multiple levels of research participants: the research subjects who might be the unit of intervention (sometimes called primary), and other research subjects from whom data is collected (sometime called secondary). So in the case just described on testing infection control measures, the hospital staff (doctors, nurses) and patients would all be research participants. How should RECs assess the study with appropriate regard for all groups of research subjects whose well-being can be impacted by the intervention? This also raises important questions for the consequential targets and nature of informed consent; that is, who should be involved in the informed consent process and when individual consent of some (secondary) participants might be impracticable, and what should be the standards for informing them of the study? If data collection involves a measurable burden for some participants, such as additional interviews, does this incremental burden necessitate greater participation in the consent process? Consent is discussed further in this article, but it is clear that having different units of intervention and data collection presents unique challenges to how practical matters of risk–benefit analysis and informed consent are carried out for HSR studies.

Informed Consent in HSR

As noted earlier, HSR presents unique challenges to the informed consent process. Consent can be obtained similarly in both HSR and clinical studies in the event of individuals receiving a particular intervention. However, in many HSR studies where interventions are administered to an entire group, the consent process has to involve authorization at multiple levels, engaging community or institutional leaders as well as affected individuals. In some studies where the intervention can be delivered at an individual level, such as with malaria bed nets, researchers may require consent from both the community leadership, as well as from individuals or households participating in the study. However, other interventions, such as adjustments to standard procedures or drugs offered at public facilities, broadly impact a large number of people for whom obtaining consent would be impracticable. In these instances, group consent (or permission) is usually obtained through representatives and often paired with community outreach and education. In some circumstances, participants still have the ability to opt out and can take voluntary actions to exclude themselves from study participation (e.g., avoiding public facilities or seeking private providers).

In HSR, that includes cluster-randomized trials of certain group interventions, individual informed consent may not be obtainable, and some have argued that ethics committees have an obligation to ensure that the justification for waiving consent is adequate (Sim and Dawson 2012; Taaljard et al. 2009; Weijer et al. 2011). For example, individual informed consent in HSR studies that focus on area-wide interventions for malaria control, such as spraying, or building speed bumps for road safety may not be possible. Moreover, some have argued that a trade-off may need to occur in regard to the decisions on the choice between individualized consent and ability to conduct valid HSR studies; indeed, if the societal value of the HSR study is high enough, it may allow beneficence concerns to outweigh individual autonomy concerns and permit practical studies to move forward (Hutton et al. 2008).

Consent involving groups of people may not be specific only to HSR, but is starting to become a "norm" in many HSR studies in LMIC. Questions remain around how groups should be defined, and how formal permissions and consent processes are being administered in LMIC. Key to this is addressing the issues of group representation, legitimacy of representatives, authority structures, and coverage of the consent process. Concern has been well documented in the literature around the validity of leaders who give consent for a group; potential exclusion of vulnerable groups including women; and ability of individuals within the groups to opt out (Cassell and Young 2002; Davis 2000; Diallo 2005; Emanuel 2004; Ijsselmuiden and Faden 1992; Weijer and Emanuel 2000). Thus, consent from groups

and/or representatives is often necessary and yet case-by-case discussions are needed to determine whether it is sufficient. HSR studies have to be sensitive to these concerns even in the presence of less invasive interventions.

