WHO guidance on
the ethics of health research priority setting

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Executive summary

Health research has brought humanity tremendous benefits. But those benefits have not been evenly distributed. Enormous disparities remain built into the global research agenda, with for-profit, non-profit, and government-supported research all still disproportionately focused on conditions that affect populations that are better-off. Meanwhile, the Covid-19 pandemic revealed ongoing challenges with coordinating research, avoiding duplication, and ensuring that the science that is conducted is socially valuable. In the face of these concerns, there is an urgent need for those involved in health research to set priorities for that research in an ethical way.

This guidance responds to continuing calls for greater equity in health research globally. It is widely accepted that decisions about the allocation of health *care* are matters of ethical concern. Consequently, policies and methodologies for health care priority setting are critiqued and revised on the basis of considerations of social justice. Likewise, it is accepted that ethics applies to the *conduct* of health research when it involves human participants or non-human animals. It is time that similar attention is applied to priority setting for health research. Justice in research should begin before the research starts.

Health research priority setting

Health research priority setting is a process through which decisions or recommendations are made about what health research questions or areas should be prioritized. On this broad definition, it not only encompasses activities that organizations currently call "priority setting exercises," but also "strategic planning," "agenda setting," and similar activities.

The ethical obligation to carry out health research priority setting

A key message of this guidance is that, as a matter of justice, there is an ethical obligation to engage in ethically informed priority setting. Decisions about what research to conduct, promote, or support should be made *explicitly, in a systematic way, and guided by ethical principles*.

This ethical obligation to set priorities in this way falls on all those who make decisions about what research is done. These decision-makers include:

- *Funders*, whether they be public or private non-profit or for-profit. Funders have opportunities to set priorities during strategic planning, but also when setting policies on eligibility criteria for funding, in deciding review criteria for grants, and in designing new programs. Different funders have different obligations and face different decision points, but all can and should set research priorities ethically.
- *Policy-makers*, including national bodies, who may publish priority topics for a country or region, and transnational bodies, who may set disease- or topic-specific global priorities.
- *Research institutions*, such as universities, who can set priorities to inform their strategic planning, allocation of internal resources, and so forth.

- *Researchers and research teams*, who can make decisions about their own research priorities, as well as participating in and using the results of larger priority setting exercises.
- *Community organizations, professional associations, and advocacy groups*, who may set priorities for their members or advocate for research conducted by others.

Though all these actors should engage in priority setting it is important to recognize that the resources available to set priorities are themselves limited. The time and resources devoted to priority setting should be *proportionate* to the available research resources and to what is at stake in the priority setting exercise.

The ethics of health research priority setting

Ethical considerations are relevant to setting the goals of priority setting as well as designing and implementing the process. This means that it is not possible to cleanly separate the ethical from the technical aspects of an exercise. Ethical questions can and should be asked during each stage of priority setting:

- *The preparatory stage*, in deciding on governance, methodology, participants, and the criteria used for comparing research options;
- *The implementation stage*, in administering surveys and running the meetings during which the criteria are applied and priorities are set;
- *The follow-up stage*, in reporting results, acting on priorities, and evaluating the priority setting exercise.

There is no single correct approach to health research priority setting. The appropriate process should reflect the nature of the priority setter, their situation, available resources, and other contextual factors. Four key ethical principles should guide the design of any priority setting process:

1. *Optimize social value*. The ultimate aim of health research should be to improve population well-being and equity as much as possible given the limited resources available.
2. *Respect special obligations*. Research priorities should be chosen consistent with the special obligations of those who will support or conduct the research, e.g., to benefit specific populations or patient groups.
3. *Assess and justify harms*. Any potential harms from research to populations who are not also potential beneficiaries should be assessed, minimized and justified. This includes harms to non-human animals, as well as harms to human third parties.
4. *Follow fair procedures*. The priority setting process that instantiates the other three principles should also be transparent, accountable, and inclusive.

How the ethical principles apply in practice varies depending on who is setting priorities and in what context. The guidance describes possible applications through each stage of priority setting (*Chapter 3: Putting the Principles into Practice*) and illustrates the principles through cases (*Chapter 5: Case studies and scenarios*). See *Appendix 5: Tools* for a flowchart and a set of guiding questions that may prove helpful in implementing the guidance.

Ethical principles for health research priority setting

Optimize social value	**Respect special obligations**	**Assess and justify harms**
A project has greater social value insofar as: • It is more likely to succeed • It would provide greater benefits if it succeeds • It would improve equity if it succeeds	Give higher priority to projects that will benefit populations to which the priority setter has special obligations	Exclude projects that would: • Violate human or animal research ethics • Generate harmful information without sufficient social benefits

Follow fair procedures Apply the other ethical principles through a process that is:

- Transparent
- Accountable
- Inclusive

The four ethical principles

Some summary points about the ethical principles and how they apply:

1. Optimize social value

- Every priority setting exercise involves using some criteria to compare research options. The criteria used should aim to capture each component of social value: (1) the likelihood that the research will produce generalizable knowledge that will ultimately benefit human health and well-being, (2) the magnitude of those benefits if they were to result, *and* (3) the extent to which providing those benefits would reduce inequity.
- For almost all research, whether it will lead to any benefits and what those benefits will be is inherently uncertain. Comparisons of social value will generally be imprecise approximations using proxy measures. Nonetheless, a good faith effort to make such comparisons is an essential part of ethical priority setting.
- Where scarce resources are being allocated, such as a pool of funds, the *cost* of alternative research options should also be considered in optimizing the social value of the research portfolio.
- How the social value of research should be conceptualized and estimated depends on the type of research. Basic biomedical science is not less important than clinical or public health research in virtue of being more distant from the ultimate beneficiaries or having greater uncertainty about its eventual application. While the social value of both can be assessed, different kinds of research will generally require different criteria to evaluate them.

2. Respect special obligations

- Priority setters should aim to optimize social value while respecting the special obligations of those involved. These may restrict the scope of the research options considered.

- Special obligations depend on the individual or entity’s role, as well as actions they have taken to incur obligations. For example:
    - *Governments* have obligations to their national populations and the governments of wealthy countries have further obligations to the global population.
    - *Not for profit funders* frequently have special obligations set out in their founding instruments, such as research into a particular disease area. Mission statements often spell out special obligations, but could be revised.
    - *Researchers* and *research units* may have special obligations to the patient populations and communities they work with. They should otherwise aim to conduct the most socially valuable research they can.

3. Assess and justify harms

- Sometimes research poses risks of harm to parties who are not expected to benefit from the knowledge the research generates. These include:
    - *Human research participants*. Research options that cannot be investigated ethically should not be supported. However, it is usually best to assess the ethics of possible research studies with human participants at the protocol development stage, not while setting research priorities.
    - *Non-human animals*. Consideration should be given to the harms that would be inflicted on non-human animals by different research options. These harms should be minimized and justified by the social value of the research. In some cases, programs of research with non-human animals should not be supported because there are comparably valuable alternatives that do not involve animals, or because the research will cause excessive suffering.
    - *Third parties/Bystanders*. Research options should be assessed for whether the results might pose risks to third parties who are not themselves likely to benefit (e.g., dual-use research). Any additional risks of harm should be minimized and justified by the social value of the research. Sometimes, such research should not be pursued because the third party risks are too high.

4. Follow fair procedures

- Health research priority setting should be conducted through a process that is procedurally fair. This requires designing an efficient process consistent with the values of *accountability*, *transparency*, and *inclusivity*.
    - *Accountability*. Lines of accountability depend on the nature of the entity concerned. For example, government bodies should be accountable to their publics. This entails obligations to (1) communicate about priorities and priority setting; (2) give opportunities for feedback; and (3) put mechanisms in place to ensure priority setting is conducted fairly.
    - *Transparency*. Most priority setters have an ethical obligation to be transparent about the process and the results of priority setting. Clear communication of results also increases the likelihood that research priorities are followed.
    - *Inclusivity*. Most priority setting exercises should involve multiple parties. In deciding whom to include, priority setters should consider the following categories of potential participants:

- Research producers (e.g., funders, researchers)
- Research users (e.g., clinicians, policy makers)
- Research beneficiaries (e.g., patients, carers)

In each category, consideration should be given to whether there is sufficient diversity of participants. Meaningful inclusion also requires engaging participants under conditions of *qualitative equality*, so that power disparities are mitigated, and everyone is able to raise their voice and be heard. Special attention should be paid to ensuring the meaningful inclusion of members of disadvantaged and marginalized groups.

ABBREVIATIONS

CAM: Combined Approach Matrix

CHNRI: Child Health and Nutrition Research Initiative

CIOMS: Council for International Organizations of Medical Sciences

COHRED: Council on Health Research for Development

DHT: District Health Team

ENHR: Essential National Health Research

FP: Family Planning

HIC: High-Income Countries

HIV: Human Immunodeficiency Viruses

JLA: James Lind Alliance

LMIC: Low and Middle-income Countries

MANIFEST: Maternal and Neonatal Implementation for Equitable Health Systems project

MAT: Monocyte Activation Test

MORU: Mahidol Oxford Tropical Medicine Research Unit

MRC: Medical Research Council

OECD: Organisation for Economic Co-operation and Development

PCORI: Patient-Centered Outcomes Research Institute

R&D: Research and Development

RFS: Research for Scalable Solutions

PSP: Priority Setting Partnership

RPT: Rabbit Pyrogen Testing

SSC: Science and Strategy Committee

WHO: World Health Organization

WTO: World Trade Organization

GLOSSARY

Accountability: “A relationship between an actor and a forum, in which the actor has an obligation to explain and to justify his or her conduct, the forum can pose questions and pass judgement, and the actor may face consequences.”[1]

Benefit: Improvement along any dimension of well-being.

Distributive justice: Fairness in how resources, opportunities, or other sources of advantage are allocated.

Dual-use research: Research whose results or products might be misused and thereby cause harm.

Epistemic injustice: Wrongs to an individual or group in terms of their treatment as knowers. This can occur when someone is treated as less credible (*testimonial injustice*) or because their experiences are not recognized in the dominant conceptual schemes used by science (*hermeneutical injustice*).

Equity: Absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g., sex, gender, ethnicity, disability, or sexual orientation).

Fair procedure: A process that is justifiable to others, including the potential producers, users, and beneficiaries of health research. This typically requires a process that is *efficient*, *transparent*, *accountable*, and *inclusive*.

Health research: Research aimed at better understanding or improving human health broadly construed. This includes research on the social determinants of health, basic science, clinical research, epidemiology, translational research, public health, and health policy and systems research, among others.

Health research priority setting: The process through which decisions or recommendations are made about what health research should be prioritized.

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[1] Bovens, Mark. “Analysing and Assessing Accountability: A Conceptual Framework.” European Law Journal, Vol. 13, No. 4, July 2007:447-468, at 447. See, also, Mulgan, Richard (2000). “‘Accountability:’ An Ever Expanding Concept?” Public Administration, 78: 555–73.

Interested parties: The parties who have an interest in the results of the research priority setting. These typically fall into three categories: research producers (e.g., scientists), research users (e.g., clinicians), and research beneficiaries (e.g., patients). Also called “stakeholders.”

Proportionality: Balance between the time and resources allocated to a priority setting exercise and the significance of the decisions being made.

Qualitative equality: The elimination of power disparities among participants in an activity or process.

Research: Any systematic investigation that is expected to generate knowledge using recognized scientific methods.

Research ecosystem: The sum of the actors who affect what research is conducted, the decision points at which allocation decisions are made, and the scarce resources that limit what health research can be conducted.

Special obligations: Ethical obligations that depend on one’s role or history.

Social value: The importance of the information generated by health research, e.g., due to the expected benefits to patients from the use of new knowledge about a disease. Social value is a function of (1) the likelihood that the research will produce generalizable knowledge that will ultimately benefit human health and well-being, (2) the magnitude of those benefits if they were to result, *and* (3) the extent to which providing those benefits would reduce inequity.

Wasteful research: Research that has no social value, e.g., because its results are not expected to lead to any benefits.

CHAPTER 1. INTRODUCTION

1. Ethics and Health Research Priority Setting

1.1 Priority setting is unavoidable

The resources available for health research at any given time are scarce. Not every valuable research project can be carried out. Investing resources in one project takes resources away from others. This means that decisions must be made about which among the many possible valuable research projects should be conducted first. *Health research priority setting* is the process through which decisions or recommendations are made about what health research should be prioritized.

There are better and worse ways to set priorities. Priority setting can be conducted on the basis of processes that are fair and efficient, rely on high-quality data, and employ sound ethical reasoning. At the other extreme, it can be done on the basis of personal preferences, financial gain, or political calculations. Either way, decisions are being made about what research will be carried out and so *priority setting is unavoidable*, whether it takes place explicitly or implicitly.

1.2 Ethics is fundamental to priority setting

The benefits that health research can generate are vital to human flourishing. Thanks to medical research, we have vaccines that can protect children from infectious diseases that once killed millions every year. Thanks to public health research, we know how diseases spread and how sanitation can stop them. Health research means we can ameliorate pain, replace organs, treat many cancers, correct vision, and much more. But the benefits of research are not received equally by all. Who is ultimately likely to benefit from future research depends on which populations, conditions, and modalities are prioritized.[2]

Since decisions about what health research is carried out are decisions about how to distribute scarce and very important potential benefits among different populations, such decisions are not merely technical. They cannot be made solely on the basis of data and modeling. These decisions

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[2] Farooq, Faheem, et al. "Comparison of US federal and foundation funding of research for sickle cell disease and cystic fibrosis and factors associated with research productivity." *JAMA network open* 3.3 (2020): e201737-e201737.

also incorporate *value judgments*, such as what counts as a benefit, how benefits ought to be distributed, and which populations should get benefits when not all can. *Ethics* is therefore a fundamental element of research priority setting—to the goals at which it aims, the way it is conducted, and who it involves.

1.3 Who sets priorities?

Almost everyone involved in health research makes decisions that affect what research gets done. Government ministries make far-reaching decisions about national strategies for health, education, and research. International organizations develop research agendas that guide the funding decisions of others. Private companies decide which disease areas to invest in and which drug candidates to take into clinical testing. Funding bodies decide how to design grant schemes and which research programmes to support within the remit of their missions. University officials decide on faculty hires, which research centres to establish, and how to apportion university research funds. Even individual researchers exercise discretion in decisions about what grants to apply for and which projects to propose within the scope of those grants' criteria.

This guidance is designed to support all these actors: governmental decision-makers, international organizations, private companies, funders, universities, researchers, and more. All of them have ethical obligations with respect to the research they decide to conduct or support and should be able to justify their own allocation decisions.[3]

The principles, tools, and case studies described in this document can guide ethical research prioritization. *But the most important message of this guidance is that decisions about what research to conduct, promote, or support should be made explicitly, in a systematic way, and guided by ethical principles*.

2. Aims and Scope

This guidance aims to: (1) Describe the ethical considerations relating to the allocation of scarce resources for health research; (2) Guide key decision-makers in incorporating these ethical considerations into their work. The terms used in this statement of aims should be understood expansively:

- "Resources" includes money, but also time, infrastructure, training, and personnel.

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[3] Pierson, Leah, and Joseph Millum. "Health research priority setting: the duties of individual funders." The American Journal of Bioethics 18.11 (2018): 6-17.

- "Research" refers to any systematic investigation that is expected to generate knowledge using recognized scientific methods. "Health research" includes any research aimed at better understanding or improving human health broadly construed, which could be research on the social determinants of health, as well as basic science, clinical research, epidemiology, translational research, public health, and health policy and systems research.
- "Ethical considerations" encompasses any value judgments relevant to how others are treated and to what benefits they are entitled.

Research priority setting may take place at different levels with implications for the scope of specific decisions or exercises. The scope may be *geographical* (e.g., global, regional, national, sub-national), *topical* (e.g., disease area, scientific discipline), or *role-based* (e.g., for a specific funder). It may be project-level, so that specific research studies are identified, or it may simply recommend broad themes (e.g., antimicrobial resistance, mental health). The priority setting may be *direct* (e.g., a funder deciding the scope of a new grants program) or *indirect* (e.g., an advocacy group drafting a research agenda for others). The ethical principles described in this document apply to all shapes and sizes of priority setting. Any decisions that affect what research gets conducted are open to ethical analysis.

3. How to Use This Guidance

This guidance is intended for use with all sorts of priority setting processes—whether large or small, identifying broad themes or choosing among specific projects. Different parts of the guidance will be more or less relevant depending on your specific situation.

Start with *Chapter 2: The Ethical Principles*. These principles should inform the design of any priority setting process. *Chapter 3: Putting the principles into practice* goes into detail on how the principles apply to activities at each stage of a priority setting exercise. Depending on your resources and needs, some or all of the activities will apply to you. *Appendix 5: Tools* may prove useful throughout. It provides a flowchart and a set of guiding questions to help ensure that your exercise addresses each ethical consideration at each stage. *Chapter 4: Existing methods and guides* relates this guidance document to the most commonly used existing methods for research priority setting. This will be relevant if you are considering using or adapting an existing method. The *case studies and scenarios* in Chapter 5 illustrate how the principles apply to different types of priority setting and different actors—they can be dipped into to understand an ethical principle better or to find a situation similar to your own. For more extensive priority setting exercises that involve many participants, consult *Appendix 2: Best practices for inclusive priority setting*. For concrete recommendations on how to compare the social value of alternative research options, see *Appendix 3: Operationalizing social value*.

CHAPTER 2. FOUR ETHICAL PRINCIPLES

Anyone who allocates resources for health research or makes recommendations for how they should be allocated engages in health research priority setting. All health research priority setting should be done *explicitly, in a systematic way, and guided by ethical principles*.

The Ethical Principles: An Overview

Any process for setting health research priorities should be designed in the light of the following four broad ethical principles. These principles are synthesized from best practices and consensus values described in the literature on health research priority setting, health care priority setting, and research ethics.[4] Of note, they specify both *substantive* and *procedural* elements, since both are essential: ethical health research priority setting is not only a matter of having a fair process, but also reaching just outcomes.

1. **Optimize social value**. There is widespread agreement that health research priority setting should aim at two broad goals: maximizing the benefits of health research to patients and populations, and reducing inequity.[5] These goals are encapsulated by the principle that health research priority setting should optimize the *social value* of research. Aiming to optimize social value aligns health research priority setting with justice, since the greater the social value of research the more its results promote just outcomes.

2. **Respect special obligations**. Some actors allocating scarce resources for health research have *special obligations* based on their roles, relationships, or history. Examples include the ethical obligations that a charity has to its beneficiaries and that clinicians have to their patients. Research priorities should be set consistent with these special obligations.

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[4] Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition*. Geneva (2016); Millum, Joseph. "Ethics and health research priority setting: a narrative review." *Wellcome Open Research* 9: 203 (2024); World Health Organization. *Making fair choices on the path to universal health coverage*. Final report of the WHO Consultative Group on Equity and Universal Health Coverage (2014); World Medical Association. *Declaration of Helsinki* 2024;

[5] Millum 2024; Nuyens, Yvo. "Setting priorities for health research: lessons from low-and middle-income countries." *Bulletin of the World Health Organization* 85 (2007): 319-321.

3. **Assess and justify harms**. Some research projects impose a predictable risk of significant harm to individuals who are not expected to benefit from the research. Such risks should be minimized and have a high burden of justification. This principle applies: first, regarding conduct towards research participants, including non-human animals; second, regarding potential harms from the use of the results of research.

4. **Follow fair procedures**. Any explicit decision about what research to prioritize (i.e., support or conduct) results from a process. The principle of *following fair procedures* entails that the process should be one that is justifiable to others, including the potential producers, users, and beneficiaries of health research. This typically requires a process that is *efficient*, *transparent*, *accountable*, and *inclusive*.

