

# Chapter 6: Ethical considerations in health systems research

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## 1. Introduction

This chapter assumes a basic (introductory) familiarity with core terms in both health systems research and bioethics; for the latter these include the core principles of respect for persons (autonomy), beneficence, and justice ([Coughlin 2008](#)). We illustrate some of the issues that these principles are intended to address with two examples:

Example 1: A measles immunisation programme for all children in a low-income country is to be created. The population density and local ecology lend itself to the proliferation of epidemics, and most children have had the infection by age three. It has been noted statistically that immunisations have the greatest impact on high mortality rates if administered by age one. Studies in high-income countries have shown that the immunological response to a measles vaccine is most effective at 15 months of age. Local research is needed to decide the ideal age at which the programme can produce the most impact on measles incidence and mortality.

Example 2: A rapidly industrialising middle-income country has been expanding their transport and communication networks, with a large growth in healthcare facilities. The newly created hospitals and medical centres were potentially capable of providing complete coverage for the entire population. The Ministry of Health is concerned that despite the investment in health facilities and services, they are largely inaccessible to many individuals. A district health officer is appointed to improve the function of the health facilities. She discovers that a serious shortage of drugs and supplies at a medical centre was the result of the hospital siphoning off most of the drugs and supplies. She is to design a study to examine the misallocation of drugs within this system.

As noted in these two slightly modified cases from the World Health Organization (WHO) ([Taylor 1984](#)), it is apparent that research that addresses these problems – or *health systems research* – is different from other types of empirical clinical or public health research, and 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 ([WHO 2009](#)). Health systems research (HSR) is defined by the WHO as “the purposeful generation of knowledge that enables societies to organise themselves to improve health outcomes and health services” ([WHO 2009](#):p7).

HSR is not usually research that focuses on the discovery or development of new interventions to improve health; rather, it is research that usually aims to understand *how* new interventions that are efficacious can be made more widely accessible to potential beneficiaries through policies, organisations and programmes ([Gilson et al. 2011](#)). While some HSR adopts the traditional randomised controlled trial (RCT) model ([JPAL undated](#)), many HSR studies are performed as non-randomised, controlled or non-controlled, prospective or cross-sectional assessments of new or modified health care programmes and strategies ([Alliance for Health Policy and Systems Research 2012a](#)). Given the macro focus of HSR, its participants and beneficiaries are often communities, hospitals, and healthcare institutions, as opposed to individuals. Since HSR has its own definitions, methods, and analytic approaches, there is an

increasing realisation that HSR raises ethical concerns that differ from those in 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 often use the same review criteria and review processes 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. Currently, it is not clear whether institutions are equipped to adequately address and ethically evaluate HSR in their research ethics committees (REC) or institutional review boards (IRB) ([Bachani et al. 2016](#), [Hyder et al. 2015](#), Hyder et al. 2012a). This is especially true for HSR in low- and middle-income countries (LMICs), where this research often plays a critical role in efforts to strengthen health systems and improve healthcare delivery.

Based on the presumption that certain kinds of ethical issues may be particularly relevant to and salient in HSR, this chapter explores several 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 LMICs. This set of issues is used to demonstrate only some of the salient features that might arise during HSR – they are not exhaustive and readers are encouraged to add to the list below.

## 2. Type of research subjects in HSR

The ‘research subjects’ in HSR studies can either be humans or non-humans, each with their own respective ethical challenges.

Example: A team of engineers in collaboration with public health workers is designing a vehicle crash reduction study on a new technology created to improve driver and passenger safety in auto rickshaws.

Non-human ‘subjects’ in HSR may include units of interventions, such as motorcycles equipped with safety features in a vehicle crash reduction study, or units of allocation, such as hospitals or schools involved in a study of cost containment budgetary strategies. When reviewing study protocols with these kinds of non-human subjects, it may be challenging for RECs to assess what role various actors should play in the authorisation and implementation of the study. For instance, when the intervention involves safety features for products, how should RECs weigh the interests of the manufacturers as well as consumers of these products? When schools or hospitals are the unit of allocation, how should the teachers and students in these institutions factor into the ethical analysis? For HSR studies, the level of impact goes far beyond individuals, and even research with non-human ‘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 human subjects, HSR studies 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), 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 be considerate 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 and how they may be differentially distributed across various study populations. 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 may develop a reputation that affects the flow and type of individual patients who visit it. This concept has been described as *group harm* by which 'members suffer it *by virtue* of their identification with or participation in the group' ([Wallwork 2008](#)). This presents complications for RECs in assessing benefits and harms 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.

### 3. Informed consent in HSR

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 authorisation at multiple levels, engaging community or institutional leaders as well as affected individuals.