An important issue is that of defining subjects for consent—irrespective of whether they are individuals or groups. For example, common requirements for informed consent may not apply to many HSR studies. In the U.S. Code of Federal Regulations (CFR), Title 45, Part 46, informed consent applies to "research subjects"—defined as those actively involved in research (Protection of Human Subjects Research 2009). However, under circumstances where no "direct" subjects are identifiable, as is the case in many HSR studies, is such a requirement for consent appropriate? For some HSR projects, the lack of identifiable human subjects and aggregation of data for analysis may lead IRBs to designate these studies as "non-human subjects research," which would exempt them from the consent requirements specified in the U.S. regulations. Furthermore, the U.S. federal regulations also waive consent when studies fulfill four conditions: the research is no more than "minimal" risk; the rights/welfare of subjects are not adversely affected; the research cannot be carried out in other ways; and the subjects will be debriefed (when appropriate) (Protection of Human Subjects Research 2009). Applying these conditions to HSR studies would mean that many of them can obtain a waiver of consent. The nature of group interventions, which often lack identifiable direct subjects and are built into health systems responses, makes HSR studies amenable to such waivers. Given that when HSR studies receive funding from U.S. federal agencies like the National Institutes of Health (NIH) or U.S. Agency for International Development (USAID) they are thus bound by these regulations, the proper application of the preceding criteria by IRBs will have implications for how consent is handled is United States-sponsored HSR. Appropriate ways to handle consent, authorization, and authentic community engagement for group-level interventions characteristic to HSR remain a challenging area for investigators and ethical review boards.

Appropriate Controls and Comparisons in HSR

The nature of control groups can vary in HSR studies, and the ways groups are compared are often not consistent with common clinical research study designs where often the absence of an intervention is considered the "gold standard" comparison for effectiveness studies (placebo controlled). For instance, if an HSR study is testing a new delivery method for a proven intervention, then the comparison group may have an older delivery method, or if an HSR study is testing a new package of existing interventions (say A and B together), then the comparison group may receive them separately (either A or B alone). In addition, the selection of these comparison locations is often not done randomly, but rather by systematic matching or even geographical or logistical convenience. As a result, comparison groups in HSR studies pose challenges to the ethical review process when these control groups receive different types of interventions; there is wide variation of possibilities of what might constitute comparison groups.

HSR presents challenges for establishing appropriate comparison groups. Unlike clinical trials, which often occur in highly controlled experimental settings, HSR often involves interventions that take place within existing, real-world settings, making it difficult to control for a variety of extraneous variables that could impact results. Therefore, many (especially low-cost) HSR studies use comparators of convenience, such as data from similar districts or cities, or quasi-experimental pre–post designs, often applying complex statistical techniques in an attempt to account for nonparities or temporal confounders. In order to ensure the internal validity of these studies, a necessary ethical requirement of all research, RECs should be equipped to evaluate the techniques used in HSR to determine if studies have adequately controlled for the challenges of imperfect comparison groups (Emanuel et al. 2004). This will have implications for the future applicability of the study findings and their social value, in addition to ensuring respect of the communities participating in the HSR study.

In addition to determining appropriate counterfactuals, that is, who should serve as the control, there is also the question of what should be provided to the control groups. Although ethical debates concerning the appropriate use of placebos versus active controls are not exclusive to HSR and have been ongoing in the literature for many years surrounding both clinical and implementation trials, these concerns are particularly acute in the context of HSR in LMIC (Emanuel el al. 2000; Emanuel and Miller 2001; Freedman 1990; Miller and Brody 2002). There may be little evidence available concerning the effectiveness of current systems of practice, making the decision of what, if anything, to test a new health system approach or combination of approaches against particularly challenging (in clinical investigations testing equivalency or superiority, there is often a much more robust evidence base about the current standard of practice). Furthermore, where an HSR study seeks to assess packages of multiple beneficial interventions that have potentially synergistic effects, what subset(s) of these interventions should be provided to the control group(s)? If the researchers are seeking to find the most cost-effective package of services to produce the desired health impact, they must balance their obligation to provide existing beneficial interventions to their participants, on the one hand, with their aim to produce information for evidence-based policy that will ultimately provide the greatest societal benefit. To further complicate the issue, given that authorization is often obtained at the group level rather than by the individual persons affected by the interventions, as discussed earlier, these individuals may be unable to voluntarily accept the risks that may be posed to them as a result of being assigned to a particular arm of the study.