Applying the ethical principles

The ethical principles should be applied to health research priority setting through a process that is *proportionate* and guards against the use of *irrelevant considerations*.

Proportionality

In general, the time and resources allocated to a priority setting exercise should be *proportionate* to the significance of the decisions being made—such as the quantity of research resources being allocated and the amount of data and input from others needed to make good allocation decisions. For example, substantially more resources, data, and input would be expected for a national funding body's priority setting exercise than that of an individual researcher, even though both make decisions about research projects that can be informed by ethical analysis.

Proportionality also applies to the frequency with which priorities should be revisited. Periodic priority setting is important—so that adjustments can be made in response to research advances, epidemiological changes, new funding opportunities, and the like. But, generally, priorities should not be revised too often. That can undermine efforts to follow the priorities that have been set and risks wasting previous research investments.

Irrelevant considerations

People have multiple and sometimes conflicting motivations for supporting and conducting research—from improving human health to making money. In the process of priority setting, it can be valuable to articulate the likely motivations of individuals and organizations so that they can be critically examined for their influence on what priorities are chosen. This makes it possible to guard against the influence of *irrelevant considerations*.[6] Irrelevant considerations may include but are not limited to:

- Status within a scientific field
- The prospect of publication in a high-impact journal
- What a CEO, dean, thought-leader, or other powerful individual currently cares about
- Career progression
- Good publicity
- Making money

Any of these considerations could be *a means* to generating social value—for example, high-impact journal publications might lead to greater uptake of research results, career progression might lead to more opportunities to pursue socially valuable research in the future, and so on. Some of them might also put constraints on what research an individual or organization can pursue. For example, they may need to make money in order to continue carrying out research. But these are not goals that *matter in themselves in the context of ethical priority setting*. For that reason, unlike the principles above, they should not guide priority-setting.

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[6] Macleod, Malcolm R., et al. "Biomedical research: increasing value, reducing waste." *The Lancet* 383.9912 (2014): 101-104, at 102.

THE ETHICAL PRINCIPLES: IN DEPTH

Principle 1. Optimize social value

1.1 Defining social value

According to the Council for International Organizations of Medical Sciences (CIOMS): "Social value refers to the importance of the information that a study is likely to produce."[7] More precisely, the amount of social value is a function of: (1) the likelihood that the research will produce generalizable knowledge that will ultimately benefit human health and well-being, (2) the magnitude of those benefits if they were to result, *and* (3) the extent to which providing those benefits would reduce inequity.[8] Research on a disease that greatly reduces patients' quality of life or cuts their lives very short is consequently more valuable; so is research on conditions that predominantly affect people who are poor, or badly off in some other way. Social value thereby captures both the moral importance of how much benefit research is expected to generate *and* how far it will alleviate inequity in outcomes. Limited resources should be distributed among research projects in the way that will generate the greatest overall social value. This means that by aiming to *optimize social value*, research priority setting promotes distributive justice.[9]

This definition of social value should be specified further by those engaged in priority setting depending on their context. That entails specifying:

- *What counts as a benefit*. Consistent with the WHO's expansive definition of health as "a state of complete physical, mental and social well-being",[10] there are dimensions of well-being that are not always thought of as components of health but may be impacted by health research. Examples might include freedom from stigma, improved autonomy, or personal security. All dimensions of well-being are potentially relevant to social value, depending on the research options being compared.

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[7] International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016, p.1.

[8] Barsdorf, Nicola, and Joseph Millum. "The social value of health research and the worst off." *Bioethics* 31.2 (2017): 105-115.

[9] Cookson, Richard, et al. "Distributional cost-effectiveness analysis comes of age." *Value in Health* 24.1 (2021): 118-120.

[10] Constitution of the World Health Organization (1948). https://www.who.int/about/accountability/governance/constitution

- *Who is a potential beneficiary*. Clinical and public health interventions can have effects beyond their direct recipients, such as through herd immunity, by relieving caregiver burdens, or via their impact on the environment. Where there are predictable and substantial third-party effects from successful research projects, they should be included in estimates of social value.
- *What equity means*. According to WHO, “Equity is the absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g., sex, gender, ethnicity, disability, or sexual orientation).”[11] This encompasses not only differences in health status among groups, but also differences in other factors relevant to well-being. How equity is best specified will depend on the scope—geographical, topical, etc.—of the priority setting exercise.

1.2 Estimating social value

Comparing the social value of different research options is an inherently uncertain enterprise. The results of research cannot be known ahead of time, nor the use to which those results will be put. Nevertheless, in order to set priorities, alternative research options need to be compared. Priority setting exercises typically use several criteria to score or rank research options to make these comparisons. These criteria should be selected with the aim that applying them will generate the greatest overall social value (consistent with following the other ethical principles). Insofar as the context allows, each component of social value—likelihood of success, magnitude of benefit, and impact on equity—should map onto one or more criteria (Figure 1).

The context and the type of research being prioritized will affect what criteria are appropriate. Roughly speaking, health research can be divided into three broad categories: basic biomedical research, clinical research, and public health research. Basic biomedical research projects often focus on understanding mechanisms, may be exploratory in nature, and may not have a specific disease target. Their translational value might also not be apparent, and even if so, it will be tenuous when the projects are conceptualised. Nevertheless, basic biomedical research is vitally important for medical breakthroughs.[12] Criteria used for evaluating the likelihood of success of basic biomedical research will typically focus on factors that improve the probability that the research leads to generalizable knowledge (e.g., experimentalist skills, statistical soundness of study designs, recruitment plans, institutional support, and so on) and factors that improve the probability of uptake (e.g., external validity, plans for publication and dissemination, coordination with other research groups, and so on), rather than the probability of defined benefits to population health and

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[11] World Health Organization. *Health Equity*. 2024. Available at: https://www.who.int/health-topics/health-equity.
[12] Ronai, Isobel, and Paul E. Griffiths. "The case for basic biological research." *Trends in Molecular Medicine* 25.2 (2019): 65-69

well-being. Likewise, where the use case for the results is not known, the magnitude of expected benefits might be evaluated with criteria that assess whether a topic is neglected, whether the results are potentially transformative, or the significance of knowledge gained for other scientific questions.

The translational value of clinical and public health research is generally more direct and more apparent. Research projects may be directed at specific patient populations and the potential interventions may be well-characterized. For example, for a particular intervention being investigated, it might be possible to get numerical estimates of how many additional lives could be saved, if the intervention proved to have a particular level of effectiveness. As such, priority setting in these categories can be more driven by quantitative estimates of the potential benefits of the research.

Note that estimates of social value should consider both possible benefits and possible losses or *harms* from research. Where the potential benefits and harms are to the *same* population, they should both be considered as components of social value. However, predictable harms to populations who are *not* potential beneficiaries of the research, including harms to non-human animals, fall under *Principle 3: Assess and justify harms*.

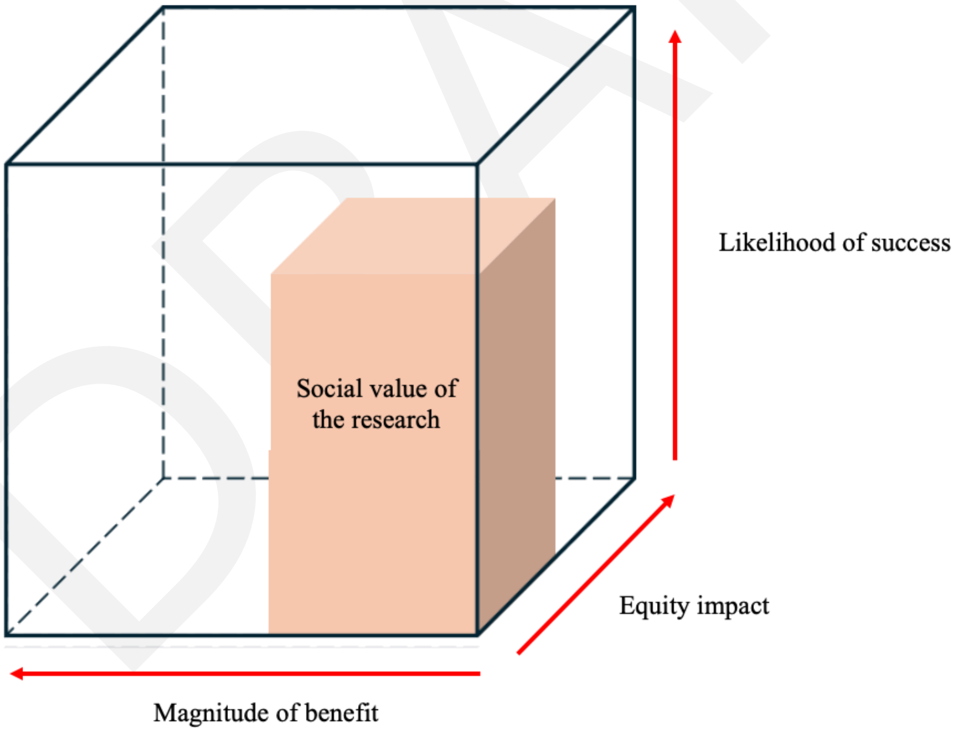

Figure 1. Estimating social value

1.3 Efficient allocation

When allocating scarce resources for research, what matters is not only the social value of each research project under consideration but also the amount of the scarce resource each would need. Two cheaper research projects might have more total social value than one more expensive project, even though the more expensive project is ranked higher than each. The scarce resources available should be allocated among possible research projects in the way that is estimated will generate the greatest overall social value. For priority setting exercises that aim only to identify broad priority themes, this point may not apply. But for any exercise that aims to recommend which specific projects should be carried out, efficiency should be explicitly taken into account.

In addition to thinking about how to efficiently allocate their own resources, decision-makers should think about what others are doing or planning.[13] At a minimum, this will involve carrying out systematic reviews and—where relevant—checking clinical trials databases or other sources of up-to-date evidence. For some priority setters, such as funders and governments, it may require active coordination. Coordination among the actors involved in health research globally is necessary to avoid waste and duplication, and to ensure a fair global distribution of research resources.[14]

1.4 Further guidance

Detailed recommendations for how to operationalize social value judgments, including several examples, can be found in Appendix 3. In addition, the case studies and scenarios in Chapter 5 illustrate how the principle of optimizing social value can be applied by different actors in various priority setting situations. Appendix 4 lists some resources and examples of good practice for coordinating research efforts to ensure efficiency.

Principle 2. Respect special obligations

Special obligations are ethical duties that one party owes to another in virtue of their role, relationship, or history, e.g., physicians and nurses' special obligations to their patients,[15] or

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[13] Antonio ES, Alobo M, Norton A, et al. Lessons learnt from developing and applying research priorities during the COVID-19 pandemic: reflections from the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). BMJ Glob Health 2024;**9**:e015278

[14] Chalmers, Iain, et al. "How to increase value and reduce waste when research priorities are set." *The Lancet* 383.9912 (2014): 156-165.

[15] Doernberg, Samuel, and Robert Truog. "Spheres of morality: The ethical codes of the medical profession." *The American Journal of Bioethics* 23.12 (2023): 8-22.

polluters' special obligations to those they harmed.[16] In contrast, *general obligations* apply to everyone. Everyone involved in health research has a general obligation to support socially valuable research. Many also have special obligations which will shape how they fulfil this general obligation.

Some special obligations are non-negotiable and will rule out particular research options from the outset. For example, a government agency might be legally mandated to support only a specific type of research (see, e.g., Chapter 5, Case 2, which discusses the US Patient-Centered Outcomes Research Institute). Other special obligations just mean that greater weight should be put on some research projects versus others. For example, a research group that is working within a particular community has ethical obligations to carry out research that is responsive to the health needs of that community.[17] That does not rule out also considering whether the research results are likely to benefit patient populations outside the community too.

Examples of actors whose priority setting might be affected by special obligations include: government bodies, non-profit funders, for-profit companies, and individual researchers (Table 1).

- **Government bodies**. Government bodies, such as national funding agencies and ministries of health, are usually accountable to other parts of the government. In addition, individual government bodies share the obligations of the government as a whole.

  Governments have obligations to treat their citizens and residents justly. Within a country, this entails supporting socially valuable research to improve population well-being and equity.

  Governments also have some obligations beyond their borders. These international obligations are greater for more wealthy and powerful countries. Supporting socially valuable research can be an important part of fulfilling these international obligations (as well as being in a country's long-term self-interest[18]). There are multiple justifications for thinking that governmental obligations extend beyond their borders.[19] These include: (1) *Beneficence*. Obligations of beneficence to help those in desperate need apply regardless of national boundaries.[20] (2) *Distributive justice*. No one chooses their country of birth. Just like with other unchosen characteristics—like race, gender, and sexuality—it is *unfair* if someone is worse off than another simply because of where they are born.[21] (3)

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[16] Tan, Kok-Chor. "Climate reparations: Why the polluter pays principle is neither unfair nor unreasonable." *Wiley Interdisciplinary Reviews: Climate Change* 14.4 (2023): e827.

[17] *International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition*. Geneva. Council for International Organizations of Medical Sciences (CIOMS) (2016): Guideline 2.

[18] Fauci, Anthony S., and Francis S. Collins. "NIH research: Think globally." *Science* 348.6231 (2015): 159-159.

[19] Millum, Joseph. "Global bioethics and political theory." *Global Justice and Bioethics* (2012): 17-42.

[20] Singer, Peter. Famine, Affluence, and Morality. *Philosophy & Public Affairs*, Vol. 1, No. 3 (Spring, 1972), 229-243.

[21] DeGrazia, David, and Joseph Millum. *A Theory of Bioethics*. Cambridge University Press (2021): 150-152.

Reparative justice. The inequalities in wealth among countries are no accident. They partly result from a long history of colonialism, exploitation, and violence. The current global economic system was shaped by the wealthy and the powerful to benefit themselves.[22]

- **Non-profit funders**. Many non-profits have mission statements or similar statements of the goals and values of the organization. These statements set out the organization's remit and can be a source of special obligations.[23] For example, if a non-profit has developed relationships with a patient community that supports its mission, it has obligations to them. Likewise, if it raises funds on the basis of its mission it is implicitly promising to spend the money in a particular way. These special obligations may narrow the scope of the research that the non-profit supports. For example, it is reasonable for an HIV/AIDS charity to support only health research relevant to people with or at risk for HIV/AIDS. It should then aim to optimize the social value of that research.

  For many non-profits, mission statements are not fixed. Those with the power to do so should consider whether to change a mission statement in order to allow the organization to support more socially valuable research (e.g., by expanding its remit from national to global, or to increase flexibility in the types of heath research supported).

- **For-profit companies**. For-profit entities exist and are able to pursue their commercial interests only in virtue of an economic system that is set up and enforced by governments. States subsidize research and development directly and indirectly through tax breaks, by adjudicating whether new technologies can be legally marketed, by enacting the laws that allow the creation of intellectual property, and by purchasing health care that is developed through health research. These governments have obligations of justice. For-profit actors therefore also have ethical obligations to society not to undermine governments carrying out their obligations.[24] At a minimum, this means that companies should pursue profit only insofar as it is consistent with carrying out socially valuable research. Business practices that make the research sector as a whole less effective at creating health technologies that improve health cannot be justified.

- **Researchers**. Many researchers are unconstrained by special obligations concerning which research projects they pursue. Those researchers should aim to optimize the social value of their research. For some, however, there may also be special obligations. For example,

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[22] Pogge, Thomas. *World Poverty and Human Rights: Cosmopolitan Responsibilities and Reforms, 2nd ed.* (Cambridge: Polity Press 2008).

[23] Pierson and Millum 2018.

[24] Pierson and Millum 2018.

researchers who are already committed to working with specific populations or communities should give some priority to research that is relevant to those groups.

Table 1. Key actors and their ethical obligations

Entity	Obligations
Government	• Support socially valuable research relevant to citizens and residents • Support international research with *global* social value (if a wealthier country)
Non-profit	• Prioritize socially valuable research consistent with mission • Consider whether mission can be changed to better align with optimizing social value
For-profit	• Pursue profit only when consistent with socially valuable research • Refrain from practices that make the overall research ecosystem less effective
Researcher	• If committed to working with specific populations or communities, give higher priority to their needs • Otherwise, optimize social value of research

Principle 3. Assess and justify harms

The conduct of research and the application of its results can cause harms as well as provide benefits. Where there is some risk of harm to the *same* population that the research aims to benefit, both expected harms and expected benefits should be included in estimates of social value. Sometimes, however, the individuals who might be harmed are not those who might be benefited by the research. Putting one individual at risk of harm in order to benefit someone else has a higher threshold of ethical justification. Such harms should be minimized and justified.

In the context of health research priority setting, this principle applies in two types of case: first, regarding the treatment of research participants, including non-human animals (*research ethics*); second, regarding potential harms from the use of the results of research (*harms from research results*). Note that the prospects of estimating harms may vary depending on the type of priority setting exercise. In thematic exercises that prioritize broad research areas, estimating harms may be more difficult or speculative than in exercises that compare specific research projects. For the former, this principle might not be applicable or concerns raised about potential harms should be addressed later when designing more specific research projects.

3.1 Research ethics

3.1.1. Research with human participants

The conditions under which health research can be unethical because it violates ethical prohibitions on the treatment of human research participants have been extensively analyzed elsewhere.[25] Among others, these include obligations to ensure that the risk-benefit ratio for participants is acceptable, to select participants fairly, and to obtain the informed consent of competent prospective participants (Appendix 4). These principles of research ethics are taken as given by this guidance and so not repeated here. During priority setting, if it is clear that a research project could not be carried out without the unethical treatment of human participants, then it can be eliminated from consideration. However, it is rare that enough information is available to make such judgments during priority setting. Such ethics review should normally be left to research ethics committees, as part of the standard path to having individual research studies approved.

3.1.2. Research with non-human animals

The use of sentient non-human animals in health research merits special mention. While the scientific merits of non-human animal models are debated,[26] and alternatives to their use are gaining steam,[27] many millions of animals are still used in medical research every year.[28] The vast majority of experiments using non-human animals are carried out for the benefit of humans, involve killing the subjects after the experiments, and impose suffering or discomfort.

There is much more disagreement over the ethics of research using non-human animals than about the ethics of research with human participants. Nonetheless, there is widespread agreement that the welfare of sentient non-human animals matters morally *to some extent*.[29] This is relevant when setting research priorities, since there are frequently choices to be made about research programs that would be very different in terms of their use of animal subjects. Whole lines of research may involve or not involve animals, may use very different numbers and species, and may entail

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[25] CIOMS (Council for International Organizations of Medical Sciences). *International Ethical Guidelines for Health-Related Research Involving Humans* (2016).

[26] See, e.g., Pound, Pandora, and Michael B. Bracken. "Is animal research sufficiently evidence based to be a cornerstone of biomedical research?." *Bmj* 348 (2014).

[27] See, e.g., Leist, Marcel, et al. "Consensus report on the future of animal-free systemic toxicity testing." *Altex* 31 (2014): 341-356.

[28] Taylor, Katy, and Laura Rego Alvarez. "An estimate of the number of animals used for scientific purposes worldwide in 2015." *Alternatives to Laboratory Animals* 47.5-6 (2019): 196-213.

[29] Beauchamp, Tom L., and David DeGrazia. *Principles of animal research ethics*. Oxford University Press, 2019.

enormous or minimal suffering. For example, one proposed research program might aim to develop a rodent model of a disease, while another works with human cells *in vitro* on the same disease. This means that questions about the justifiability of harms to non-human animals cannot all be postponed until the point when individual studies are reviewed.