Example: With the incidence of malaria growing in a city in Burundi, the Ministry of Health approved an intervention designed by researchers in Sweden to alter standard procedures on malaria prevention and control. Seeking informed consent from individuals would be impractical, and so the research ethics committee and the Ministry of Health opted for group consent from each village.

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. Alternatively, individual informed consent in HSR studies that focus on area-wide interventions such as spraying for malaria control or building speed bumps for road safety, may not be possible.

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 (for example avoiding public facilities or seeking private providers). Since in many types of HSR (and this includes cluster-randomised trials of certain group interventions), individual informed consent may not be obtainable, 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](#)). A trade-off may need to occur in decisions regarding the choice between individualised consent and ability to conduct valid HSR studies; indeed, if the societal value of the HSR study is high enough, it may allow concerns of greater benefit 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 LMICs. Questions persist about how groups should be defined and how formal permissions and consent processes are being administered in LMICs. Key to this is addressing the issues of group representation, legitimacy of representatives, authority structures, and coverage of the consent process. For example, concerns have 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 et al. 2005](#), [Emanuel et al. 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.

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 United States (US), informed consent applies to 'research subjects' defined as those actively involved in research ([Protection of Human Subjects Research 2009](#)). However, in 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 and RECs to designate these studies as 'non-human subjects research', which would exempt them from the consent requirements specified in the US regulations.

Furthermore, the US federal regulations also waive consent when studies fulfil 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 could 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. Appropriate ways to handle consent, authorisation, and authentic community engagement for group-level interventions characteristic to HSR remain a challenging area for investigators and ethical review boards.

#### **4. 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.

Example 1: Health systems researchers have designed a study to provide local taxi drivers 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 are being collected on mothers and infants within the intervention community.

Example 2: A hospital has recently decided to introduce quality assessment activities for infection control by teams of health providers. However, the hospital plans on collecting outcome data on hospital-acquired infections among patients admitted to those hospitals.

In the first example, the local taxi drivers were the unit of intervention, while the outcomes data were collected on mothers and infants, which would be the unit of data collection/observation.

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 (sometimes called secondary). In the second example, the teams of health providers are the unit of intervention, and the outcome data are collected from hospital-acquired infections among patients, which is the unit of observation. Furthermore, 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 decide 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? It is clear that having different units of intervention and data collection presents unique challenges for how practical matters of risk benefit analysis and informed consent are carried out for HSR studies.

## 5. Risk assessment in HSR

Risk assessment in HSR is considered an area with serious practical and ethical challenges for HSR in many contexts ([Peters et al. 2009](#)). 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.

Example 1: To reduce the incidence and prevalence of smoking in Mumbai, India, a health systems research group wants to use social media as their intervention for smoking prevention. A member of the research group is concerned that a social media campaign against smoking could overtly stigmatise current smokers or the message could get inaccurately modified somewhere in the communication chain, proliferating harmful misinformation.

Example 2: A team of researchers at a prominent university in Uganda plan on designing a programme to provide conditional cash transfers as incentives to pregnant women to deliver their children in a hospital, arguing that institutional newborn delivery results in better outcomes. A health economist at the university advises that the 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 be a more macro threat by distorting local economic markets.

While the use of sound and appropriate designs to minimise risk still applies in HSR studies, different approaches might be needed for both assessment and mitigation. As noted in the above examples, 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.

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. 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 the local leadership granting authorisation for the research may not represent these subgroups. 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 marginalised 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, 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.

## 6. Defining benefits, beneficiaries, and fair benefits in HSR

Research subjects in LMICs do not always have access to the same standard of care enjoyed by subjects in high-income 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.

Example: A researcher in Bangladesh has designed a study that examines health systems issues within his city. His study protocol calls for 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 standard of care available may not be equivalent. He knows that in his application to the research ethics committee, though this may seem like equivalent treatment of patients using different facilities, variation between those facilities will mean that in reality there may be substantial disparities.

Arguably, the very concept of standard of care continues to remain ambiguous ([Hyder and Dawson 2005](#), [London 2000](#)). This ambiguity results in challenges in assessing the implications of opposing standard of care arguments, in recognising important differences in their supporting rationales, and even in identifying the major source of disagreement ([London 2000](#)). For example, others have attempted to address the standard of care debate from a health systems perspective, arguing that the structure and efficiency of national health systems have been neglected in arguments about the standard of care in research ([Hyder and Dawson 2005](#)).

Addressing the current global variability is a challenge, especially in elucidating benefits, beneficiaries, and the range of responsibilities in offering benefits to participants in global health systems research, particularly in satisfying the requirement of research to provide social value. One ongoing debate is 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 (for example benefits like capacity building) and after the trial concludes (for example post-trial access and benefit sharing) ([Lairumbi et al. 2011](#)). This conversation reflects the current bias in research ethics literature to consider the

individuals enrolled in studies as the primary participants and beneficiaries. However, 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 more important for HSR. Few guidelines discussing beneficiaries of research include the 'larger community/host country', further highlighting how one of the main beneficiaries in HSR may be under-recognised when applying these guidelines for review of HSR studies.