Another relevant factor for many cluster-based studies arises when they use a staged introduction or stepped wedge design, in which the intervention is rolled out sequentially to participating groups or clusters so that even

the control groups receive the intervention by the end of the study. This could pose validity threats due to varying external conditions over time or contamination from neighboring clusters via information diffusion, and may also raise issues of justice and fairness for the clusters receiving the intervention so much later than their counterparts (Brown and Lilford 2006). While staged roll-out is often considered to be more ethically acceptable than providing no intervention to control groups, there is still the risk that the control communities will feel unfairly disadvantaged. These types of specific issues must be understood within the overall aim of HSR—to inform real-world practice and produce social value. In the interest of good science, RECs must be better equipped to evaluate these options and determine whether HSR studies have adequately considered appropriate comparison groups (Emanuel 2004).

Risk Assessment in HSR

Traditional risk assessment for clinical research studies focuses on physical risks to participants, with some additional attention to psychological and social risks associated with participation. However, the types of risks associated with HSR studies can be quite different from clinical research, often with the largest risks manifesting in social, financial, or communal harms. For example, identifying and quantifying risks in an HSR study on using social media for smoking prevention in a population or the use of financial incentives for promoting institutional newborn deliveries (conditional cash transfer) requires a much more in-depth understanding of the underlying social conditions and system level factors. For instance, a social media campaign against smoking could overtly stigmatize current smokers or the message could get inaccurately modified somewhere in the communication chain, proliferating harmful misinformation. And incentives for women to deliver in a facility could expose participants to a variety of harms in places where home birthing is the norm, not to mention the potential of the cash transfers to distort local economic markets as a more macro threat. While the use of sound and appropriate designs to minimize risk still applies in HSR studies, different approaches might be needed for both assessment and mitigation. In fact, this has been considered an area with serious practical and ethical challenges for HSR in many contexts (Peters et al. 2009).

The issue of risks also relates back to appropriate modes of consent. In typical clinical research, participants are directly informed of the potential risks, and by consenting they express their willingness to accept these risks as part of their participation. As discussed earlier, there are many HSR designs in which individuals may not have this opportunity to directly consent to the exposure to risks associated with the study. Further concerns arise when potential risk levels vary across subsets of the population group, especially when these subgroups may not be represented by the local leadership granting authorization for the research. One could imagine communities in which a practice under investigation might go against the norms of a religious or cultural minority or some study objectives may disproportionately burden the extremely poor. When risks are evaluated at an aggregate level across the population and marginalized groups are not represented in decision making, the potential for undue burden and disregard for these subgroup values have clear ethical implications related to distributive justice and respect for persons.

Although many HSR studies are typically classified as low-risk, a risk–benefit analysis remains important and requires broader interpretation of how harms may result. Some of these present new challenges in defining "minimal risk," since knowledge of negative group characteristics might pose social concerns in how a health system treats members of that group. Moreover, defining who is at risk (see earlier section on research subjects), inclusive of all types of research subjects, varies in HSR and may include several stakeholders involved in a study, such as providers, recipients, beneficiaries, observers, institutions, and tribes. Considerations for risk assessment therefore have to go well beyond a simple focus on individual participant concerns in HSR studies. Additionally, monitoring systems would need to be set up to report adverse consequences resulting from the research so that these harms are appropriately captured during implementation.

Inclusion of Vulnerable Groups in HSR

HSR often involves vulnerable populations, especially in LMIC, where the general population's impoverished condition may already place them at historical disadvantage. This type of vulnerability raises ethics concerns around risks for exploitation, coercion, and abuse. The *Guidelines for Biomedical Research Involving Human Subjects* by the Council for International Organization of Medical Sciences (CIOMS) specifically state: "Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied (Guideline 13)" (Council for International Organizations of Medical Sciences 2002).

However, many HSR studies, especially in LMIC, are in fact conducted with the primary aim of reaching vulnerable groups and providing access to existing or proven interventions for those communities. When such groups are the focus, the assessment of risks associated with these vulnerable populations continues to remain a challenge, since it is also ethically important to try out new ways of delivering and accessing care in the same population to have relevance. Paternalistic protection of vulnerable groups from HSR might delay the opportunity to find solutions to some of the most important health system challenges, especially in the context of LMIC. Identifying when it is acceptable to pilot health systems innovations intended for broad scale-up among particularly vulnerable groups, who may realize the most benefit but conversely may be subject to further harm as systems researchers explore new techniques, is therefore a characteristic challenge in the ethical review process of HSR.