When choosing among research projects involving non-human animals, at a minimum, priority setters should: (1) Choose projects so as to minimize harms to animals given the scientific aims of the research; and (2) Choose only research projects where the harms to animals are likely to be justified by the social value of the knowledge gained through the research. Depending on one's views on the ethics of animal use, more demanding criteria might also be justified.[30]

3.2 Harms from research results

The *results* of research can also lead to harms. For example, reports of a study looking at the genetic correlates of mental health conditions in an indigenous population might pose some potential risks to that population (e.g., if reporting were to reinforce prejudices in the wider population).[31] It might also present a prospect of benefit (e.g., if the research guided the development of treatments). When the risks and expected benefits are to the *same* population they can be aggregated as part of a social value calculation. However, sometimes the results of research pose a risk of harm to one population while the expected beneficiaries are predominantly from another population. Suppose that the genetic research just described was conducted because this relatively isolated population allowed a specific scientific question about gene-environment interactions to be answered—one whose benefits, if any, would likely be received by different, less marginalized patient groups. Then the risk to the indigenous population would not be balanced by benefits to them from the knowledge gained. Such research would be very hard to justify.

Other examples of research that poses risks of harm to non-beneficiaries in this way may include research that will predictably lead to serious environmental harms and "dual-use research." Dual-use research is research whose results or products might be misused and thereby cause harm.[32] For example, scientists might experimentally manipulate a pathogen to see what would make it more transmissible. This might help learn about how to combat the pathogen but also opens up the possibility of accidental or malign release of a more dangerous infectious disease.[33] Potential

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[30] DeGrazia, David, and Tom L. Beauchamp. "Beyond the 3 Rs to a more comprehensive framework of principles for animal research ethics." *ILAR journal* 60.3 (2019): 308-317

[31] Millum, J., Campbell, M., Luna, F., Malekzadeh, A., & Karim, Q. A. (2019). Ethical challenges in global health-related stigma research. *BMC medicine*, *17*, 1-9.

[32] National Institutes of Health. Office of Science Policy 2023. *Biosafety and Biosecurity Policy*. https://osp.od.nih.gov/policies/biosafety-and-biosecurity-policy/.

[33] World Health Organization 2020. *What is dual-use research of concern?* https://www.who.int/news-room/questions-and-answers/item/what-is-dual-use-research-of-concern.

environmental harms and harms from dual-use research should be assessed during priority setting. Where research poses a plausible risk of serious harm to those who are unlikely to be beneficiaries, there is an additional burden of justification.

Principle 4. Follow fair procedures

Who makes decisions about research and *how* they make them is critical to the legitimacy of allocation decisions and to the likelihood that the resulting research will actually benefit those in greatest need. The principle of *following fair procedures* entails that the decision-making process that implements the previous three ethical principles should be one that is justifiable to others, especially those who are affected by the conduct or results of the research. This entails that the processes by which priority setting decisions are made should be consistent with the values of *accountability* and *transparency*. It also frequently requires the *inclusion* of other parties in decision-making.

4.1 Accountability

Accountability involves "a relationship between an actor and a forum, in which the actor has an obligation to explain and to justify his or her conduct, the forum can pose questions and pass judgement, and the actor may face consequences."[34] So, for example, a minister may be accountable to parliament, and individual parliamentarians may be accountable to the public.

In the context of priority setting, accountability has three main elements: (1) communication; (2) opportunities for feedback; and (3) the enforcement of procedural fairness. To whom a priority setter should be accountable varies. For example, government bodies should typically be accountable to their publics when setting research priorities. They should communicate to the public how they have set research priorities, on what basis, and who participated. Members of the public should have the opportunity to weigh in on those priorities and how they were set, not just when included as participants in a priority setting exercise but before and after the exercise. There should be some mechanism through which procedural fairness is enforced (such as an opportunity to appeal or a complaints procedure).[35] Other priority setters should consider to whom they might

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[34] Bovens, Mark. "Analysing and Assessing Accountability: A Conceptual Framework." *European Law Journal*, Vol. 13, No. 4, July 2007:447-468, at 447. See, also, Mulgan, Richard (2000). "'Accountability:' An Ever Expanding Concept?" *Public Administration*, 78: 555–73.

[35] Cf. Daniels, Norman, and James E. Sabin. "Accountability for reasonableness: an update." *Bmj* 337 (2008): a1850.

have an obligation to be accountable and what that looks like.[36] A good starting point is to look at the special obligations identified under Principle 2.

4.2 Transparency

Transparency is important for thorough accountability, to counter corruption, and to build trust.[37] All priority setting exercises should be transparent with participants regarding their scope and methods. Participants, in turn, should be transparent regarding potential conflicts of interests. In addition, information on both the process and the results of priority setting should normally be made available to those who are directly affected by it. Priority setters should pay particular attention to ensuring access for individuals or groups to whom they are accountable. Participants likewise have

For the larger priority setting exercises carried out by funders and national or international bodies, at a minimum, reports of the process and its outcomes should be made available on a publicly accessible website. As described in Chapter 3, there is also normally an ethical obligation to disseminate the products of priority setting to participants in the priority setting exercise, potential users of the results, and other interested parties. This may then require more active communication strategies—through journal articles, social media, mailing lists, or other more targeted means. Care should be taken to match both the method and content of communications to the intended audiences. For example, if priorities are being set for research with a specific patient population, the process and outcomes should be communicated in a way that is understandable and accessible to members of that population.

4.3 Inclusion

The question of *who* should be included and *how* should be asked for each stage of priority-setting—preparatory, implementation, and follow-up. It is especially critical to do so for the preparatory stage because it determines who leads the priority-sitting process.

Though levels of inclusion lie on a spectrum, more is not always better. Decisions about how many participants will be involved and how extensively should be sensitive to the need for *proportionality* in priority setting. They should reflect:

- What is at stake (e.g., the quantity of resources being allocated)

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[36] Pratt, Bridget. "Towards inclusive priority-setting for global health research projects: recommendations for sharing power with communities." *Health Policy and Planning* 34.5 (2019): 346-357.
[37] Ball, Carolyn. "What is transparency?" *Public Integrity* 11.4 (2009): 293-308.

- The time and resources available for priority setting
- The special obligations of the priority setter
- How much input is needed from others in order to make justifiable decisions

For example, a doctoral student deciding on their project is allocating few resources and likely does not have a budget for priority setting. It would be excessive to expect them to engage in an intensive and inclusive priority setting process. At the other extreme, a government ministry setting national research priorities is allocating much more, has more time and resources, and has special obligations requiring accountability to its population. It should aim for a deeply inclusive process.

4.3.1. Whom to include

Reasons for inclusion

Given the wide variety of actors who allocate resources for research and the contexts in which they act, it is essential to critically reflect on the reasons for inclusion. Asking *why* other parties should be included will guide principled decisions about *who* should be included and *how*. Tokenism should always be avoided. The reasons why it may be valuable to include individuals or representatives of a group fall into three categories:

a. **Epistemic:** Including members of a group may increase the *accuracy* of priority setting. For example, patient perspectives may be essential to find out which aspects of a disease most affect quality of life, scientific experts may be best placed to judge the solvability of specific problems given the state of scientific knowledge, and so forth.

b. **Pragmatic:** Including members of a group may increase the *impact* of priority setting. For example, involving community members in priority setting may increase trust in subsequent research, including policy-makers may make it more likely that a set of priorities gets uptake, and building capacity within an organization may lead to priority setting being sustained over time.[38]

c. **Intrinsic:** Members of a group sometimes have the right to be included in decisions that affect them. For example, this may apply to when a priority setter is accountable to a particular group (e.g., national priority setting exercises should involve public

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[38] Goold, Susan Dorr, et al. "Evaluating community deliberations about health research priorities." *Health Expectations* 22.4 (2019): 772-784; Kapiriri L., Arnold E., Campbell S., Kapata- Chanda P., Ngosa W. and Humainza B. Approaches to Health Research Priority Setting: A Reference Manual Synthesizing the Literature and Demonstrating the Potential Use of the Manual. McMaster University, 2017; Tomlinson, Mark, et al. "A review of selected research priority setting processes at national level in low and middle income countries: towards fair and legitimate priority setting." *Health Research Policy and Systems* 9 (2011): 1-7, at 5.

participation) or is working within a specific community (e.g., research groups in defined communities should involve community members in priority setting). It also applies to research collaborations, where each of the research groups or institutions involved should be represented in decision-making.

Ensuring diversity of participants

As well as identifying the individuals and groups to be included it is important to pay attention to the *breadth of participants*. Ensuring sufficient breadth entails:[39]

- Sufficient *range* of participants from each category (e.g., research producer, research user, research beneficiary), so participants span the spectrum of actors in each category and a wide spectrum of demographics. Participants can then collectively represent the diversity of interested parties.
- Sufficient *mass* of participants from each category and across demographics, so that there are enough individuals representing each group for their voices to be effective.

4.3.2. How to include

Inclusion is not as simple as just asking people what they think. Meaningful inclusion occurs when participants are able to raise their voice *and* be heard.[40] The amount of say participants have depends on *when* they enter the priority-setting process and their *level* of participation. They have greater say when included earlier and at a higher level.[41] Participants should be included under conditions of *qualitative equality*, which requires mitigating power disparities, structuring the process to empower everyone to be involved, and ensuring that differences in social status do not lead to the contributions of some participants being valued over those of others.[42] Particular care should be taken with respect to the inclusion of more disadvantaged and marginalized groups. If their valuable perspectives are to have an effect on what priorities are set, they must be included

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[39] Pratt, Bridget, Maria Merritt, and Adnan A. Hyder. "Towards deep inclusion for equity-oriented health research priority-setting: a working model." *Social Science & Medicine* 151 (2016): 215-224.

[40] Cornwall A. (2011). 'Whose Voices? Whose Choices? Reflections on Gender and Participatory Development'. In: Cornwall A, editor. *The Participation Reader*. New York, NY: Zed Books, pp. 203-223.

[41] Crocker, David A. *Ethics of global development: Agency, capability, and deliberative democracy*. Cambridge University Press (2008); Goulet D. (1995). *Development Ethics: A Guide to Theory and Practice.* New York, NY: Apex Press.

[42] Pratt et al. 2016.

in ways that give them genuine representation and give their representatives genuine voice (see Appendix 2).

Qualitative equality among researchers

Collaborative partnerships among researchers and research groups frequently generate concerns about power disparities and power sharing. Such concerns have been raised, in particular, in the context of collaborations between HIC and LMIC research groups. HIC researchers may have greater access to funds, institutional support, or other resources. In some cases, LMIC researchers find themselves excluded from decision-making, or treated more as data collectors or field workers, rather than partners.[43] As with other interested parties, it is important that LMIC partners take part in decisions under conditions of qualitative equality. In addition to this guidance, more specific assistance with fair research partnerships can be found through the Research Fairness Initiative,[44] as well as the relevant academic literature.[45]

4.4 Further guidance

Chapter 3 provides detailed recommendations on applying the principle of following fair procedures at each stage of priority setting. Appendix 2 outlines some best practices for the meaningful inclusion of members of more disadvantaged and marginalized groups in health research priority setting.

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[43] Ward, Claire Leonie, et al. “Defining Health Research for Development: The perspective of stakeholders from an international health research partnership in Ghana and Tanzania.” Developing world bioethics 18.4 (2018): 331-340; Parker, Michael, and Patricia Kingori. “Good and bad research collaborations: researchers’ views on science and ethics in global health research.” *PloS one* 11.10 (2016): e0163579.

[44] Research Fairness Initiative. https://rfi.cohred.org

[45] Faure, Marlyn C., et al. "Mapping experiences and perspectives of equity in international health collaborations: a scoping review." *International journal for equity in health* 20 (2021): 1-13; Horn, Lyn, et al. “The Cape Town Statement on fairness, equity and diversity in research.” *Nature* 615.7954 (2023): 790-793; Pratt, Bridget. "A multidimensional account of social justice for global health research." *Bioethics* 37.7 (2023): 624-636; Voller, Shirine, et al. "What makes working together work? A scoping review of the guidance on North–South research partnerships." *Health policy and planning* 37.4 (2022): 523-534.

CHAPTER 3. PUTTING THE PRINCIPLES INTO PRACTICE

Part 1: Three Stages of Priority Setting

Most priority setting exercises can be divided into three stages: the preparatory stage, the implementation stage, and the follow-up stage.[46] The specific activities for each stage will vary depending on your particular situation, needs, and resources (Table 2). The time and resources invested into priority setting should always be *proportionate* to what is at stake (as discussed in Chapter 2). In all cases, the ethical principles apply and should guide decision making about how to design, carry out, and follow up on your priority setting exercise. This chapter describes typical activities for each stage, synthesized from the various methods that have been used in priority setting exercises. It illustrates how the ethical principles should be considered for each.

Appendix 5 includes a flowchart summarizing these activities and the key ethical considerations that relate to each. In addition, it includes a tool with guiding questions to help priority setters incorporate the ethical principles into the design of their priority setting exercise. These guiding questions can be answered during the preparatory stage activities and then consulted throughout.

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[46] Nasser et al. Prioritization of Research. In: *WHO guidance on research methods for health emergency and disaster risk management*. Geneva: World Health Organization; 2021; Viergever, Roderik F., et al. "A checklist for health research priority setting: nine common themes of good practice." *Health research policy and systems* 8.1 (2010): 1-9.

Table 2. Typical research priority setting activities by stage

Preparatory stage	Implementation stage	Follow-up stage
a. Define the context and scope b. Decide on governance c. Choose or design a method d. Identify interested parties e. Build foundations with interested parties f. Determine interested parties' level of participation and when they participate g. Collect data h. Decide criteria for prioritization i. Generate research options	a. Decide criteria for prioritization (if not part of the preparatory stage) b. Generate research options (if not part of the preparatory stage) c. Administer surveys d. Run meetings e. Apply criteria	a. Report the results b. Act on the priorities c. Monitor and evaluate

Stage 1: Preparation

The preparatory stage covers all the activities up to actually setting priorities. Typical activities for the preparatory stage include:[47]

a. Define the context and scope

Following the REPRISE framework,[48] defining the context and scope may cover:

1. Defining the geographical scope (e.g., global, national)

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[47] See Ghaffar, A., et al. (2009). The 3D combined approach matrix: An improved tool for setting priorities in research for health. In Geneva: Global Forum for Health Research; James Lind Alliance, The James Lind Alliance Guidebook Version 10 (2021); Montorzi, G., S. De Haan, and C. IJsselmuiden. "Priority Setting for Research for Health: a management process for countries." Geneva: Council on Health Research for Development (COHRED) (2010); Nasser et al 2021; Okello, David, and Pisonthi Chongtrakul. A manual for research priority setting using the ENHR strategy. COHRED, 2000; Rudan, I. "Global health research priorities: mobilizing the developing world." *Public Health* 126.3 (2012): 237-240; Terry et al. A systematic approach for undertaking a research priority-setting exercise. Guidance for WHO staff. Geneva: World Health Organization; 2020; Viergever et al. 2010.

[48] Tong, Allison, et al. "Reporting guideline for priority setting of health research (REPRISE)." *BMC Medical Research Methodology* 19 (2019): 1-11.

2. Defining the health area, field, or focus (e.g., diabetes, tobacco, healthcare delivery)
3. Defining the intended beneficiaries (e.g., patient groups)
4. Defining the target audience for the priorities (e.g., policy makers, funders, researchers)
5. Identifying the research area or level (e.g., public health, clinical research, basic science)
6. Identifying the types and granularity of research questions (e.g., etiology, implementation science, drug and vaccine development)
7. Defining the time frame (e.g., five-year plan, one-off or periodic priority setting)

In addition, it will be helpful at this point to identify the resources that are available for priority setting, the timeline of the exercise, and check whether the scope of the proposed exercise is covered by any existing published set of research priorities.

If you are using the ***Guiding Questions for Ethical Research Priority Setting*** tool, the questions from parts 1 – 5 should be answered now. The answers to those questions will be a valuable resource when incorporating the ethical considerations into this and the following activities.

Ethical considerations:

- In deciding the scope, consider the *special obligations* of the priority setters or any other parties to whom the priorities are directed (Chapter 2.2). For example:
    - If setting national priorities for a government, consider what obligations are owed inside and outside of the country's borders. In particular, high-income countries may have substantial ethical obligations to other populations.
    - If setting priorities for a funder, consider the funder's mission, commitments to donors, and/or relevant legislation. For example, a cancer research charity will have its scope restricted to cancer; a government funder may be legally required to focus on some conditions, types of research, or potential beneficiaries.
    - If setting priorities for clinician-researchers, consider whether there are patient populations whose needs should be prioritized. For example, a researcher whose clinical work is with a particular community may have obligations to conduct research that benefits that community.
- Pragmatic considerations may also limit the scope. For example, researchers setting priorities must consider their expertise and the available sources of funding.
- Within what is allowed by special obligations and pragmatic considerations, consider making the scope as wide as possible. Having a more open scope gives participants a better opportunity to choose priorities that will optimize the *social value* of the research.

- There should be *transparency* about the scope of priority setting and why. This can help prevent participants and potential beneficiaries having unrealistic expectations.[49]
- In deciding what resources to allocate to priority setting, consider what will be necessary for a systematic, evidence-based, and ethical priority setting exercise. Bear in mind that the resources used for research priority setting should be *proportionate* to what is at stake. While conducting priority setting is an ethical obligation and so some resources should be allocated to it (Chapter 1), the appropriate investment will vary. For example, a large global health funder developing its five-year strategic plan should assign more resources to priority setting than a small funder deciding how to spend a one-off pot of additional funds.

b. Decide on governance

Decisions must be made about the governance structure and leadership of the priority setting exercise. Those who lead the exercise should have the relevant technical and interpersonal skills.[50] Depending on the nature and extent of the exercise, it may be necessary to put together a team, which could include a steering committee, expert advisory group, project manager, workshop facilitators, and so forth.

Ethical considerations:

- The leadership team should be constituted so that they are *accountable* to their constituents, if any. For example, if this is a governmental priority setting exercise, it should be clear how citizens and residents can have input and which governmental officials take responsibility for the process and its outputs.
- Governance structures should be *transparent*, so that they are communicated to participants before and during priority setting and reported afterwards.
- Consider *inclusion* when deciding who should lead priority setting and who should be involved in its governance. For larger priority setting exercises, the team should ideally include members of groups who are expected to be producers, users, and beneficiaries of research, including members of disadvantaged and marginalized groups. Power-sharing is more effective when it is incorporated into priority setting from the preparation stage. This means that interested parties may need identifying (1.d.) before finalizing the governance structure.

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[49] Pratt, Bridget. "Towards inclusive priority-setting for global health research projects: recommendations for sharing power with communities." *Health Policy and Planning* 34.5 (2019): 346-357.
[50] Nasser et al. 2021: 124.

- In multinational research collaborations, particular care should be taken that leadership represents all the countries involved and that researchers from less well-resourced institutions are included as equal partners.

c. Choose or design a method

Your *method* lays out the exact steps that your priority setting process will take—i.e., what activities in what order from preparatory through the priority-setting and the follow-up stages. A number of different methods for research priority setting have been published (Chapter 4). In addition, there are useful guides that provide overviews of how to set up and manage a priority setting exercise.[51] Many priority setting exercises adapt existing methods or design their own to suit their needs and context. Recommendations for how to use this guidance alongside some common methods are given in Chapter 4. If you design your own method, it may still be valuable to look at the published methods for insights.