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 healthcare delivery systems, actual provision of treatment, human and material capacity building, and health systems strengthening. It is also important to regard 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.

## 7. Nature of interventions in HSR

Ethical challenges that are intervention-specific in HSR vary from concerns around scientific rationale to distribution of benefits to sustainability issues. For instance, in the case of HSR testing new delivery methods (for example 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 (such as community health workers versus facility-based delivery).

Example: The most common cause of newborn mortality is preterm birth. A local community in a low-income country has been using the 'kangaroo mother care' intervention for preterm infants weighing less than 2kg, which includes skin-to-skin contact, support of the relationship between mother and child, as well as exclusive and frequent breastfeeding. This form of care has been shown to reduce infant mortality in some hospital-based settings in low- and middle-income countries. A community health worker and researcher wishes to use the population-level experience as a proof-of-concept to undergo a large-scale trial of testing this new method of delivering care in Zambia.

Where there is not much 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 as noted in the example above?

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 meagre 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 (for example 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](#)).

Similarly, another ethical concern is the potential for harm with new health delivery methods and associated safety issues. 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 insufficient prior evidence available to inform the ethical review process.

A critical concern with HSR is that it can also blur the distinction between research and non-research processes. For example, 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 generalisable 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 especially 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.

Finally, in LMICs where a lack of access to health interventions exists, ethical concerns around future availability become salient. Will the community involved in the trial continue to have access to beneficial services provided as part of the study? While the issue of post-trial 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 (during a study) 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 study 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 analyse and respond to the results of an HSR study and raise questions about what obligations exist for research institutions and funders conducting such work.

In sum, 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. Therefore, typical interventions in HSR can 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 programme 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.

## 8. 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, such as placebo-controlled studies, where the 'gold standard' involves comparing an 'intervention' group with a 'non-intervention' group. 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). The selection of these comparison locations is also 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; and there is a wide variation of possibilities in what might constitute comparison groups.

Example: A study to evaluate the efficacy of a new health safety curriculum in local medical centres is underway in Dodoma, Tanzania. Participants from the intervention group share their knowledge with members of the control group via social networks and staff transfers. The control group's integrity is effectively compromised and the extent of the 'contamination' is difficult to assess and threatens to undermine the interpretation of the magnitude of the findings.

HSR presents challenges for establishing appropriate comparison groups. As compared to clinical trials, it is more difficult in HSR studies to control for a variety of extraneous variables that could impact results. This is due to the fact that HSR often involves interventions that take place within existing, real-world settings, while clinical trials occur in highly controlled experimental settings. 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 non-parities 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 for the communities participating in the HSR study.

In addition to determining 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 LMICs ([Emanuel et al. 2000](#), [Emanuel and Miller 2001](#), [Freedman 1990](#), [Miller and Brody 2002](#)). If there is little evidence available concerning the effectiveness of current systems of practice, it becomes difficult to choose what to test a new health system approach or combination of approaches against (if anything), whereas 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 against their aim to produce information for evidence-based policy that will ultimately provide the greatest societal benefit.

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. 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. This could pose validity threats due to varying external conditions over time or contamination from neighbouring 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](#)). 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 et al. 2004](#)).

## 9. Inclusion of vulnerable groups in HSR

As the volume of research in LMICs increases, the role (and protection) of the highly vulnerable (for example women or stigmatised groups) in research among the poor or generally vulnerable groups becomes a serious challenge.

Example: A Malawi HIV clinic has created a programme to incentivise HIV testing and collection of test results. Recently, self-identifying gay and lesbian individuals, a highly stigmatised and vulnerable group in Malawi, were seen entering the clinic and were later beaten by an unidentified mob.

These especially disadvantaged groups are often left out of general improvements in healthcare due to lack of access or lack of power, and become further marginalised. 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 centres may not translate to benefits for this subgroup. Furthermore, as seen in the above example, interventions aimed at stimulating demand for services may overlook the social or cultural risks to individuals if they pursue these services. Thus, including these concerns for particular vulnerable subgroups who face acute risks and whose position may not be represented in many models for group authorisation 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 pose in a study. This is an increasing challenge in addressing the ethical issues of conducting much-needed HSR in LMICs and remains largely unexplored.