Another issue of increasing concern, especially as the volume of research in LMIC increases, is the role (and protection) of the highly vulnerable (e.g., women or stigmatized groups) among the poor or generally vulnerable groups. These specially disadvantaged groups are often left out of general improvements in health care due to lack of access or lack of power and become further marginalized. For instance, in locales where freedom of movement is restricted for women, their access to basic health services may be limited. Therefore, improvements in the delivery of services at health centers may not translate to benefits for this subgroup. Furthermore, interventions aimed at stimulating demand for services may overlook the social or cultural risks to individuals if they pursue these services. For example, consider a program incentivizing HIV testing and collection of test results. Aside from the potential of social stigma that could result from being seen entering an HIV clinic in some settings, persons could face threats of violence, a particular concern for a program aiming to increase uptake of HIV testing among men who have sex with men (MSM) in places where this group is highly stigmatized. Thus, including these concerns for particular vulnerable subgroups who face acute risks and whose position may not be represented in many models for group authorization is an important consideration that needs special attention when evaluating risks and benefits associated with HSR. It is uncertain how well RECs in general are equipped to address the specific concerns that these highly vulnerable subgroups bring in a study. This is an increasing challenge in addressing the ethical issues of conducting much needed HSR in LMIC and remains largely unexplored.

Defining Benefits, Beneficiaries, and Fair Benefits in HSR

In a recent paper, Liarumbi and colleagues elucidated the current global variability in "defining benefits, beneficiaries, and the scope of obligations for providing benefits" to participants in global health research, particularly in satisfying the requirement of research to provide social value (Lairumbi et al. 2011). The article highlights current debates on whether the individual participants in a study or the communities from which they are drawn should be counted as the beneficiary, with implications for what is due to each during the course of the study (e.g., ancillary care and capacity building) and after the trial concludes (e.g., posttrial access and benefit sharing). The paper and the guidance documents it reviews reflect the current bias of the research ethics literature to consider studies enrolling individuals as the primary participants and beneficiaries. However, as noted earlier, because the goals of HSR are to make improvements at the systems level and units of intervention in HSR are groups, with individuals as indirect beneficiaries, this dialogue about what is due to individuals versus broader communities is ill suited for the HSR context. Only 7 of the 19 guidelines reviewed in Lairumbi and colleagues included the "larger community/host country" as a beneficiary of research, again highlighting how one of the main beneficiaries in HSR may be underrecognized when applying these guidelines for review of HSR studies.

Furthermore, in the reviewed documents, benefits like improvements to the local health system or capacity building, where included, are characterized as "ancillary" benefits, those instrumental to conducting a valid study, or those required for ensuring fair benefits and realization of social value to participating communities (CIOMS 2002; Lairumbi et al. 2011; NBAC 2001). In HSR, these exact benefits are central aim of studies, so this formulation in the guidelines does not easily translate to the HSR context.

Several international and national ethics guidelines support provision of diverse types of benefits during and after studies, yet many of the benefits in HSR may be left out, such as improvements in health care delivery systems, actual provision of treatment, human and material capacity building, and health systems strengthening. It is also important to think of more equitable distribution of existing resources as benefits in HSR; this means that addressing inequities in health provision is another form of benefit often considered in HSR studies, especially those that work on larger communities or countries. As a result, it appears that commonly used international and some national research ethics guidelines might not be addressing the forms and types of benefits in HSR, or the beneficiaries of HSR, and thus their usage by ethics committees poses challenges for review of HSR studies. A more nuanced discussion of what counts as a benefit in HSR and which benefits are due to communities versus their members is needed to guide research designs and REC decisions about the obligations of health systems researchers to participating groups and individuals during and after the trial.