Ethical considerations:

- Whether they follow a published method or devise one themselves, priority setters should use *some systematic process* that allows research options to be compared in a structured way. Because decisions about health research are decisions about how to allocate scarce and valuable resources, there is an ethical obligation to make those decisions systematically, on the basis of evidence, and consistent with ethical principles.
- The method chosen should be *proportionate* to the resources available for priority setting and what is at stake.
- The method should be chosen or designed with the *four ethical principles* in mind. Consider:
    - Given the context and scope of your priority setting, is it reasonable to think that this method will *optimize the social value* of the research options selected? (See, especially, sections 1.g., 1.h., 1.i., 2.e., 3.c. in this chapter)
    - Are any *special obligations* taken into account? (See, especially, 1.a., 1.b., 1.d.)
    - If relevant, are there points in the decision-making process where research options will be examined for whether the research would involve *unjustified harms*? (1.i., 2.e.)
    - Would the use of this method be *procedurally fair*? Given available time and resources, are all relevant interested parties *included* in a way that ensures the

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[51] Kapiriri L., Arnold E., Campbell S., Kapata- Chanda P., Ngosa W. and Humainza B. Approaches to Health Research Priority Setting: A Reference Manual Synthesizing the Literature and Demonstrating the Potential Use of the Manual. Mcmaster University, 2017; Montorzi et al. 2010; Terry et al. 2020.

desired level of participation? (1.b., 1.d., 1.e., 1.f., 2.c., 2.d.) Do follow-up activities—such as dissemination and evaluation—meet obligations of *transparency* and *accountability*? (3.a., 3.b., 3.c.)

d. Identify interested parties

The parties who have an interest in the results of the research priority setting typically fall into three categories: research producers (e.g., researchers, funders), research users (e.g., clinicians, policy makers), and research beneficiaries (e.g., patients, carers). Where it is not obvious who these parties are, it may be valuable to undertake a "stakeholder analysis."[52] The preparatory stage will include making decisions about who among the interested parties to include and so also about outreach to members of those groups (1.e.).

If you are using the ***Guiding Questions for Ethical Research Priority Setting*** tool, the questions from part 6 should be answered now in order to inform this and the following activities.

Ethical considerations:

- Who is included and how they are included is the core of *inclusion*.
    - Consider the epistemic, pragmatic, and intrinsic reasons for including members of different groups (Box 1).
    - Consider whether identified stakeholders span all three categories—research producers, research users, and research beneficiaries—and relevant demographics so that the diversity of participants matches the diversity of interested parties.
    - Consider whether there are enough individuals representing each category and demographic for their voices to be effective.
    - Consider what special efforts should be made to ensure participation from members or representatives of disadvantaged and marginalized groups (see Appendix 2).
- In addition to thinking about who should be included in the priority setting exercise, consider to whom you are *accountable*. This may be relevant to how the results of an exercise are reported, and to monitoring and evaluation (3.a. and 3.c.).
- The *special obligations* of priority setters or those to whom priorities are addressed may be relevant to the "stakeholder analysis." For example, government bodies may have special obligations to citizens and residents with implications for who should be included and to whom they are accountable.

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[52] Terry et al. 2020: 9.

- Consider what level of engagement would be *proportionate* to the resources available for priority setting and what is at stake. For smaller priority setting exercises, it may be neither practical nor a good use of resources to try to include *all* parties who might have an interest in the results of priority setting. Nonetheless, it can be valuable to identify them so that a principled decision can be made about inclusion and for follow-up (particularly reporting (3.a.)).

e. Build foundations with interested parties

Once the interested parties are identified and plans made for whether and how to include them, usually some sort of outreach and relationship-building will be necessary. Building foundations with interested parties may inform the design of the priority setting method, it can build knowledge and comfort with prospective participants, and it is an opportunity to inform potential audiences about the exercise and get buy-in.

Ethical considerations:

- For any priority setting process, the goals of *inclusion* will be best served by *forming connections* and *building trust* with participants.[53] Consider how relationships and trust can be built or made stronger before priority-setting starts.
- Consider the environmental supports that may help people to participate as equals and to the best of their ability. These might include training for those who need it, creating a pairing or mentoring system, accommodation of varying needs, and other strategies. Such considerations are particularly important for members of disadvantaged or marginalized groups.[54]

f. Determine interested parties' level of participation and when they participate

For interested parties who will be included in the priority setting process, a decision should be made about their appropriate level of participation (Figure 2). Levels of participation range from pure collaboration (e.g., representatives of all interested parties take part in workshops to solicit research options, decide on criteria for prioritizing among them, and jointly make decisions about the final list) to pure consultation (e.g., members of a group are surveyed and the information they provide feeds into the priority setting exercise) to simply being informed of the results of priority

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[53] Pratt, Bridget. "Achieving inclusive research priority-setting: what do people with lived experience and the public think is essential?" *BMC Medical Ethics* 22 (2021): 1-14.
[54] Pratt 2021.

setting.[55] Some priority setting processes involve a mix of consultation and collaboration (e.g., a group is surveyed about their health problems, criteria are decided by the priority setting team, and then the group is involved in a workshop applying the criteria to possible research options). In Figure 2, shared decision-making reflects collaboration, whereas proposal sharing, information giving, and providing feedback comprise consultation.

Ethical considerations:

- It is sometimes appropriate to involve different groups in different ways. For example, some might be involved in decision-making and others simply surveyed for input on technical questions (2.c. and 2.d.). It is always important to connect *who* is included and *how* they are included to the reasons *why* they should be included.
- Of those who provide information, distinguish the different types of relevant knowledge that they may have (e.g., judgments about how likely it is that a research question can be answered should not be made by patients; judgments about the relative importance of reducing pain versus improving mobility should not be made by scientists who lack clinical or lived experience of a condition).
- In making decisions about the level of participation, consider with whom there is an obligation to share decision-making power. In particular:
    - To whom are you *accountable*?
    - How might sharing power improve the *social value* of the results of your exercise (e.g., by ensuring that *equity* considerations are raised and heard)?
    - On whom will the decisions being made have a substantial *impact*?
- The final process should be one that is justifiable to all interested parties, even those who are not included as collaborators.
- For *transparency*, participants should normally be asked to declare any potential conflicts of interests. Consider whether the process needs to be altered in any way to address conflicts of interests and whether any conflicts are serious enough to be exclusionary.

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[55] Pratt, Bridget. "Sharing power in global health research: an ethical toolkit for designing priority-setting processes that meaningfully include communities." *International Journal for Equity in Health* 20.1 (2021): “Ethical Toolkit Worksheet 4A. Designing Priority-setting Worksheet: Questions for Reflection and Discussion.”

Figure 2. A spectrum of modes of inclusion[56]

Shared decision-making	Proposal-sharing	Information-giving	Providing feedback	Mere informing
Being part of the group who makes decisions when planning and conducting research priority-setting.	Providing recommendations for research priorities or for the criteria used to select or rank research priorities without decision-making power.	Providing information about one’s context.	Sharing opinions about research priorities set by others, e.g., what are the most relevant and important on the list.	Being informed about the research priorities set by others.
Deep inclusion		↔		Shallow inclusion

Box 1. Whom to include and how

Step 1. Epistemic reasons for inclusion

1. Decide what information will be needed in order to make principled, informed decisions.
2. Work out how to obtain that information. Some information may come from consulting people, other information may be available elsewhere (e.g., literature reviews, existing priority setting exercises).
3. For information that will be gathered from people:
    a. Map the different types of information needed to the individuals and groups who will be included.
    b. For each, consider how they should be included, i.e., what level of participation, when in the process, and so on. Groups might—or might not—be included separately and using different methods. For example, one might gather data from patients about their health care experiences through surveys and focus groups. One might gather estimates from scientists about the probability of success for research options through a Delphi process.
4. Special care should be taken to include disadvantaged or marginalized groups in ways that allow them to meaningfully participate (Appendix 2).

Step 2. Pragmatic reasons for inclusion

1. If including additional individuals or groups in order to gain trust or buy-in, ensure that the priority-setting process is in fact trustworthy and merits their buy-in.
2. Consider the following questions:
    a. Whose buy-in is necessary for the priority setting to be effective? How can those groups be included?

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[56] Pratt et al. 2016. Adapted from Arnstein, Sherry R. “A ladder of citizen participation.” *Journal of the American Institute of Planners* 35.4 (1969): 216-224

b. How might strategies for gaining trust or buy-in conflict with other aspects of the priority setting process?

c. Are there interested parties who should be included but who pose a risk to ethical decision-making (e.g., powerful funders or politicians who may have disproportionate influence on the outcome, participants with conflicts of interests)? How could those risks be mitigated?

3. Given the answers to 2a-c, consider how any additional individuals or groups should be included, i.e., what level of participation, when in the process, and so on.

Step 3. Intrinsic reasons for inclusion

1. Consider the following questions. Affirmative answers support intrinsic reasons to include members of particular groups in decision-making around priority setting.

a. Is the priority setter accountable to a defined population?
- E.g., government agencies to their public.

b. Does the priority setter have existing obligations to a defined population?
- E.g., a relationship with a patient population or a specific community; a long-standing collaborative research partnership

c. Are there identifiable groups that these decisions will have a big effect upon?

d. Are the groups that these decisions will have a big effect upon who are particularly disadvantaged, at-risk, disempowered, or unheard?
- E.g., in setting priorities for HIV research this could apply to intravenous drug users, sex workers, adolescents.

2. For each, consider how they should be included, i.e., what level of participation, when in the process, and so on.

3. Special care should be taken to include disadvantaged or marginalized groups in ways that allow them to meaningfully participate (Appendix 2).

Step 4. Ensuring breadth

1. Consider the individuals and groups identified in steps 1-3 as a whole.

a. Is there a sufficient range of participants, such that they represent the diversity of interested parties?

b. Is there a sufficient mass of participants, so that there are enough individuals representing each group for their voices to be effective?

g. Collect data

Effective priority setting requires gathering, analyzing, and organizing the relevant data that will be used as inputs into the process. Depending on the context, this might include information about:[57]

- The state of scientific knowledge on relevant biological mechanisms and pathology
- Existing interventions, including biomedical and behavioral modalities

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[57] Ghaffar et al. 2009: 11; Montorzi 2010: 7.

- Public health needs, including data on burden of disease, health system performance, access to the social determinants of health
- Disparities in health and well-being, such as how the disease burden is distributed among groups stratified by age, race or ethnicity, gender, sexual identity, disability, immigration status, geography, and others
- The research governance structures within a country
- What research within the scope of the exercise has already been conducted or is ongoing
- Previous research priorities, identified through other priority setting exercises, in identifying missing evidence when developing public health guidance, and in publications
- How the health care system operates
- What patients, carers, clinicians, policy-makers, or other research users want

At a minimum, collecting data will require reviewing the relevant scientific literature, databases, government reports, and so on. Depending on the context, it might also require consulting subject-matter experts, clinicians, or decision-makers, or even surveying research producers, users, or beneficiaries. Note that many priority setting exercises rely on the knowledge of the individuals involved in setting priorities (hence the *epistemic* reasons for inclusion (Box 1)). Not all knowledge gaps must be filled during the preparatory stage.

In addition to gathering data, it is likely that the data will need some analysis and organization. For more extensive priority setting exercises, consider whether a framework like the Combined Approach Matrix would be helpful for identifying data needs and presenting the relevant information (Chapter 4).

Ethical considerations:

- Consider whether the data that has been collected will allow prioritization on the basis of *social value*. For example, if epidemiological data is not stratified by gender, socio-economic status, geography, or other potentially important characteristics, then it will not be possible to take into account *equity* regarding those characteristics. If the costs of different research options are not available to priority setters, then it will not be possible to allocate resources *optimally*. Where knowledge gaps are identified, consider if it is possible to fill them or how to otherwise reduce their negative impact on the exercise. This might include, e.g., flagging the gaps for participants, acknowledging them in reports, and considering whether filling the gaps is itself a research priority.
- Where participants in a priority setting exercise will draw on data, consider how to present it in a way that they are able to access and understand. Information should be tailored to

the needs of users. For example, if patients will be involved in priority setting, research options should be described so that they can be readily understood by non-scientists.

h. Decide criteria for prioritization

An important component of any process used for setting priorities is the criteria that will be used to compare research options. Depending on the method chosen, these criteria may be set in the preparatory or the priority setting phase (depending on whether the participants in the exercise are also setting the criteria). The four ethical principles discussed in Chapter 2 provide a framework for thinking about priority setting criteria. However, they are likely too general to use directly. Instead, context-specific criteria need to be developed for the specific priority setting exercise.

Ethical considerations:

- There should be criteria that capture each component of *social value*, i.e.,
    - The magnitude of potential benefits from research
    - The degree of disadvantage of potential beneficiaries (according to relevant dimensions of equity)
    - The likelihood that the research project will be successful
    - Where relevant, the relative costs of different research options should be considered, e.g., the amount of resources that a research project would require

  Appendix 3 goes into detail on how to define social value for a specific priority setting context and operationalize the definition, as well as giving some examples of how this has been done.
- For research that is more distant from translation into practice, including basic biomedical research, it will not be possible to directly estimate the effects on health and well-being that would result from a successful research project. In these cases, proxy indicators for the components of social value need to be devised.
- Consider whether *special obligations* mean that greater weight should be given to some research options over others (e.g., a middle-income country governmental agency might give greater weight to benefits to its own population while still taking regional or global needs into account[58]).
- For exercises where the research options are likely to include *non-human animal research*, criteria should be included to compare options according to the harms they will cause to non-human animal subjects.

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[58] Barsdorf, N. W. (2012). South Africa's Duty to Support Health Research for the Global Poor. Available at: https://bora.uib.no/bora-xmlui/handle/1956/5995.

- Consider whether *harms from research* to third parties are a plausible concern, given the scope and topics of the priority setting exercise. If so, include criteria to flag research options that pose such risks.
- Consider whether some criteria should be weighted to reflect their relative importance.[59]
- Consider whether the criteria should be decided on by a wider group than the team leading the priority setting exercise, i.e., whether this activity should take place during the next phase (2.a). Doing so *includes* more interested parties in setting the terms for the exercise. The ethical considerations regarding conducting surveys and running meetings may then apply (see sections 2c and 2d below).

i. Generate research options

In order for priorities to be set, there needs to be a set of options to prioritize. In a few cases—e.g., for a funder receiving investigator-initiated grant proposals—these options will already be given, for most priority setting exercises, they will need to be generated. Generating research options involves listing potential research areas or research questions that the priority setting exercise will rank or choose among. Depending on the method used, this can be part of the preparatory stage or the setting priorities stage. After an initial list of research options has been drafted, it can be refined by:[60]

- Making the research questions or potential areas of inquiry more precise
- Eliminating research questions that have already been answered (following a review of the scientific literature)
- Eliminating research options that are overlapping or duplicative

Ethical considerations:

- *Assess and justify harms*. If the research options are specific enough, consider if any are likely to pose high enough risks of harm—directly or through the knowledge generated—to be of concern at this early stage. Some research options might be eliminated at this point; others should be flagged as needing particular attention during the priority setting phase.
- *Inclusion*. Consider whether the initial list of research options is being generated by a sufficiently diverse set of individuals. For example:
    - Should researchers from multiple disciplines be consulted?
    - Are respondents geographically diverse?

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[59] Yoshida, Sachiyo, et al. "Setting health research priorities using the CHNRI method: III. Involving stakeholders." *Journal of global health* 6.1 (2016).

[60] See, e.g., James Lind Alliance (2021): 43-60.

  - Should clinicians, carers, and/or patients be consulted? (Note that generating research options for a condition is not the same as finding out what matters most to people affected by the condition.)
- If research options are generated through surveys or meetings, consult sections 2c and 2d from *Stage 2: Implementation* below.

Stage 2: Implementation

The second stage is where priorities are actually set—that is, where selected criteria are applied to choose among research options to generate a list of priorities. In priority setting exercises that center around a workshop, this would be the activities that happen at the workshop. Other exercises will be more spread out over time. For example, the James Lind Alliance method involves interim prioritization via a survey following by final prioritization of shortlisted research options at an in-person workshop. The type and number of steps involved in setting priorities should be decided when selecting or designing your method. It will depend on your needs and resources.

Typical activities for the setting priorities stage include:

a. Decide criteria for prioritization (if not part of the preparatory stage)

b. Generate research options (if not part of the preparatory stage)

c. Administer surveys

Whether for preliminary data gathering, gathering research options, or even setting final priorities, many priority setting exercises involve administering surveys to participants.

Ethical considerations

- Considerations concerning *inclusion* can be very important when designing and administering surveys. Bear in mind, here as elsewhere, that the goal is not to simply include more people: what is needed is appropriate inclusion, so that the right people are asked the right questions to find out the information that is needed for ethical priority setting. Haphazard efforts to broaden inclusion can dilute the voices of the people whose opinions actually matter. Relevant questions to consider regarding surveys might include:

  - Should members of this group be surveyed rather than engaged in person? Surveying a group rather than engaging them in person typically means that its members have less power in the priority setting process. However, it may make it possible to engage more people and will generally be less resource intensive.
  - If the survey is online, will all members of the target population be able to access it? If not, are there alternative ways to administer the survey?
  - Is the survey written at a level that will be understandable to all respondents? Can those with visual or hearing impairments complete it?
  - In what languages will the survey be available?
  - Does the survey raise concerns about confidentiality, sensitive topics, or other issues relating to participant protection?
- Comprehensive guidance on the ethics of survey research is outside the purview of this guidance and can be found elsewhere.[61]

d. Run meetings

Most research priority setting exercises involve one or more meetings, which might be in-person or online. It is usually at such meetings that final decisions are made about the research agenda or list of priorities that the exercise produces. Depending on the scope of the exercise and the resources available, it may be better to have independent trained facilitators run meetings.

Ethical considerations

- Considerations related to *fair procedures* come to the fore when designing and running meetings.
- Meetings should be designed and run with the governing aim of ensuring *qualitative equality* among participants. This means that everyone has a fair opportunity to share their ideas and to influence the priority setting process and outcomes.
  - Consider whether the process of decision-making raises concerns about *epistemic injustice*. For example, will patients be listened to, even if they do not use medical terminology? Will the views of scientists be given excess weight, even when they are speaking outside of their technical expertise?

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[61] Oldendick, Robert W. "Survey research ethics." *Handbook of survey methodology for the social sciences* (2012): 23-35.

  - To mitigate power disparities, it is important to assess what types of power disparities exist between participants and to apply strategies to reduce them, e.g., setting ground rules that privilege speaking time for less heard voices, using facilitators skilled at drawing out less heard voices, and holding the priority-setting process in a location where less powerful participants feel comfortable.[62]
  - In some cases, it may be useful to employ a "stepped approach" to promote qualitative equality. This is a facilitation method where small groups meet first to deliberate. Then those small groups come together to deliberate about the topic.
- Consider whether there should be several meetings with different participants. This can allow broader participation, it means that meetings can have different functions (e.g., brainstorming research options versus applying prioritization criteria), and it can mitigate power imbalances by ensuring that particular individuals or groups do not dominate.
- Special efforts should be made to design the priority-setting process so that more disadvantaged and marginalized groups can effectively participate (see Appendix 2).

e. Apply criteria

Whether it happens as a survey response or during a meeting, the criteria used for prioritization have to be applied at some point. This can be done through developing consensus or through some metric-based approach, such as by using an algorithm to aggregate participants' scores.[63] Either way the process can involve several iterations of deliberation, feedback, and scoring, depending on the method chosen.