HSR often involves vulnerable populations, especially in LMICs, where the general population's impoverished condition may already place them at historical disadvantage. This type of vulnerability raises ethical concerns around risks of exploitation, coercion, and abuse. The *International Ethical 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 LMICs, 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 compromise the opportunity to find solutions to some of the most important health system challenges. One characteristic challenge in the ethical review process of HSR is identifying when it is

acceptable to pilot health systems innovations intended for broad scale-up among particularly vulnerable groups, who may realise the most benefit but who may, conversely, be subject to further harm as systems researchers explore new techniques.

Vulnerable populations suffer and face the worst burden of health due to system weaknesses, reinforcing the need to emphasise the larger notion of fairness ([Daniels 2006](#)). Fairness is an important consideration in the ethical review of HSR, especially as it relates to communities and populations that may become vulnerable, not because of inherent weakness, but because of the context in which they are operating ([Bamford 2014](#), [Hurst 2014](#), [Hyder et al. 2014](#)). Thus, on the one hand, HSR responds to such lack of fairness by trying to identify strategies to reduce inequalities; however, at the same time, the conduct of HSR can affect fairness. Therefore, RECs need to evaluate this potential impact for each proposed study.

## 10. Conclusion

There are several limitations to the conceptual exploration above that are worth considering. First, the definition of HSR varies depending on the type of research, location, or source considered and makes consideration of this field challenging. However, a unified definition is necessary, 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 grey zone between research and non-research and that can be considered part of the HSR agenda in LMICs. Two examples include: (1) quality assurance methods, which are used for performance management and research; data may be collected to inform practice only or become part of formal research activities in HSR ([Heiby 1993](#), [1998](#), [Reinke 1995](#), [Zeitz et al. 1993](#)); and (2) public health surveillance activities, which 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 categorisation of HSR as either research or non-research 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 generalisations that can stand merit even though specific exceptions can be defined.

Fourth, the diversity of HSR extends beyond the typical examples that have been provided, and can include the conduct of long-term HSR in the same site, such as the use of HSR in demographic surveillance sites across LMICs. 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](#)). Important conversations and areas for further exploration for HSR ethics include vulnerable populations, big data, ancillary care obligations, distribution of responsibility, and the potential (and possible moral obligation) of health systems research to help reduce health disparities between and within countries ([Bamford 2014](#), [Dereli et al. 2014](#), [Gupta 2014](#), [Hurst 2014](#), [Hyder et al. 2014](#), [Olson 2014](#), [Pratt 2014](#), [Rennie 2014](#)).

Since health systems research, especially in LMICs, is substantively different from other types of research with its own set of objectives, approaches, methods, and analytic goals it warrants special or nuanced considerations in its ethical review. Some of these ethical concerns may be more salient than the usual ethics review of other types of research such as clinical research (Annex Table 1). 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, untailed review can result not only in practical inefficiencies, but also in unjustified research activities and inadequate protection of participating communities and individuals.

Ethical review of HSR does not always fit with the existing review paradigm born from the typical clinical research setting ([Hyder et al. 2014](#), [London et al. 2012](#)). Additionally, more exploration is needed to understand the possible breadth of ethics issues that may apply to HSR in various contexts, and there is much to be learned from overlapping disciplines that have particular relevance to larger HSR concerns, such as health systems transformations ([Daniels 2006](#)). 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 favourable 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](#)).

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. In order to have appropriate ethical review of HSR, there is a need to have a deeper understanding of how to apply traditional ethics review criteria in ways that are relevant to the features of HSR, and further guidance to researchers and reviewers addressing the broader issues arising in the context of systems-level interventions.

## Annex

**Table 1: Ethics considerations of special relevance in HSR in LMICs**

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

### *Some questions to promote thinking about ethics issues*

1. Take one of the eight ethical issues identified above and list three reasons why you: (1) agree that it is different for health systems research; and (2) think it is similar to other types of research.  
Probe: Then list three ways in which you feel this specific ethics issue can be addressed by health systems researchers.
2. You are about to start a health systems research study in a district of Uganda with 30 villages. The study will train community health workers in 15 villages on child health in year 1 and then provide the same training to workers in the other 15 districts in year 2. The study will monitor childhood diseases in all villages for two years. Describe three ethical concerns you might have in this study. Who do you think should give consent for the study in the district?  
Probe: What risks is the population being exposed to and how would you manage them if you were the study director?
3. What other ethical concerns (apart from the eight above) can you think of that may be particular to health systems research that differentiate it from clinical research?  
Probe: And do you know of other ethical frameworks within public health that might address these other ethical concerns?
4. What counts as a benefit in health systems research and which benefits are due to communities versus their members?  
Probe: How can this guide research designs and research ethics committees' decisions about the obligations of health systems researchers to participating groups and individuals during and after a trial?
5. Can you identify actual health systems research studies wherein ethical considerations may have been overlooked by the current review process?

Probe: Do a PubMed search and review some studies.

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