Another key issue for a discussion of benefits is that research subjects in LMIC do not always have access to the same standard of care enjoyed by subjects in wealthier countries. Establishing a standard of care becomes difficult with varying types of health systems that are often the context (and the object) of HSR studies. Hence, notions of "best care available," which have been promulgated in research ethics guidelines, may not be relevant if they are applied to LMIC health systems. Arguably, the very concept of standard of care continues to remain ambiguous, resulting in arguments that are not always clearly distinguished (Hyder and Dawson 2005; London 2000). In a pertinent paper, London argues that this ambiguity results in challenges in assessing the implications of opposing standard of care arguments, in recognizing important differences in their supporting rationales, and "even to locate the crux of the disagreement in some instances" (London 2000). Others have attempted to address the standard-of-care debate from a health systems perspective, arguing that the structure and efficiency of the national health system have been neglected in arguments about the standard of care in research (Hyder and Dawson 2005). For instance, a study protocol may rely on referring patients/participants to their local facility for receipt of appropriate care, but due to health systems inefficiencies, the quality of these facilities or the care available at them may not be equivalent (Hyder and Dawson 2005). This further

complicates the ethical review process for HSR studies because what may seem like equivalent treatment of the study groups on paper may be quite disparate in reality.

DISCUSSION

This article posits the concern that since health systems research especially in low- and middle-income countries is substantively different from other types of research—with its own set of objectives, approaches, methods, and analytic goals—there may be some special or nuanced considerations that should factor into its ethical review. Some of these would be more salient than the usual ethics review of other types of research such as clinical research (Table 1). In other words, an ethics review of HSR that uses exactly the same criteria and ethical analysis as for clinical research may place an overemphasis on features that are not particularly relevant in HSR, and may not adequately capture the unique kinds of benefits and risks present in HSR. Thus, untailored review can result not only in practical inefficiencies, but in unjustified research activities and inadequate protections of participating communities and individuals. Therefore, this article attempts to highlight some of these issues and hopes that this will generate a wider global dialogue on ethics considerations of particular relevance in HSR.

In a recent article by London and colleagues, incentives for health promotion are used as an example of challenges in ethical review of specific types of HSR (London et al. 2012). That case study proposes that HSR using incentives as an intervention intended to produce better health outcomes ought to be subjected to a different ethical review process. The authors assert that "common concerns about using incentives to increase participation in research, such as that attractive incentives will undermine autonomy, are misplaced when incentives are used to overcome economic obstacles or lack of effective motivation, and when recipients are incentivized to engage in health-related behaviors or practices with which they are already familiar and which they regard as beneficial or worthwhile" (London et al. 2012). The case study demonstrates how traditional approaches to thinking about incentives in research as a threat to self-determination may interfere with ethical assessment of conditional cash transfer programs that have the potential to be autonomy enhancing, since they may facilitate or welcome behavior change and overcome motivational behaviors (London et al. 2012). Recognizing that the standard review of using incentives in research is ill-suited for this HSR approach, the authors propose recommendations for how ethical review should be adapted to better evaluate appropriate use of incentives as an intervention, not just an inducement for participation. This is an excellent illustration of how ethical review of HSR does not always fit with the existing review paradigm born from the typical clinical research setting.

Ethics issues that are particularly salient within the context of HSR for the whole health system are best exemplified by a framework for the ethical review of health systems transformations (Daniels 2006). Daniels asserts that efforts to transform health systems constitute "social experiments" on a population; Daniels uses the "benchmarks of fairness" methodology to illustrate which elements he believes ought to be included in an evaluation of these social experiments. The international version of this framework integrates three central goals of fairness: equity, efficiency, and accountability. Five benchmarks address dimensions of equity (intersectoral public health; financial barriers to equitable access; nonfinancial barriers to access; comprehensiveness of benefits; equitable financing), two benchmarks focus on clinical efficiency and administrative efficiency (efficacy, efficiency, and quality improvement; administrative efficiency), and two benchmarks concern aspects of accountability and choice in the system (democratic accountability and empowerment; patient and provider autonomy) (Daniels 2006). This example assesses key ethics concerns for HSR at a very macro level—again highlighting both the particularities from other research and the specificity of concerns. Daniels's framework offers one approach to identifying and understanding ethical issues with particular relevance to larger HSR concerns. However, more exploration is needed to understand the possible breadth of ethics issues that may apply to HSR in various contexts.