Ethical considerations

- If research options are sufficiently specific to make judgments, projects that are likely to cause *unjustifiable harm* should be eliminated at this point. This might be because the suffering inflicted on non-human animals would be too great; or it might be because of potential third-party harms from the use of the results of the research.
- The criteria should be applied with the goal of *optimizing the social value* of research, consistent with any *special obligations* (see 1.h.).
- Consider whether a consensus-based or metric-based approach is preferable for your context. Each has pros and cons. Consensus-based approaches require participants to take account of the views of others. However, they require careful facilitation to manage power

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[62] Pratt, Bridget. "Engagement as co-constructing knowledge: A moral necessity in public health research." *Bioethics* 33.7 (2019): 805-813.
[63] Viergever et al. 2010: 5.

dynamics. Metric-based approaches can ensure that every participant gets an equal say. However, if the priority setters want participants to take account of others' opinions, then discussion and feedback needs to also be built into the process, prior to the final scoring.

Stage 3: Follow-up

Assuming that stages 1 and 2 were carried out correctly, the final priorities should be consistent with any special obligations and unethical research options should have been eliminated. But the principles of *optimizing social value* and *following fair procedures* still have implications at this stage. *Social value* will not be optimized unless steps are taken to implement the priorities—whether by carrying out the highest priority research oneself or disseminating the priorities to others. *Accountability* will not be achieved without feeding back the outputs of priority-setting to participants, and assessing whether the priority-setting process itself was fair and achieved its goals.

If you are using the ***Guiding Questions for Ethical Research Priority Setting*** tool, the questions from part 7 should be answered now in order to inform the follow-up activities.

The following activities should be considered during follow-up:

a. Report the results

Reporting the results of priority setting includes all activities relating to publication, outreach, and dissemination. Exactly what should be reported, in what form, and to whom will depend on the nature of the priority setting exercise and who carried it out.

Ethical considerations

- *Optimizing social value*. In any case where the results of priority setting might be of value to others, they should be made publicly available. Depending on the audience, this might be through academic publications, presentations, websites, newsletters, or direct communication (e.g., to representatives of funders or government ministries).[64] Timely reporting and effective dissemination are essential to getting uptake of the research priorities. They also reduce the chance of duplicative priority setting.

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[64] See, e.g., James Lind Alliance 2021: 82.

- *Transparency* is particularly important for larger exercises and those conducted by entities with special obligations to the public. The methods used in setting priorities should be reported as well as the findings. Consider using the REPRISE reporting checklist to structure these reports.[65]
- There are ethical obligations based on *reciprocity* to share the results of priority setting with the parties who participated in any part of the exercise (just like there are obligations to share research findings with participants).
- *Accountability* may require not only that the methods and results of priority setting are made publicly available, but also that plans for action based on the identified priorities are set out.

b. Act on the priorities

The easiest way to ensure that a set of research priorities gets taken up is to use them oneself. Whether this is possible and what form it will take depends on the priority setter, i.e., whether they conduct research themselves, directly support research, or are simply developing an agenda for others to follow.

Ethical considerations

- Where possible, there is an ethical obligation to conduct research in line with the final priorities, or to directly support it in other ways. For example:
  - *Funders* should consider directly commissioning high priority research; earmarking funding for priority research areas; and/or designing grants programs to encourage and select applications that fit the priorities.
  - *Researchers* should consider carrying out the highest priority research; identifying funding opportunities consistent with the priorities; and/or finding training opportunities and collaborators that would enable them to carry out the research.
  - *Governments* should consider whether there are changes to law, policy, sources of government support, or other activities that would enable scientists to better pursue the priorities. For example, in addition to directly funding research, this might involve identifying bureaucratic barriers to priority research and coordinating funders and researchers working in the country around the national priorities.

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[65] Tong, Allison, et al. "Reporting guideline for priority setting of health research (REPRISE)." *BMC medical research methodology* 19.1 (2019): 1-11.

  - *Research institutions* should consider redirecting funding and other institutional resources towards the priorities; adjusting career incentives to match carrying out priority research; and hiring individuals working in priority areas.

c. Monitor and evaluate

Priority setting is not a one-off exercise. After an exercise is completed, it is important to evaluate how it went so that lessons can be learned for future exercises. This includes what worked and what needs improving in the preparatory and priority setting phases, as well as whether the overall process was in fact fair. The results and lessons learned from one exercise should feed into the next to improve the process of priority setting.[66] The priorities will eventually need to be revisited, as the landscape of health and research changes and as—hopefully—some of the high-priority research is carried out.

After the results of a priority setting exercise have been published and disseminated, it is important to monitor its effects. In the short-term these might include measuring awareness of the priorities, and in the longer-term changes to what research is carried out, new interventions, and impacts on well-being.[67]

Ethical considerations

- Anyone carrying out research priority setting should monitor and evaluate the process and results in order to ensure that the priority setting increases the *social value* of research. This includes monitoring dissemination, uptake, and, eventually, whether and when research priorities need to be revisited.
- Many actors—including governments and funders—have obligations of *accountability* and *transparency* which mean that they should report on their monitoring and evaluation, as well as provide opportunities for interested parties to challenge or comment on the priorities.[68]
- Consider whether and how participants can be asked to evaluate the priority setting process in which they were *included*.

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[66] Nasser et al. 2021: 131.
[67] Terry et al. 2020: 25.
[68] Nasser et al. 2021: 131.

CHAPTER 4. EXISTING METHODS AND GUIDES

A number of methods for running research priority setting exercises have been published and used extensively. The present guidance is not intended as an alternative to these published methods, but may help you think about whether to adopt one in whole or in part. Below, the most commonly cited methods for research priority setting are described and discussed.[69] Some methods are best thought of as *components* to be incorporated into a bigger priority setting process. Others are *complete* methods in the sense that they prescribe how each stage of priority setting should be carried out. The following sections describe how the *component methods* can be incorporated into an ethical priority setting process (Section 1) and how this guidance can complement the *complete methods* (Section 2).

In addition to the published methods, several guides provide helpful recommendations for priority setting exercises without prescribing specific designs.[70] There is also existing WHO guidance on research priority setting for WHO staff. Section 3 of this chapter discusses some overlaps and differences between that guidance and the present guidance.

In considering the use of an existing method for your priority setting exercise, bear in mind:

- There is no one-size-fits-all method for research priority setting. Each method has pros and cons and should be considered in the light of your specific circumstances, needs, and resources.

- In many cases, designing your own process will be the best way to ensure that you are able to set priorities in a systematic, evidence-based manner on the basis of sound ethical principles.

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[69] Other methods not described here include: *Listening for Direction* (Lomas, J., Fulop, N., Gagnon, D., & Allen, P. “On being a good listener: setting priorities for applied health services research.” *The Milbank Quarterly*, 81.3(2003): 363-388); adaptations of the *Choosing All Together (CHAT)* exercise to health research (Goold, Susan Dorr, et al. “Members of minority and underserved communities set priorities for health research.” *The Milbank Quarterly* 96.4 (2018): 675-705); and “value of information” analysis (Fleurence, Rachael L., and David J. Torgerson. “Setting priorities for research.” *Health policy* 69.1 (2004): 1-10).

[70] Kapiriri L., Arnold E., Campbell S., Kapata- Chanda P., Ngosa W. and Humainza B. Approaches to Health Research Priority Setting: A Reference Manual Synthesizing the Literature and Demonstrating the Potential Use of the Manual. Mcmaster University, 2017; Montorzi et al. 2010; Nasser et al. 2021.

- Consider borrowing from the different methods to create an adapted method that suits you.
- Even if an existing published method is chosen, it is still essential to think systematically through the ethical considerations that apply to your specific situation.

2.1. Component methods

The combined approach matrix (CAM) and the Delphi method are sometimes described as priority setting methods in their own right. However, it may be helpful to view them instead as providing components for a priority setting exercise. These components can be incorporated into a broader process designed by the priority setter.

The combined approach matrix (CAM)

The combined approach matrix (CAM) is a tool that is used to "classify, organize and present the large body of information that enters into the priority setting process."[71] The core of CAM involves gathering data to complete a matrix with two dimensions (*public health* and *institutional*) or three (adding an *equity* dimension). The public health dimension includes information on disease burden, determinants of disease, the present level of knowledge about disease, the cost and effectiveness of existing interventions, and current resources flows. The institutional dimension is used to assign this public health information to different levels: individual, household, and community; health ministry and other health institutions; non-health sector; and governance. When the equity dimension is included, this requires assessing whether there are also differences between social groups, such as gender and income groups.

The completed matrix presents all the relevant information relating to a priority setting process in a systematic way. In addition, it reveals knowledge gaps (and filling those knowledge gaps might be research priorities). According to the authors of the CAM, it can be used by "institutions, local or national governments, development agencies, academics and individual researchers."[72] Practically, it requires gathering and synthesizing a lot of information, so whether it should be used will depend on whether all that information is needed and whether there are sufficient resources and time to complete it.

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[71] Ghaffar A, Collins T, Matlin SA, Olifson S. The 3D combined approach matrix: an improved tool for setting priorities in research for health. Geneva: Global Forum for Health Research (2009): 14.

[72] Ghaffar et al. 2009: 40.

The CAM and this ethics guidance

- The CAM does not constrain the form that priority setting takes, it just guides the collection, analysis, and presentation of data for a priority setting exercise. A process using the CAM should therefore be designed in the light of the four key principles and taking note of the ethical considerations enumerated in Chapter 3 for each stage of priority setting.

- Given how data-intensive the CAM is and how much interpretation must be imposed on the data in order to populate the matrix, care must be taken to identify and defend any value judgments that are embedded in it.

- *Applicable ethics guidance sections (Chapter 3)*:
    - **1.g. Collect data**.

The Delphi method

The Delphi method is a process through which information and opinions from a group of experts are gathered and synthesized. Originally developed for forecasting, the Delphi method is now used in various situations where there is limited information so predictions cannot be based on models.[73] There are several variants of the method, but the basic idea is that priority setters convene a panel of experts who answer questions or rank options. Their responses, including their reasoning, are compiled and then circulated to the same panel of experts. The exercise is repeated one or more times.[74] A Delphi exercise may aggregate the expert panel members' scores or it may aim for consensus.

Research priority setting exercises often incorporate some form of the Delphi method as one component. Usually, it is used for applying criteria to rank research options, but it can also be used for developing the criteria themselves and for generating lists of research options.[75]

The Delphi method and this ethics guidance

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[73] Turoff, Murray, and Harold A. Linstone. *The Delphi method: techniques and applications*. Addison-Wesley Publishing Company, Advanced Book Program (2002).

[74] de Meyrick, Julian. "The Delphi method and health research." *Health education* 103:1 (2003): 7-16.

[75] Yoshida, Sachiyo. "Approaches, tools and methods used for setting priorities in health research in the 21st century." *Journal of global health* 6.1 (2016).

- Where the Delphi method is used for the implementation stage of priority setting, special consideration should be given to how it relates to *fair procedures*. An application of the Delphi method is usually not replicable, which poses challenges for *transparency*. Care must also be taken that appropriate *inclusion* is not undermined. For example:
    - Solely including experts on a panel means that that part of the process will not include other voices, such as those of the users or beneficiaries of research. Thought should be given to how those voices will feed into the process.
    - Feeding back scores to the panel or having them discuss the pros and cons of research options has advantages in terms of critical engagement and knowledge exchange. However, it risks more dominant or powerful individuals having excessive influence on the results.
- *Applicable ethics guidance sections (Chapter 3)*:
    - **1.d. Identify interested parties**
    - **1.f. Determine interested parties' level of participation**
    - **1.h./2.a. Decide criteria for prioritization**
    - **1.i./2.b. Generate research options**
    - **2.d. Run meetings**
    - **2.e. Apply criteria**

2.2. Complete methods

The Child Health and Nutrition Research Initiative (CHNRI) method

The CHNRI method was developed by researchers to help set priorities for research into child health and nutrition. The method has since been used for various health topics and in different contexts.[76] The CHNRI process starts with a technical working group who define the context of the priority setting exercise (e.g., target population, target disease burden). The working group

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[76] Rudan, Igor, et al. "Setting health research priorities using the CHNRI method: VII. A review of the first 50 applications of the CHNRI method." *Journal of global health* 7.1 (2017).

surveys a large sample of experts to identify a set of candidate research options. Depending on the context, these experts might include policy makers and program managers, in addition to scientific researchers. The survey of experts generates "an exhaustive list of the competing research options by addressing main risk factors and possible interventions."[77] After this list is cleaned up (e.g., by removing duplicates and integrating related ideas), the experts are surveyed again. This time they independently score each candidate priority on a set of criteria. The CHNRI method provides five "standard" criteria for prioritization among research options: (i) answerability, (ii) effectiveness, (iii) deliverability, (iv) maximum potential for disease burden reduction, and (v) effect on equity. This is not set in stone, so the criteria used can be changed and, in practice, often are.[78] The criteria can also be weighted, so that more importance can be assigned to one criterion than another across the exercise. The weights are developed by surveying external stakeholders from the wider community. This allows these non-experts to give input regarding values. The weights are applied to the experts' scores, which are aggregated to rank all the candidate research options.

The CHNRI method and this ethics guidance

- The five standard criteria used to score research options can be mapped to the three components of *social value* (Appendix 3). As noted, many CHNRI exercises have used different criteria—adding to or subtracting from the standard set. In all cases, care should be taken that the scores can realistically be interpreted as estimates of each component of social value (without under- or over-counting) *and* that the overall score makes sense as an estimate of social value.

- The standard CHNRI method does not include consideration of the relative cost of conducting the research projects being prioritized. Where possible, this should be incorporated into the process.

- The CHNRI method can be run and reported in a *transparent* manner and in some respects is a model of *procedural fairness*—for example, it does not allow the opinions of any individuals to have outsize weight or, indeed, to influence what others input to the process. However, the method is also predominantly driven by scientific expertise. It is therefore important to consider whether your priority setting context is appropriate for such an exercise. Should there be input from non-scientific groups, such as clinicians, carers, patients, or members of the public? Will an exercise that does not include their perspectives

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[77] Igor Rudan, Shams El Arifeen, Robert E. Black A Systematic Methodology for Setting Priorities in Child Health Research Investments (2006): 5.

[78] Rudan, Igor, et al. "Setting health research priorities using the CHNRI method: VII. A review of the first 50 applications of the CHNRI method." *Journal of global health* 7.1 (2017).

reflect what matters to them? Are there pragmatic reasons to involve non-scientists at some stage of the process?

- *Applicable ethics guidance sections (Chapter 3)*:
    - Technical working group:
        - **1.a. Define the context and scope**
        - **1. b. Decide on governance**
        - **1.d. Identify interested parties**
        - **1.h./2.a. Decide criteria for prioritization**
    - Survey:
        - **1. g. Collect data**
        - **1.i./2.b. Generate research options**
        - **2.c. Administer surveys**
    - Prioritization:
        - **2.e. Apply criteria**
    - Determining weights:
        - **2.c. Administer surveys**

The Essential National Health Research (ENHR) strategy for priority setting

The ENHR strategy is a priority setting method designed by the Council on Health Research for Development (COHRED) for use in national priority setting exercises.[79] The method starts with the team convening the priority setting exercise setting up a working group of stakeholders to decide how the priority setting exercise will be run and to conduct a "situation analysis" to gather

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[79] Okello D, Chongtrakul P, COHRED Working Group on Priority Setting. *A manual for research priority setting using the ENHR Strategy*. Geneva: Council on Health Research for Development (2000).

relevant data.[80] An initial list of research ideas is generated from the "situation analysis and inputs from various stakeholders."[81] The working group also decides on the criteria and the scoring method for ranking research options, which are agreed by consensus. The final priorities are set at a national workshop. This workshop includes a larger group of stakeholders, who should represent the different groups with interests in health research in the country. These may include researchers, health service providers, communities, professional associations, industry, politicians, donors, and international agencies.[82] The workshop participants use the criteria to score the research ideas to produce a national research agenda.

The ENHR strategy and this ethics guidance

- Insofar as this method is used to set national priorities, its focus will naturally be on what is most important to the citizens and residents of that country. However, consideration should still be given to the scope of the exercise given potential international obligations—for example, whether regional or international needs should be taken into account.

- The ENHR strategy emphasizes the importance of bringing together all interested parties. Including politicians, donors, and representatives of the private sector may be highly valuable for getting full information and obtaining buy-in from key decision-makers. However, it raises many of the challenges concerning *inclusion* mentioned in Chapters 2 and 3. Particular care should be taken with regard to the design of the overall process and the workshop at which priorities are set, so that they do not disempower disadvantaged and marginalized groups (Appendix 2).[83]

- *Applicable ethics guidance sections (Chapter 3)*:
    - Working group stage
        - **1.a. Define the context and scope**
        - **1.b. Decide on governance**
        - **1.d. Identify interested parties**
        - **1.e. Build foundations with interested parties**

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[80] Okello and Chongtrakul 2000: 10.
[81] Okello and Chongtrakul 2000: 11.
[82] Okello and Chongtrakul 2000: 3.
[83] Okello and Chongtrakul 2000: 8-9.

    - **1.f. Determine interested parties’ level of participation**
    - **1.g. Collect data**
    - **1.h./2.a. Decide criteria for prioritization**
    - **1.i./2.b. Generate research options**
  - National workshop
    - **2.d. Run meetings**
    - **2.e. Apply criteria**

The James Lind Alliance (JLA) framework

The James Lind Alliance, “brings patients, carers and clinicians together in Priority Setting Partnerships (PSPs) to identify and prioritise the unanswered questions or evidence uncertainties that they agree are most important for research to address.”[84] These PSPs are comprised only of patient, carer, and clinician groups—that is, only individuals with actual experience of the health area for which research priorities are being set—because these groups are thought to have special insight into what research evidence is actually needed by patients and their clinicians. The composition of PSPs are carefully balanced so that clinicians do not outnumber patients and carers. This is to ensure that the patient and carer voices are heard. Meanwhile, they exclude “representatives of the pharmaceutical industry, other commercial businesses, or those in the research community who are not also clinicians, patients or carers.”[85] The JLA view is that these groups may bias the results of priority setting away from what really matters to the users and beneficiaries of research evidence and that they already have opportunities to influence the research agenda.

The first stage of the JLA method involves the organizers of the PSP gathering “uncertainties” from existing guidelines and systematic reviews, and from surveys of patients or service users, carers, and clinicians. These uncertainties are checked by the organizers for whether they are in scope, overlapping questions are removed, and the remainder are stated in the form of “indicative questions.” Questions that have already been answered in the literature are then removed to leave a long-list of questions. A survey of stakeholders is used to conduct interim priority setting, which

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[84] James Lind Alliance. *The James Lind Alliance Guidebook, Version 10* (2021): 5.
[85] James Lind Alliance 2021: 10.

reduces the long-list to a short-list of 20-30 questions. Survey responses from patients and carers are given the same weight as responses from clinicians. The final stage involves a workshop of 12-30 patients, carers, and clinicians. The participants in the workshop aim to develop consensus on a top-10 list through small group discussion and ranking exercises (using the "Nominal Group Technique"). The JLA Guidebook states that: "The aim of the Top 10 is to highlight important areas for research, but not necessarily to come up with the specific research questions."[86]

The JLA method and this ethics guidance

- The JLA method is the most directive of the priority setting methods discussed here. It therefore leaves less discretion to make adjustments according to the ethical principles described in this guidance. Of note, the method dictates which groups will be included and decisions about which uncertainties merit highest priority are made using the criterion of what participants regard as most important (rather than, e.g., through applying specific criteria corresponding to the components of social value). The relative costs of answering research uncertainties are also not considered in the JLA method.

- The key strength of the JLA method is that it is designed so as to identify what matters to those directly affected by a health condition and to elevate the voices of those who might otherwise not be heard.