HSR studies ought to reflect fair terms of social cooperation between communities and researchers, be relevant to the health needs of the host communities, and have a favorable risk-benefit ratio (Emanuel et al. 2004). Such responsiveness to host communities helps form collaborative partnerships in which all stakeholders (participants, researchers, brokers) are considered moral equals of each other. These concerns are important for HSR, as research resources themselves can have a direct impact on the distribution of opportunities in a community related to jobs, training, placement of facilities, or site selection, with implications for distributive justice and fair equality of opportunity. This discussion can even be extended to include certain public health ethics obligations discussed in the literature, such as social duty, reciprocity, solidarity, stewardship, trust, and accountability (Baum et al. 2007; Swain et al. 2008; Thompson et al. 2006; Upshur 2002).

As highlighted in the earlier discussion of U.S. federal regulations, the current research ethics guidelines, which were developed largely for clinical trial purposes, may turn out to be either insufficient or inappropriate to guide HSR. This might be true for U.S. federal regulations which on the one hand may exempt many types of HSR for review, and on the other hand might impose research ethics criteria that are inappropriate for HSR. This might call for a reevaluation of such guidelines in the future.

Despite the examples given earlier, this article recognizes that there are several limitations to the conceptual exploration presented. First, the definition of HSR varies depending on the type of research, location, or source considered and makes consideration of this field challenging. However, recent work has suggested a unified definition, and global meetings are now focusing on further defining and enhancing the field (Alliance for Health Policy and Systems Research 2012a; 2012b; Global Forum for Health

Research 2004). Second, there are activities that are often in the gray zone between research and nonresearch and that can be considered part of the HSR agenda in LMIC. For example, quality assurance methods are used for performance management and also research, and data may be collected to inform practice only or become part of formal research activities in HSR (Heiby 1993; 1998, Reinke 1995; Zeitz 1993). Similarly, public health surveillance activities are not traditionally considered research but may be part of HSR—for example, where a new disease surveillance system is being pilot tested for the first time (Lee and Thacker 2011; Lee et al. 2012). These types of approaches, when used in HSR, can add further complexity to ethics considerations. As a result, the mutually exclusive categorization of HSR, as either research or nonresearch, by ethics committees and current guidelines is a source of challenge for the field.

Third, a discussion focused on teasing out differences between HSR and other research tends to downplay the many similarities across all types of health research; in many instances the differences are less stark and similarities more common. However, a conceptual exploration has to use some real-world generalizations that can stand merit even though specific exceptions can be defined. Fourth, while this article discusses usual types of HSR, it does not address the conduct of long-term HSR in the same site, such as the use of HSR in demographic surveillance sites across LMIC. Such longitudinal and often long-term HSR (years or decades in the same sites) can lead to different types of ethics issues associated with more dynamic concerns (Hyder et al. 2012b).

HSR is necessary to ensure health systems strengthening, quality of care, and evidence-informed public policy creation. HSR researchers must carefully define their intent and goals and openly clarify the values that may influence the premises and design of their protocols. This article argues for some special consideration of HSR during ethics review and calls for a wider dialogue on this issue. We believe that ethical review of HSR is appropriate, but it must be a more nuanced and informed approach to ethical review that accommodates the specific challenges raised by HSR. Such challenges may be overcome by existing ethics committees by implementing specific strategies, such as outreach to ethics committees in LMICs about co-opting members with expertise in social and cultural context of international studies where HSR is being undertaken, special training on research in lower resource contexts, and utilizing resources available at conferences such PRIM&R (Public Responsibility in Medicine and Research). In order to have appropriate ethical review of HSR, a deeper understanding is needed on how to apply traditional review criteria in ways that are relevant to the features of HSR, and to have further guidance addressing the broader issues arising in the context of systems-level interventions. ■

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