- In deciding whether to use the JLA method, consider whether the key gap in knowledge needed for priority setting on a health topic concerns what matters to research users, carers, and patients.

- For those interested in acting on the priorities generated by a PSP, it may be necessary to engage in further priority setting to incorporate the probability of success in resolving a research uncertainty and the cost of doing so. These considerations are in addition to the fact that the uncertainties in the top-10 are ranked as highly important for users and beneficiaries.

- *Applicable ethics guidance sections (Chapter 3)*:

    - Gathering and reviewing initial uncertainties

        - **1.a. Define the context and scope**

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[86] James Lind Alliance 2021: 8.

        - **1.b. Decide on governance**
        - **1.g. Collect data**
        - **1.i./2.b. Generate research options**
        - **2.c. Administer surveys**
    - Survey to reduce long-list to short-list
        - **1.d. Identify interested parties**
        - **2.c. Administer surveys**
    - Workshop
        - **1.d. Identify interested parties**
        - **1.e. Build foundations with interested parties**
        - **2.d. Run meetings**
        - **2.e. Apply criteria**

2.3. Guides

A number of useful guides summarize published methods and give practical advice on carrying out priority setting exercises.[87] The present ethical guidance should complement such guides. This section discusses the existing WHO guidance on research priority setting—*A systematic approach for undertaking a research priority-setting exercise: Guidance for WHO staff*—and how this guidance should be thought about in relation to it.

A systematic approach is aimed at WHO staff who are carrying out a priority setting exercise.[88] Such exercises are typically global in scope and aim to delineate high-level priorities for a specific disease or health topic, such as tuberculosis, nutrition, or maternal and child health.[89] *A systematic*

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[87] Kapiriri et al. 2017; Montorzi et al. 2010; Nasser et al. 2021.

[88] Terry et al. *A systematic approach for undertaking a research priority-setting exercise. Guidance for WHO staff*. Geneva: World Health Organization; 2020.

[89] Terry, R. F., et al. "An analysis of research priority setting at the World Health Organization–how mapping to a standard template allows for comparison between research priority setting approaches." *Health research policy and systems* 16.1 (2018): 1-11.

approach divides priority setting into four stages—plan, implement, publish, monitor and evaluate—and delineates key activities for each stage. The present guidance should complement the process of designing a method to match one's context as recommended by *A systematic approach*, to make sure all the ethical principles are taken into consideration. Such a method might draw on some of the other research priority setting methods described above.

Incorporating the ethics guidance

If following *A systematic approach*, relate its four stages to the three stages above as follows:

A systematic approach	**This guidance**
Phase 1: Plan Phase 2: Implement	Preparatory and implementation stages
Phase 3: Publish Phase 4: Monitor and evaluate	Follow-up stage

The recommendations of the present document are intended to be consistent with *A systematic approach*, while going into a greater level of detail and specificity regarding the ethical considerations at each stage. Bear in mind:

- Where *A systematic approach* lists three categories of criteria for comparing research options,[90] this guidance recommends four categories: probability of success, cost, magnitude of benefit, and impact on equity. The last two break "public health benefit" into two components in order to emphasize the importance of incorporating equity into judgments of social value from the outset.

A systematic approach	**This guidance**
Public health benefit	Magnitude of benefit
	Impact on equity
Feasibility	Probability of success
Cost	Cost

- As a document for WHO staff, not all of the recommendations in *A systematic approach* will apply in the same way to other actors involved in priority setting. For example, the ethical obligations concerning scope, the involvement of interested parties, and carrying out prioritized research vary from actor to actor.

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[90] Terry et al. 2020: 16.

CHAPTER 5. CASE STUDIES AND SCENARIOS

In this chapter, case studies and scenarios illustrate how the ethical principles can be applied by different decision-makers in different contexts.

The *case studies* describe real cases where priority setting decisions were made. In each case, the most relevant ethical principles are listed. This does not mean that the case demonstrates a perfect application of the principle in question. Rather, the case provides a good opportunity to reflect on the principle in a context, and to see how real-world actors, doing their best to set priorities fairly and effectively, might apply it under particular circumstances.

The *scenarios* are fictional, but are based on actual situations in which individuals or organizations may find themselves setting priorities (and where they can make implicit priority setting explicit). For these scenarios, recommendations are made for how the ethical principles should be applied.

Part 1. Case studies

Case	Priority setter	Level	Ethical principles
1. Developing a research agenda on climate change and health research in India: a proportionate approach to setting research priorities	Research organization	National	Optimize social value Follow fair procedures
2. Inclusion and shared decision-making in rural Eastern Uganda	Research partnership	Research project	Optimize social value Follow fair procedures (inclusion)
3. Putting priorities into practice – the James Lind Alliance Priority Setting Partnership on Type 2 Diabetes	Non-profit funder	National	Optimize social value (putting priorities into practice) Follow fair procedures (transparency, inclusion)
4. Engaging under-served groups in health research priority setting in Southeast Asia	Research programme	Multi-level	Optimize social value (equity), fair procedures (inclusion)
5. Setting national research priorities	[IN PREPARATION]		
6. Incorporating equity into the family planning research and learning agenda for Uganda	[IN PREPARATION]		

7. Optimizing social value research within a narrow scope – the Patient-Centered Outcomes Research Institute	
8. An international agenda for migration research	[IN PREPARATION]
9. Rapid Research Prioritization - Long COVID	[IN PREPARATION]
10. Informing a national research agenda for care improvement of hypertensive disorders of pregnancy in Ghana – a priority setting partnership	[IN PREPARATION]

Part 2. Scenarios

Scenario	**Priority setter**	**Level**	**Ethical principles**
1. Alternatives to animal models: the case of Rabbit Pyrogen Testing (RPT)	Research organization	Research program	Assess and justify harms
2. Choosing a lab	Individual scientist	Research program	Optimize social value
3. Designing the review process for investigator-initiated grant applications at a national funder	National funder	National	Optimize social value
4. Strategic planning for a philanthropic funder	International non-profit funder	International	Optimize social value, special obligations, assess and justify harms, fair procedures

Part 1. Case studies

Case 1. Developing a research agenda on climate change and health research in India: a proportionate approach to setting research priorities[91]

Ethical principle(s): Follow fair procedures, Optimise social value

Priority setter: Research organization

Level: National

Background:
India, the most populous country in the world and home to about 17% of humanity, is projected be one of the worst sufferers of climate change. The country is already experiencing an increased frequency and intensity of extreme weather events such as heatwaves, flooding, and drought, as well as high levels of air pollution. Overall, climate change is causing negative health consequences to individuals and communities. It is widely acknowledged that finding practical solutions to the health effects of climate change necessitates trans- and multi-disciplinary research. A national research agenda for climate change and health research in India is needed to guide this research.

The George Institute for Global Health, a research organization, committed resources for a five-member team to work part-time on this priority setting exercise for a period of 3-4 months. The team was provided limited internal resources to carry out the task. Its goal was a set of priorities that could be consulted by any researcher planning research on climate change and health in India.

Ethical issues:
There were two ethical issues which the project team grappled with in the initiation phase.

(1) **Choosing an appropriate methodological approach**. The available comprehensive systematic methodological approaches for health research priority setting (e.g., the Essential National Health Research strategy, the Child Health and Nutrition Research Initiative, or the James Lind Alliance framework) are resource intensive. They require substantial commitments of time, funding, and experiential learning around the methodology if they are to be carried out well. With no external funding, this was a challenge for the project team. However, following fair procedures (particularly being inclusive and transparent) is key to any research priority setting exercise. The team needed to find a way to do that with its limited time and resources.

(2) **Defining scope:** Setting the scope for research priority setting for climate and health research was challenging. How could the exercise balance the scientific need to understand the impact of climate change, together with the more urgent need for interventions to protect health from climate change, for adaptation and mitigation efforts, and the emergent need for policy, governance, and

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[91] Author: Soumyadeep Bhaumik (George Institute)

decision-making tools? A broader scope would mean that more resources would be required to act on the priorities. A narrower scope would potentially be a source of injustice as it would lead to the exclusion of one domain of research or another and so make it more likely that the needs of some populations would not make it onto the agenda.

Discussion:
The team thus had to develop a rapid low-cost bespoke and systematic approach to set research priorities. A decision was made to have a broader—and so more inclusive—scope. This meant accepting that not everything on the final research agenda would be carried out soon, but would be more just. They therefore aimed to develop a research agenda for the following categories:

1. Research on impact of climate change on health and disease.
2. Research on interventions to protect health from climate change.
3. Research on climate change adaptation and mitigation efforts.
4. Research on policy, governance, and decision-making tools.

The research priority setting exercise would be carried out in two phases:

Phase I. Systematic mapping of literature of research on climate and health and an online survey to collect additional research questions. The long list of questions was synthesized to create a list of research questions for the next phase. Anyone Indian could contribute questions. The team would use a snowballing approach to find respondents, reaching out through existing communication networks, including national committees, professional healthcare bodies, societies, newsletters, and patient and public engagement groups. Respondents were categorized as: (1) Researchers; (2) Healthcare workers or healthcare administrators, public health or climate practitioners, policy makers; and (3) General public, climate change and/or health advocates. Between 100 – 250 people would be involved.

Phase II. An online survey through which questions are rated for prioritization using a nine-point Likert Scale to develop the consensus research agenda. The same respondents could also take place in this ranking. Participants rate each question on a Likert scale of 1–9 wherein a rating of

- 1–3 corresponds to “research question of limited importance”.
- 4–6 to “important research question, but not critical”; and
- 7–9 to “research question of critical importance”

The broad scope aims to optimize social value by not excluding any topic which is of value to a key group of people. Among other things, an equity-focus was ensured by identifying the equity-related populations for which research questions were relevant. For example, instead of the question—“What strategies are used to relieve heat and cold stress and associated productivity losses?”, they would have— “What strategies do different groups (farmers, brick-kiln workers, delivery gig workers …) use to relieve heat and cold stress and associated productivity losses?”

The bespoke approach offers the benefit of being resource-efficient and includes members of all groups of people to whom the research is relevant – recognising that people ought to be involved in decisions which affect them.

While the process is transparent and inclusive, it does have limitations—in particular, those who do not know English or are not online will be excluded. While not perfect the bespoke approach tries to optimally balance involvement, given the limited time and resources for carrying out the priority setting exercise.

Questions for reflection:
1. From the perspective of justice, is it better to aim for a research agenda with many topics (so not excluding any group's needs) or with fewer (so focused on what is potentially most urgent or important)?
2. What are the pros and cons of having participants use a simple Likert scale for rating research questions?
3. If the institute running this exercise had more resources, should it spend them on expanding the exercise and including more participants, or should it save them for carrying out high-priority research?

Case 2. Inclusion and shared decision-making in rural Eastern Uganda[92]

Ethical principle(s): Follow fair procedures (Inclusion), Optimize social value.

Priority setter: Research partnership

Level: Research project

Background:
The *Maternal and Neonatal Implementation for Equitable Health Systems (MANIFEST) project* was conducted in rural Uganda by researchers at Makerere University between 2011 and 2016. The study was conducted in partnership with the Future Health Systems consortium. The overarching topic of maternal and neonatal health was selected through "a systematic review on access to health services in Uganda and a *consultative* meeting … where attendees included international- and national-level stakeholders".[93] The objective of the project was primarily to improve "access to quality maternal and neonatal health services in a sustainable manner."[94]

The MANIFEST project included two phases:

> (1) *Planning phase* to select specific research questions and design the intervention to be tested. This phase included consultations on a national, district, and subcounty level and was conducted using a Participatory Action Research approach.
>
> (2) *Implementation and monitoring phase*. The intervention that was tested focused on three areas identified during consultation: (i) community mobilization and sanitization; (ii) savings and transport; (iii) health systems strengthening,[95] with the goals of empowering the community's birth preparedness and building capacity for health providers.[96] Areas where the intervention was implemented were compared to a control area.

Shared decision-making by researchers at Makerere University and district health teams of the three districts participating in the project (Pallisa, Kibuku and Kamuli) informed both phases of the project, contributing to shaping the priorities of the project and its development.

Ethical issues:

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[92] Author: Enrico Galvagni (University of Edinburgh). Thanks to Bridget Pratt for comments on this case study.

[93] Pratt B, Hyder AA. "Linking Participatory Action Research on Health Systems to Justice in Global Health: A Case Study of the Maternal and Neonatal Implementation for Equitable Health Systems Project in Rural Uganda." *J Empir Res Hum Res Ethics*. 2018 Feb;13(1):74-87, pp. 77-78.

[94] Ekirapa-Kiracho E, Tetui M, Bua J, Muhumuza Kananura R, Waiswa P, Makumbi F, Atuyambe L, Ajeani J, George A, Mutebi A, Kakaire A, Namazzi G, Paina L, Namusoke Kiwanuka S. "Maternal and neonatal implementation for equitable systems. A study design paper." *Glob Health Action*. 2017 Aug; 10 (4), p. 7.

[95] MANIFEST Research Brief: Improving maternal and newborn health outcomes in Kamuli, Kibuku and Pallisa Districts in Eastern Uganda, p. 1. https://www.mnh.musph.ac.ug/wp-content/uploads/2016/10/0-MANIFEST-Research-Brief.pdf

[96] Ekirapa-Kiracho et al., 2017, pp. 10-11.

The study used a Participatory Action Research approach that "advocates for the partnership of researchers with the research subjects or communities."[97] The active engagement of community stakeholders was at the core of MANIFEST's design and its objectives. The intervention design of this project exemplifies the process of systematic inclusion of stakeholders at various stages of the project development.

MANIFEST's overarching topic of maternal and neonatal health was chosen not only on the basis of a review on Uganda health services but also through a consultative meeting with national and international stakeholders and a national workshop. The rural districts participating in the process were selected on the basis of two criteria. First, researchers wanted to avoid data duplication and therefore excluded the Western region of Uganda where the United States Agency for International Development (USAID) was developing research projects on maternal and neonatal health.[98] Second, researchers wanted to maximize the sustainability of successful interventions to make sure that any improvement in access and quality of maternal and neonatal health services would continue after the completion of the study.[99]

The intervention design of the project was also informed by substantive stakeholder inclusion, including a "two-phase process of consultation across three levels (national, district, and subcounty), lasting nearly 1 year, and shared decision-making by Makerere researchers and DHTs [district health teams]."[100] Several strategies were used to empower participants in these meetings. They included: "(a) dividing into small groups at meetings to discuss certain issues, (b) dividing vulnerable populations (e.g., teenage mothers and disabled women) into their own groups to discuss certain issues, (c) having DHT members lead meetings rather than Makerere researchers, (d) running meetings primarily in local languages rather than English, and (e) holding meetings at locations within the subcounty."[101] This led to an intervention that was designed to address barriers to accessing care as identified by community members.

The inclusion of stakeholders and communities remained an integral part of the project beyond the selection of topic and the planning phase. Interviews and focus groups were used during the implementation of the project "to collect data about the perceived quality of maternal and newborn services"[102] and ensure that the project development was aligned with the communities' priorities. The implementation and monitoring phase of project also included constant assistance of district health team members, to facilitate stakeholders' meetings at both district and subcounty level.[103] The post study intervention and research uptake plan included input from the Makerere team, the MANIFEST research protocol, stakeholder analysis, the initial project's national dissemination workshop, and community members.[104]

Discussion:

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[97] Ekirapa-Kiracho et al., 2017, p. 8.
[98] Pratt B & Hyder AA., 2018, p. 87.
[99] Pratt B & Hyder AA., 2018, pp. 79-80.
[100] Pratt B & Hyder AA., 2018, p. 78.
[101] Pratt B & Hyder AA., 2018, p. 79.
[102] Ekirapa-Kiracho et al., 2017, p. 13.
[103] Ekirapa-Kiracho et al., 2017, p. 13.
[104] Pratt B & Hyder AA., 2018, p. 80.

This case illustrates how research producers, research users, and research beneficiaries can be *included* at different stages of the development of a project and thereby contribute to shaping a project's priorities. A range of stakeholders were involved in the choice of area of intervention and the setting of research questions. Meanwhile, community members were included in designing the intervention and the implementation of the study. This shows how systematic inclusion can shape a project based on the community's needs. The project took steps towards non-elite participation by including members or representatives of disadvantaged groups (though, as with any priority setting process, inclusion requires strategies to manage power differences and promote equal voice, not just representation).

The case study also illustrates how the *optimization of social value* interacts with the principle of *following fair procedures.* The inclusion of stakeholders in the MANIFEST project augmented the project's equity and its probability of success, therefore contributing to the optimization of social value. Inclusion of stakeholders was key in identifying the research questions and in steering the project in its implementation and monitoring phase. Considerations of social value (including avoiding duplication of results and ensuring post-study sustainability) were used to decide in which districts the study would be carried out. Due to the need of harmonization with other existing projects and technical considerations of sustainability, stakeholder input was not collected to set the geographical scope of the project.

Questions for reflection:

1. Do you think that the process used to plan the MANIFEST project increased its social value? What evidence would tell us one way or the other?
2. What special obligations did the Makerere University researchers have and how should that affect their priority setting?
3. How early in the development and design of public health interventions should community members be involved?

Case 3. Putting priorities into practice – the James Lind Alliance Priority Setting Partnership on Type 2 Diabetes

Ethical principle(s): Optimize social value (putting priorities into practice), follow fair procedures (transparency, inclusion)

Priority setter: Non-profit funder

Level: National

Background:
The James Lind Alliance (JLA) is a non-profit organisation that brings together patients, carers and clinicians in Priority Setting Partnerships (PSPs) aiming to identify unanswered questions in a specific health-related domain and prioritize a top-ten list of research questions (see Chapter 4 for more details).

In 2015, Diabetes UK and the James Lind Alliance created a PSP with the aim of identifying priorities for future research on type 2 diabetes. A steering group composed of people affected by type 2 diabetes, carers, and health care professionals led the PSP. The process included the distribution of a questionnaire to over 70,000 people with type 2 diabetes, carers, and health care professionals asking for questions about type 2 diabetes that they would want to have answered. 2,588 individuals responded with 7,978 total questions. These were collated into 114 questions that were ranked by 1,506 individuals through another survey. A shortlist of the 24 most prioritised questions was created. Finally, representatives of people with type 2 diabetes, as well as carers and health care professionals from various backgrounds participated in a workshop facilitated by the James Lind Alliance where the top ten priority questions were chosen.[105] The priority list was published by Diabetes UK and JLA in 2017.[106]

Diabetes UK aimed to put the priorities into practice by explicitly encouraging the development of research projects that would fill a gap identified by the priority questions. A list of funded research projects with reference to the addressed priority questions is publicly available.[107]

Ethical issues:
The aim of JLA's PSPs is to identify research questions whose answers matter to those who are affected by a health condition. By excluding those who lack direct experience of the condition, they ensure that the voices of patients and carers are elevated. Patients and carers were part of the leadership team for the PSP and participants in the workshop were balanced so that health care

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[105] Finer, Sarah, et al. "Top ten research priorities for type 2 diabetes: results from the Diabetes UK-James Lind Alliance Priority Setting Partnership." *Lancet Diabetes and Endocrinology* 5.12 (2017).
[106] Diabetes UK and James Lind Alliance. *Your priorities for Type 2 diabetes research: The top 10* (2017). Available at:. https://www.diabetes.org.uk/resources-s3/2017-10/1196_PSP%20lay%20report_DIGITAL%20SPREADS.pdf
[107] James Lind Alliance. *Type 2 Diabetes PSP: working to address the priorities*. 16 June 2021. Available at: https://www.jla.nihr.ac.uk/news/type-2-diabetes-psp-working-to-address-the-priorities/27913

professionals would not dominate. The resulting top-ten list gives voice to thousands of people affected by type 2 diabetes, their carers, and those who treat them.

An important component of optimizing social value is ensuring that the priorities identified are acted upon. The collaboration between JLA and Diabetes UK made this more likely. Once the priority list had been generated, Diabetes UK had an obligation to fund research accordingly.

Discussion:

The James Lind Alliance PSP on type 2 diabetes allowed Diabetes UK to shape their priorities based on the needs and values of the community of people living with type 2 diabetes, their carers, and healthcare professionals. The method allowed people from these groups to give input at various stages of the priority setting process. This exemplifies one approach to appropriate *inclusion*.

The goals of the priority setting process are also served by *transparency* about the exercise and its outcomes. This allows those who might want to use the top-ten list to understand what it represents (i.e., questions that matter to patients and those who care for them, but not every important question relating to type 2 diabetes). It also provides a way to hold research funders—like Diabetes UK—accountable for whether they act on the priorities that have been identified.

Questions for reflection:

1. Does Diabetes UK have an obligation to act on the results of the PSP? What about other funders who support diabetes research?
2. Was the procedure used to choose the top-ten list fair? What would make it more fair?
3. Does this prioritization process follow the ethical principle of *optimizing social value*?

Case 4. Engaging under-served groups in health research priority setting in Southeast Asia[108]

Ethical principle(s): Optimize social value (equity), fair procedures (inclusion)

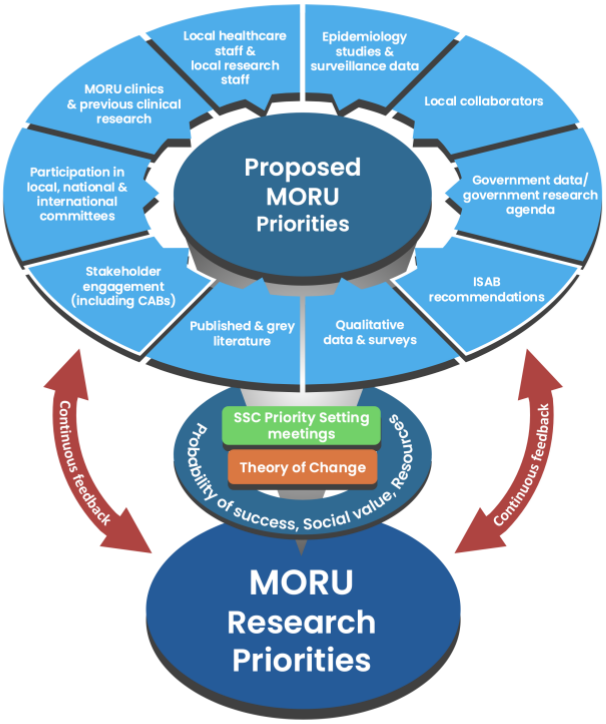
Priority setter: Research programme

Level: Multi-level

Background:
The Mahidol Oxford Tropical Medicine Research Unit (MORU), established in 1979, is an international research programme within the Nuffield Department of Medicine at the University of Oxford, with its administrative hub in Bangkok.

MORU has two levels of priority setting. It sets health research priorities for the network at the thematic level every 5 to 7 years. In addition, the Science and Strategy Committee (SSC) makes priority setting decisions at the project level through monthly meetings. This continuous process of priority setting is shaped by a combination of community engagement, research data, collaborative networks and other activities (Figure 3).

Figure 3. MORU's continuous priority setting process (figure by Kanpong Boonthaworn)



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[108] Author: Phaik Yeong Cheah (Oxford University).

Our deep-rooted relationships with local communities through clinics and healthcare services offer insights into their health needs. Collaborations with local health institutions and partners ensure our work aligns with national health goals and addresses specific local challenges. Additionally, participation in agenda-setting committees and guidance from an Independent Scientific Advisory Board (ISAB) help align our research with broader health policies regionally and globally.

We manage a network of six community advisory boards representing under-served communities (e.g. ethnic minority groups, hill tribe communities, migrants) and regularly consult them, along with other community groups. Our oldest advisory board, the Tak Province Community Ethics Advisory Board which has members from Karen migrant communities, has been active for more than 15 years. These regular meetings ensure that the perspectives and needs of under-served populations are integrated into our research planning and prioritization. By engaging with the advisory boards, we identify health needs that may not be apparent from existing data or other priority-setting processes, such as those conducted by governments.

In September 2023, we began a formal priority-setting exercise at the thematic level for the period from October 2025 to September 2032. The results of this process will guide our core funding application to support the MORU core research team and essential infrastructure.

Our goal in this exercise is a portfolio of research that will maximize health benefits while reducing inequities for the most disadvantaged groups, such as children at risk of severe malaria and under-served communities like migrants and hill tribe communities. We aim to balance international, national, and local needs. Our research has global impacts, including contributions to malaria elimination and new antimalarial development, and plays a key role in fulfilling national research agendas in Laos and under-served areas on the Thai-Myanmar border and in Chiang Rai.

A series of workshops were held among the SSC members between September 2023 and October 2024. The SSC firstly determined the criteria for setting research themes: local, national, and international needs; MORU's expertise; availability and capabilities of research networks MORU is part of; availability of research infrastructure; previous collaborations; continuity of research; and competitive edge.

Using these criteria, the SSC decided on the MORU mission and aims. Our overarching mission is to conduct research to improve the health and wellbeing of people in low-resource settings. We chose to focus on low-resource settings because global challenges such as climate change, antimicrobial resistance, pandemics and conflicts disproportionately communities living in low-resource settings. These settings often face the greatest health disparities and require targeted research to address their unique needs. The four aims that fit with the overarching mission were:

1. Identify, characterise and address infectious disease burdens through research
2. Improve pregnancy outcomes and child health through research
3. Increase the public health impact of our research
4. Strengthen our research culture and research capacity

Special consultations with under-served communities

To maximise equity for our research agenda for 2025-2032, we are conducting special consultations with under-served communities from October 2024 to September 2025. We define under-served communities based on the UK National Institute for Health Research criteria, which describes them as groups less represented in research despite their health needs.[109]

We envisage that results of this project will be used in two different ways. Firstly, they are intended to contribute to our project-level priority setting by identifying health needs that are not obvious from existing data sources or other sources. Secondly, our experience of engaging with these groups will serve as a case study of how such engagement can be conducted and what challenges it may bring.

Ethical issues:
Engaging with under-served communities presents several challenges. There is low health and health research literacy. Power hierarchies can affect interactions, making it crucial to approach discussions sensitively. Managing expectations is important to ensure that community members do not anticipate outcomes beyond what is feasible. Asking questions in a culturally appropriate manner is essential. Not all under-served communities can be identified or included in research.

Discussion:
Our starting point is our community advisory boards and other existing community groups.[110] They are familiar with us and can provide honest feedback. They have some background on health research. The group members know each other and are used to providing feedback to researchers. These groups also serve as a conduit for ongoing interaction, rather than relying on one-off consultations. This allows members time to reflect on our questions. While these individuals may not represent their entire communities, they often reflect common concerns. They may also be able to point us to other under-served communities.

Facilitators for these special consultations are experienced in engaging with under-reached groups. They will be supported by local facilitators familiar with the participants' culture and languages. This ensures that participants can freely express their views in their native tongue, making them feel more comfortable and open during discussions.

"Priority setting" may not be well translated in local languages. We will instead use the term "health challenges" or "health needs". We frame questions in a way that encourages participants to think about the future. For example, we might ask, "What health challenges do you think your children might encounter when they reach school age?"

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[109] National Institute for Health and Care Research. *Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project*. 07 August 2020. Available at: https://www.nihr.ac.uk/improving-inclusion-under-served-groups-clinical-research-guidance-include-project

[110] Cheah PY, Lwin KM, Phaiphun L, et al. Community engagement on the Thai-Burmese border: rationale, experience and lessons learnt. *Int Health* 2010; 2(2): 123-9; Ean M, Tripura R, Sothea P, et al. A youth advisory group on health and health research in rural Cambodia. *Glob Bioeth* 2024; 35(1): 2361968; Tolppa T, Hussaini A, Ahmed N, et al. Establishment of a patient and public involvement and engagement group to support clinical trials in Pakistan: Initial lessons learned. *Res Involv Engagem* 2024; 10(1): 98

Good facilitation is necessary, especially when working with languages that lack written forms and official recognition such as hill tribe languages in northern Thailand, making it challenging to find qualified translators. For example, the cultural concept of “krengjai” and “arnar” (consideration for others to the point of self-sacrifice) in Thailand and Myanmar can complicate open communication.[111] Additionally, health issues are often intertwined with other concerns, such as education and agriculture, making it difficult to separate them.

We may also use participatory visual methods to enrich the discussions and allow participants who prefer to express themselves using visual methods.

Questions for reflection:

1. Given limitations on how much our research group can achieve, how do we manage expectations when engaging with under-reached communities about their health needs?
2. Given that we have limitations in terms of time and resources, to what extent should we try to reach under-served communities during priority setting?

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[111] Khirikoekkong N, Asarath SA, Nosten S, et al. Culturally responsive research ethics: How the socio-ethical norms of Arr-nar/Kreng-jai inform research participation at the Thai-Myanmar border. *PLOS Glob Public Health* 2023; 3(5): e0001875.

Part 2. Scenarios

These fictional, but realistic examples have been written to illustrate how this ethics guidance should be applied to some common and important decision-making scenarios.

Scenario 1. Alternatives to animal models: the case of Rabbit Pyrogen Testing (RPT)[112]

Ethical principle(s): Minimize and justify harms

Priority setter: Research organization

Level: Research program

Background:
Rabbit Pyrogen Testing (RPT) is a popular in vivo method for the detection of fever-producing substances, consisting of injecting multiple doses of a testing solution in rabbits' ear veins and monitoring their body temperature via rectal probe. As most countries and markets require parenteral drugs and vaccines to be tested for pyrogens, the RPT is a common and widespread test. RPT causes considerable suffering to the animal subjects, including restriction, distress, and pain. It often concludes with their euthanasia.[113] These harms, together with the existence of effective in vitro alternatives, generate important ethical objections to RPT.

The monocyte activation test (MAT) is an alternative to RPT consisting of the use of cryopreserved human peripheral blood mononuclear cells to detect the presence of pyrogens in a compound. This method uses human monocytes which have toll-like receptor more relevant to detect human pyrogenicity than the alternative RPT options. MAT's validity has been evidenced in recent studies.[114] Given the existing infrastructures and trained personnel, however, the current use of MAT is often more burdensome in the short run than RPT due to its costs as well as a lack of knowledge and training to use MAT.[115] As of 2023 more than 25,000 rabbits are still used every year for RPT in the Europe Union alone.[116]

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[112] Author: Enrico Galvagni (University of Edinburgh). Thanks to Elliott Lilley for comments on this case study write-up

[113] Animals (Scientific Procedures) Act 1986. Available at: https://assets.publishing.service.gov.uk/media/5a8064dbed915d74e33fa2c7/Vol_3_Regulatory_use_or_toxicity.pdf

[114] E.g., C.L.A. Utescher, K.L. Buosi, V.F. Botosso, et al. Monocyte activation test (MAT) as a possibility of replacement for the rabbit pyrogen test in hyperimmune sera Braz. J. Pharm. Sci., 54 (2018), Article e17530.

[115] Mozier, N. (2019). MAT as a Developmental Pyrogen Test Tool. In: Williams, K. (eds) Endotoxin Detection and Control in Pharma, Limulus, and Mammalian Systems. Springer, Cham. https://doi.org/10.1007/978-3-030-17148-3_15.

[116] G. Cirefice, K. Schütte, I. Spreitzer, E. Charton, S. Shaid, L. Viviani, M. Rubbrecht, I. Manou The future of pyrogenicity testing: phasing out the rabbit pyrogen test. A meeting report Biologicals, 84 (2023), Article 101702, 10.1016/j.biologicals.2023.101702

Scenario:

A senior pharmacologist employed in a prominent research institution has secured a grant to investigate new anti-inflammatory compounds. She now faces a choice between designing two different sets of experiments to test the efficacy and safety of the new compounds. Experimental design A evaluates these features by using RPT, while experiment design B does so by using MAT. Given the existing infrastructure in the scientist's lab, option A can be carried out without needing to train any additional personnel. Option B has up-front costs and requires new training, as well as sourcing the equipment and components for the new test. The pharmacologist estimates that this will result in the testing costing 30% more and taking 6 additional months to complete. This is time and money that could be spent on additional pre-clinical experiments exploring the properties of the new compounds. On the other hand, option A requires substantial exploitation of non-human animals, while option B can be carried out fully in vitro. Since the pyrogen tests used in developing the drugs are likely to be those that are then used for batch-testing approved product, this decision will also have ramifications for resource use and harm to non-human animals further down the line.

Ethical issues and discussion:

If there were no alternative to RPT, it might be possible to justify its use. Whether its use would be justified for this specific research program would depend on the number of rabbits harmed, how badly they were harmed, and the social value of the research program. Only if the harms were necessary and the social value of the research sufficiently high would it be ethically acceptable.

In this scenario there is an alternative to RPT, but it is more expensive and more time-consuming. Could the extra cost and time justify not using MAT?

It is hard to say that the extra cost and time is so substantial that using RPT rather than MAT is *necessary*. After all, much greater additional costs and delays are imposed in order to protect human participants from smaller risks of harm. Studies like this one should use in vitro methods even when the costs of doing so are somewhat higher than in vivo alternatives.

In certain countries or regions, MAT is unavailable either because human blood products cannot be used for commercial purposes or because MAT is not part of the national pharmacopeia. In these cases, an individual research group would have to weigh the potential benefits of the study against the non-negligible harm to non-human animals before deciding which research project to conduct.

Questions for reflection:

1. In what sense is the pharmacologist engaged in *priority setting*, when she chooses whether to use RPT or MAT?
2. If there were no alternative to RPT, should the experiments go ahead?
3. Should funders take the use of non-human animal subjects into account when they are deciding which grant applications to support?

Scenario 2. Choosing a lab[117]

Ethical principle(s): Optimize social value

Priority setter: Individual scientist

Level: Research program

Background:

Many researchers are skeptical of the proposition that researchers can, a priori, identify more socially valuable basic science research. There is good reason for this skepticism: often, basic science does not yield practical benefits for decades, and the clinical (and other) implications of scientific research can be hard to predict. For instance, Osamu Shimomura was studying bioluminescent jellyfish when he discovered green fluorescent protein. Green fluorescent protein had little scientific import for the next 30 years, but has since proven invaluable in microbiology research, allowing researchers to visualize intracellular processes and thereby paving the way for breakthroughs in HIV, cancer, neuroscience, and other kinds of research.[118]

However, while it is often difficult identifying more socially valuable projects, it is not impossible. Often, motivated researchers can identify more socially valuable projects, even in the basic sciences.

Scenario:

In high school, Sarah excelled in her science classes, and she became interested in pursuing a career as a scientist. When she was 17, her father survived a heart attack, and she decided to focus on developing novel treatments for heart disease, which she knew was also the leading cause of death worldwide. When she started college, she applied to join many labs. Two professors offered her positions, but only one worked on heart disease research, so she joined that lab. The lab focused on developing monoclonal antibodies to reduce inflammation, thereby preventing the development of atherosclerotic plaques.

Sarah enjoyed being a scientist—she liked the day-to-day tasks of her research, and the lab had a healthy culture, where members prioritized teaching and assisting with each other’s projects. During her senior year, she was thrilled when a manuscript based on a project she had assisted with was accepted to a top cardiology journal. But as she prepared her applications to PhD programs, and drafted essays about the research she hoped to pursue over the next six years, cognitive dissonance began to creep in.

On the one hand, it would be easy for her to continue doing the kind of research she had already been doing: she had developed relationships with researchers working on inflammation and coronary artery disease, was familiar with ongoing work in the field, and had developed a strong background in the relevant science and lab techniques. On the other hand, she had become

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[117] Author: Leah Pierson (Harvard University).

[118] https://www.nobelprize.org/uploads/2018/06/shimomura_lecture.pdf

increasingly skeptical about the clinical relevance of the lab's work: while the therapies they were studying had shown some promise in mice, she did not have a lot of faith in their mouse models. Their mice developed severe, diffuse coronary artery disease practically in utero, rather than in old age, rendering their disease very different from the coronary artery disease humans develop. Making matters worse, she knew the anti-inflammatory drugs they were developing would be astronomically expensive if they ever made it to market, rendering them inaccessible to most patients. If the findings in mice held up, they were also likely to have a substantial side-effect profile—including a higher risk of infectious disease and cancer—which would make them less appealing as prophylactic treatments. (She suspected that it was for these reasons that pharmaceutical companies had shown little interest in supporting the lab's work.)

When she began her PhD, she decided to work in a lab focusing on cardiovascular disease related to inflammation, but prioritizing projects that struck her as more scientifically relevant, clinically useful, and liable to have a significant public health impact. Rather than working to develop novel monoclonal antibodies, the new lab was studying the anti-inflammatory properties of statins—cheap, widely available drugs. The mouse models they used in the lab had been used for years, and several successful anti-inflammatory drugs had been developed using these models. She believed that her research would help cast light on the fact that patients experiencing chronic inflammation (due to, for instance, smoking or other diseases) would benefit from statins, even if they did not have high cholesterol. This, she suspected, would both illuminate inflammation as an important but underappreciated contributor to atherosclerotic disease and help broaden the indications for statins, potentially preventing heart disease in hundreds of millions of people.

Ethical issues and discussion:

In the above scenario, Sarah faced an ethical choice that involved a trade-off: she could choose to continue working in the same research area (which would be easier and more comfortable) or move into a related, but new area (which would be more difficult but would allow her to do more socially valuable work). Specifically, while working in the statin lab would require her to make new connections and familiarize herself with a somewhat different area of research, making this shift would allow her to conduct research that is more socially valuable, in that it: (1) has a higher chance of providing benefits, (2) would benefit larger numbers of people, (3) would provide more significant benefits to each, and (4) would aid disadvantaged populations.

Of course, her prediction that the statin lab is doing more socially valuable work could be incorrect, but Sarah's hypothesis that the lab studying statins will, *in expectation*, do more to improve population health seems reasonable. Many researchers find themselves in similar situations—where there is a divergence between doing what is easy and doing what is socially valuable—at points in their careers. In these scenarios, it is tempting to try to justify doing the easy thing by invoking cases like Shimomura's, where research that few might have predicted would become socially valuable did. But this guidance recommends that researchers should aim to prioritize research that has higher expected social value when feasible.

Questions for reflection:

1. Should individual try to optimize social value, like Sarah does, or should they trust that funders and governments will set priorities at a system-wide level?

2. How, if at all, is Sarah's personal experience with heart disease relevant to her decisions about research?
3. Is there anyone Sarah ought to consult when making her decisions about what research questions to focus on?

Scenario 3. Designing the review process for investigator-initiated grant applications at a national funder

Ethical principle(s): Optimize social value

Priority setter: National funder

Level: National

Background:
The medical research council (MRC) of a middle-income country has been asked to evaluate its process for funding investigator-initiated proposals. Currently, broad priority themes for the country are identified by a national committee every five years. These are based on an assessment of several factors, including the national burden of disease and the health needs of disadvantaged populations. Priorities for the present five-year cycle include HIV/AIDS and tuberculosis, maternal and child health, non-communicable diseases, and mental health, among several others. Investigator-initiated grants are eligible for funding provided that they are relevant to one of the priority themes. Eligible grant proposals then go through peer review by a panel of scientists with relevant expertise. The highest scoring proposals are then funded in order until available funds are exhausted. The MRC allocates about 50% of its funding through these investigator-initiated grants.

The current review criteria for investigator-initiated grants are:

- The scientific rigor and feasibility of the planned research
- The qualifications and track record of the applicants
- The suitability of the host institution
- How innovative the research is
- The significance of the research in terms of advancing science or changing practice

These criteria are specified in more detail in the guidelines for reviewers who are asked to score each proposal on each criterion.

Scenario:
The process for determining broad priority themes at the national level is fixed by legislation that the MRC does not have the power to change. However, it is free to consider different approaches to grant funding, including making calls for applications much more targeted, changing the review criteria, and changing the composition of the review panel.

A survey of researchers, clinicians, and community advocates has suggested pros and cons of the current system. On the one hand, it is perceived as being flexible and not excessively directive. Researchers are free to identify opportunities and pursue scientific ideas without being controlled by government bureaucrats who do not understand the science. On the other hand, the degree of autonomy means that the research that is funded does not always respond to the health problems of those with the greatest needs. For example, very little research is funded on mental health despite its high disease burden, and some clinicians and advocates perceive a bias in favor of new biomedical interventions and away from public health and behavioral research.

Ethical issues and discussion:

Researchers are often better placed to identify scientific opportunities than policy makers. This can lead to socially valuable research projects that would not have been carried out if research decisions were all made in a top-down manner. The flexibility of having investigator-initiated proposals can be maintained in this case by preserving the two-step process of requiring research proposals to fall under broad priority themes and then subjecting those proposals to review.

However, the current peer review criteria could be amended in order to make it more likely that applying them will optimize the social value of research supported by the MRC. Comparing the peer review criteria to the components of social value suggests that proposals are primarily being reviewed against probability, not against the other components. For example, assessing the scientific rigor and feasibility is a way to assess whether the research is likely to be completed and to lead to generalizable knowledge if it does. Looking at the track record of the applicants and the host institution likewise will primarily give evidence about whether they will be able to carry out the research they are planning. “Innovation” and “significance” might get at other aspects of social value, but it depends on exactly how they are interpreted.

The peer review criteria should therefore be amended so that the magnitude of benefit, the equity impact of research, and the costs of projects are also considered. This might involve asking ask reviewers to consider questions such as:

- How prevalent is the condition or conditions targeted by the research and how bad are they for patients?
- If the research project were successful, what benefits would be likely to result?
- Are the populations who would benefit disadvantaged in some way?
- Given the importance of the knowledge gained, is the cost of the proposed research reasonable?

The exact form of the additional criteria and the guiding questions used in scoring against them would need to be specified differently depending on the types of research a review panel was assessing (e.g., public health research, clinical research, bench science, or a mix of types).

Two further issues are worth considering. First, the review panels are currently comprised of scientists. Should patients, clinicians, or other non-scientists be included? The answer to this question depends on whether adding non-scientists would add sources of knowledge that the existing review panels lack (e.g., that having patients or clinicians involved will actually lead to research that is more relevant to patients). It would be worth piloting different ways to compose the peer review panels to see whether the process and results are thereby improved.

Second, improving the criteria used to review individual proposals will not address problems with the imbalance of funding across different thematic areas, such as the low funding directed to mental health. There are different ways to address this problem. One would be to apportion funding to each broad thematic area. Naturally, this would lose some of the value gained by having such flexibility for investigator-initiated grant proposals. An alternative would be to weight the scores given to proposals so that projects on more neglected themes would get higher scores than those that are already well-covered. Either way, solving this problem would require having some sense of what the overall portfolio should look like (e.g., that it should average out over time to reflect the national disease burden).

Questions for reflection:

1. The discussion above suggests adding criteria for reviewing grants so that the magnitude of benefits and the potential equity impact of research are explicitly considered. What are the pros and cons of adding criteria in this way, rather than just having reviewers focus on the quality of the science?
2. Is it inequitable if this funder's spending on mental health research is not proportionate to the burden of disease caused by mental health conditions?
3. Should patients, clinicians, or other non-scientists be included on review panels? Would it be better to just make sure that the scientists on the panels were suitably diverse in terms of expertise and discipline?

Scenario 4. Strategic planning for a philanthropic funder

Ethical principle(s): Optimize social value, special obligations, assess and justify harms, fair procedures

Priority setter: International non-profit funder

Level: International

Background:

Many research funding organizations undertake periodic strategic planning exercises. Among other organization-level changes, strategic planning presents an opportunity to rethink what they fund and how. In other words, it is an opportunity for priority setting. Typically, the research priority setting involved in strategic planning is *thematic*, rather than *project-level*. It involves activities such as identifying broad research areas that will be priorities, designing funding programs, and rebalancing support across different areas. It does not generally involve granular decisions about specific research studies.

There are many different types of funder with different mandates and organizational structures. For example, a national governmental funding agency is very different from a philanthropy. The scope and nature of funders' strategic planning exercises will also be varied. Nevertheless, the ethical principles for health research priority setting can provide a structure for thinking systematically through the process.

Scenario:

A medium-sized philanthropic health research funder based in a high-income country is starting its strategic planning process. The organization is funded by a mix of donors, including individuals and private foundations. It has an annual budget of approximately US$100 million, of which about 80% is distributed to outside researchers who apply for multi-year grants. The funder's mission statement directs it to apply the best science to alleviate the burden of infectious diseases in LMICs.

Strategic plans cover five-year periods. The next is due to go into effect in just over a year's time. Previously, the funder's priorities have been largely based on recommendations from board members—a group comprising distinguished academics and other experts in global health—who advise the director of the organization. He and other members of the management team have the final say. Recently, the organization has been criticized for letting its strategic direction be dictated by an "old boys' club" and failing to reflect "equity concerns." The board has therefore asked for advice on how to design the process to explicitly and systematically take ethical considerations into account.

The team assigned to design the strategic planning exercise look at the previous strategic plan, the structure of the organization, the current portfolio, and existing processes for decision-making. Their report back to the board will provide an overview of what an ethics-informed strategic planning process might look like—in terms of how big-picture themes should be identified and in terms of how the process and criteria for investigator-initiated grant applications might be revised. The exact details will be filled in once this is approved by the board.

Ethical issues:

1. Scope. The team starts with the funder's special obligations, since those will determine the scope of possible research priorities. The organization is funded by donors on the understanding that it will pursue its mission, so that limits the scope. All research should be relevant to infectious diseases that affect populations in LMICs. Beyond that they recommend leaving the scope as open as possible, so as not to rule out potentially valuable areas of research a priori.

2. Social value. The funder should be setting priorities with the aim of maximizing the social value of the research it supports consistent with its other obligations (in particular, consistent with its mission to support infectious disease research for LMICs). The team identify the following strategic opportunities to improve the social value of the funder's portfolio:

a. The funder's current high-level priority themes are not aligned with the global burden of infectious disease and do not seem to reflect what other funders are doing. Not taking the prevalence and severity of different diseases into account makes it less likely that the research supported will have the greatest impact on health. Not taking the funding portfolios of other funders into account means that some diseases and types of intervention are likely to get disproportionate funding; plus, duplication is likely. In both cases, some adjustment is needed to ensure that the broad priority themes are the most socially valuable possible. Priority setting should aim to identify priority themes that respond to the burden of disease (with special emphasis on those diseases that are worst for patients and affect people who are worst off), while identifying gaps not filled by other funders.

b. The criteria used to score grant applications direct reviewers to mostly focus on the quality of the science and the capacity of the applicant and their institution to complete what they propose. This means that the funder's untargeted funding ("response-mode funding") is mostly considering one component of social value (i.e., probability of success) and mostly ignoring the others (i.e., the magnitude of benefit and the impact on equity). Both the scoring criteria and the weighting of scores might be reconsidered in the light of optimizing social value (see *Scenario 3. Designing the review process for investigator-initiated grant applications*).

c. Currently, grant applications have to be led by a principal investigator (PI) from the high-income country in which the organization is based. LMIC researchers can be included only as co-PIs. There is a risk that this arrangement limits the extent to which proposed studies respond to local needs, since local investigators are more likely to have insight into what is needed in their context and what patients, clinicians, and community members want. This restriction should be reconsidered. A further advantage of allowing LMIC researchers to be PIs is that this will help build local research capacity, with knock-on effects for more socially valuable research in the future.

3. Unjustified harms. For most of the existing portfolio, there is a low chance of third-party harms. Two areas stand out:

a. The organization has supported—and may support in the future—lab work with viruses and bacteria of zoonotic potential. These should be examined to ascertain whether they are justified, necessary, and whether the review processes in place are adequate to evaluate safety precautions. A higher bar for funding such projects in terms of their expected social value might be required than for other investigator-initiated research.

b. Over the last decade, there have been considerable advances in developing alternatives to animal models for screening and safety testing of potential drugs. Given this, support for non-human animal research should be comprehensively re-evaluated to decide whether (and when) it should still be supported. The strategic planning process is an opportunity to reflect on the criteria that are being used for approving non-human animal research proposals.

4. Fair procedures. A process needs to be put in place to generate options for possible priority research themes and to then prioritize among those options. Decisions about this process should consider:

- Who to include in the process of generating options? In order to generate a wide range of possible priority areas, ask members of each of the core constituencies: research producers (scientists), users (clinicians, public health workers), and beneficiaries (patients, communities).
- Who to include in the process of prioritizing among the options? In addition to asking those with relevant knowledge (epistemic reasons), there are also pragmatic and intrinsic reasons to include representatives from national bodies (e.g., medical research councils, ministries of health), and from communities and patient groups. This can help to get local buy-in, hear diverse perspectives, and provide a check that the prioritized options are genuinely responsive to the needs of LMIC populations.
- How to generate the criteria for prioritizing among the options? The criteria should facilitate assessing: whether a proposed theme falls within scope; the relative social value

of prioritizing that theme over others (as discussed above); and, potentially, whether there are concerns about unjustified harms.

- Given time and resource constraints, plus the fact that this is a funder-level exercise not for a specific country or population, the team does not propose implementing one of the existing comprehensive methods. Use of a Delphi process could be considered, provided that it includes all the relevant parties. Likewise, since the funder supports infectious disease research all round the world, an in-person meeting in an LMIC may not be required. Conducting an in-person workshop to prioritize among the options is one alternative; but another could be one or more online meetings. The latter could potentially include a wider range of participants who are more geographically dispersed.
- Everything should be documented and the priorities and how they were reached published online and disseminated to the groups directly affected by them.

Many details remain to be filled in and consideration given to what resources can be devoted to strategic planning. However, if the funder is guided by these points, its strategic planning will be able to incorporate the ethical considerations that matter, it will be based on defensible principles and good data, and it will be equitable in process and substance.

Questions for reflection:

1. What differences are there between thematic and project-level priority setting exercises when it comes to optimizing the social value of research?

2. If a priority setting exercise is global, so there is not a specific patient population or community already identified, what should inclusion look like?

3. Should philanthropic funders aim to follow national research priorities or to fund research that governments cannot or will not support?

CHAPTER 6. FREQUENTLY ASKED QUESTIONS

Ethical principles

- What should we do when the ethical principles conflict?
    - Sometimes the ethical principles will all point in the same direction; but often they may appear to conflict. For example, the research project that has the greatest expected benefit may not be the one that would most improve equity in a population. The components of social value must then be weighed against each other. Or, one research project might have greater social value globally, while another would provide greater benefits to a funder's national population. The obligation to optimize social value would then have to be balanced with the funder's special obligations. As always in ethics, there is no formula and reasonable people may disagree about the relative importance of different principles. Working out how to balance different considerations will rely on the good judgment of those involved. Trade-offs between important values should be made on the basis of justifiable reasons. More important decisions about trade-offs should be documented and transparently reported.

- What if participants in a priority setting exercise raise ethical considerations that are not mentioned in the guidance?
    - This guidance provides a framework for incorporating ethics into research priority setting, but it does not claim to be comprehensive or to cover all situations. The ethical principles described in this document will always need to be specified and interpreted for the particular context of a priority setting exercise. Further, it is always possible that additional ethical considerations might be raised that apply to one's specific context. If participants in an exercise agree that there are additional relevant ethical considerations, the process should be designed so as to take them into account

- How can research priority setting promote global justice?
    - The vast inequalities in the world will not be rectified simply through better priority setting. Nevertheless, setting research priorities explicitly, in a systematic way, and guided by the ethical principles described in this guidance should help to align the health research that is conducted towards the promotion of global

justice. If priorities are set ethically and those priorities are followed, they should promote social value. Since social value combines concern for improving population well-being and equity, aiming at social value entails aiming at social justice.

- Are these principles different than those found in other WHO guidance documents? Why the inconsistency?
    - Depending on the specific topic, guidance documents may emphasize different ethical principles or organize them in different ways. It is not expected that the ethical principles laid out in this document are *inconsistent* with those that WHO states elsewhere. Nor are the principles in this guidance radical (though the implications for research if they are put into practice might be dramatic). They are synthesized from widely accepted frameworks for setting priorities in health care and research, as well as for research ethics.

Social value

- Does research priority setting mean there is no place for curiosity-driven research? Will research priority setting kill innovation?
    - Many important scientific discoveries appear to have been driven mainly by curiosity about how the world works, rather than purely instrumental thinking. At the same time, a great deal of research, especially health research, is goal-directed: that fact is reflected in the way that our current health technologies reflect our health needs. The correct balance to strike between these two is itself a difficult and important research question.[119] At the very least, priority setting should allow space for curiosity-driven research insofar as there is evidence such research will lead to valuable discoveries—i.e., insofar as letting scientists follow their interests is likely to ultimately promote valuable goals.

      Note that there is a separate question concerning how far decisions about research projects should be driven from the top-down or the bottom-up. When funders decide what studies should be carried out and then look for scientists to carry out those studies, or when they specify criteria for grants very narrowly, this is top-down decision-making (or "strategic funding"). When funders provide support to researchers but leave it up to them what to investigate, or when they leave the eligibility criteria for grants very open, this is bottom-up decision-making (or "response mode funding"). Whether one way of making research decisions leads to more valuable research in the long-term is an open question.

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[119] Institute for Progress. Metascience. 2024. Available at: https://ifp.org/category/metascience/.

- The social value of basic biomedical research is often not apparent or is hard to determine. Does it mean that it should be de-prioritized?
    - It is undeniable that basic biomedical research has led to many scientific breakthroughs that have been vitally important to improving human health (so some has very high social value). It is also true that we cannot predict the exact direction of scientific progress (so it is hard to estimate the social value of specific projects). Because the ultimate effects of basic biomedical research are so hard to determine, estimates of the social value of basic science projects are more uncertain—that is, they have a wider margin of error. But that does not mean that this type of research has lower social value.

      This guidance encourages efforts to prioritize among basic science projects on the basis of social value, *insofar as that is possible*. Suggestions for how to do so can be found in Appendix 3. More research is needed on how to prioritize among basic science projects, as well as how to balance research portfolios between basic and more applied science.

- What does research priority setting mean for humanities and social sciences?
    - Where they are not competing for the same resources as health researchers, the question of how to justify humanities or social sciences research funding or prioritize among projects is outside the remit of this guidance. However, where research projects in the humanities and social sciences are competing for the same limited funds for *health research*, they should be judged by the same broad criteria as other health research. Some social science projects have a greater prospect of ultimately leading to social benefits than others. To some extent this is predictable. Likewise, with health research in the humanities.

- Does the "Optimize social value" principle rule out research on rare diseases?
    - Rare disease research presents a challenging case for research priority setting. All else equal, the social value of developing (e.g.) a new, accessible cure for a common disease is greater than the value of developing one for a rare disease. In this regard prevalence is relevant to social value and more common diseases would get higher priority. However, there are several circumstances in which it may be reasonable to include rare diseases in priority lists. These include:
        - A condition may be underfunded even given its rarity because of the amount of funding going into more common diseases from other funders.
        - A condition may be very bad for individual patients. This is true of a number of rare congenital conditions. There will be equity reasons to

    prioritize such diseases, as well as reasons based on the magnitude of the potential benefit from a transformative treatment or prevention modality.
    - Rare diseases are themselves common, affecting an estimated 300 million people worldwide.[120] Research on rare diseases may have the prospect of benefiting many patients if it focuses on features that are common to multiple rare diseases or if information gained about one disease is likely to be valuable for learning about other diseases (e.g., the research focuses on improving the diagnostic journey or treating symptoms shared by multiple rare diseases).

- Is building research capacity a component of social value?
  - It is relatively common for those funding and those carrying out research to also support capacity building, e.g., through training technical staff and future researchers. The primary value of this capacity building is that in the long run it will lead to more high-quality research being conducted, which will promote social value. Where priority setters are deciding what resources to expend on carrying out research versus building capacity they are making a decision about the allocation of scarce resources. In such cases, it makes sense to include building capacity among the options to prioritize and treat it as a source of social value.

Inclusion

- Who should I include in my priority setting exercise?
  - Inclusion should be guided by reflection on the epistemic, pragmatic, and intrinsic reasons for including different groups (Chapter 2, Principle 4; Chapter 3, Activities 1d, 1e, 1f). Special consideration should be given to including members of groups to which the priority setter is *accountable.* In addition, it may be valuable to think through categories of potential participants: research producers, research users, and research beneficiaries.

- How should I engage stakeholders who don't have the relevant knowledge to understand the research topic?
  - Priority setting exercises typically involve some learning for all participants, so that they understand the methods and goals of the exercise, as well as any necessary technical information. Some participants may be less familiar with health research or with the underlying science than others. There is a substantial

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[120] Baynam, Gareth, et al. "Global health for rare diseases through primary care." *The Lancet Global Health* 12.7 (2024): e1192-e1199.

    literature on best practices for patient and community engagement in research[121] and a wide range of ways in which interested parties can be involved in research priority setting.[122] See, also, Appendix 2.

- I don't have enough time and resources to allow all the relevant interested parties to take part in the exercise. Does it mean that my results will not be valid?
    - All priority setting exercises are constrained to some extent by limited time and resources. This does not invalidate the results. Even if it is limited, a good-faith effort to systematically and ethically set explicit priorities will lead to better decisions than no priority setting exercise at all. In cases in which the participation that is possible falls far short of the ideal, you should reflect on how this is likely to affect the results of priority setting. For example, will it mean that you don't hear the perspectives of patients or of members of more disadvantaged groups? If so, how might this skew the results and how can it be mitigated? Chapter 5, Case 3 describes a priority setting exercise that involved difficult decisions about what to do with the limited resources available for carrying out the exercise.

Animals and the environment

- How does the environment relate to social value? Is the environment important only insofar as it impacts human beings?
    - Health research can have negative (or positive) effects on ecosystems and the local or global environment. For example, a research project that develops a home-based care intervention that can substitute for hospital care might have a positive impact by reducing the emissions and other waste associated with hospital-based health care. This matters *at least* insofar as it affects humans and sentient non-human animals. Whether environmental effects matter further is a matter of debate among philosophers and ethicists. In all cases, caution should be taken in terms of the ability to *estimate* and *compare* the expected effects on the environment, which can be quite distant from the research being carried out.

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[121] Participants in the Community Engagement and Consent Workshop. Consent and community engagement in diverse research contexts. *J Empir Res Hum Res Ethics*. 2013;8(4):1–18; Pratt, B. & de Vries, J. (2018). "Community engagement in global health research that advances health equity." *Bioethics* doi/full/10.1111/bioe.12465; Reynolds L, Sariola S. The ethics and politics of community engagement in global health research. *Crit Public Health*. 2018;28(3):257–68; Tindana PO, Singh JA, Tracy CS, Upshur REG, Daar AS, Singer PA, et al. Grand challenges in global health: community engagement in research in developing countries. *PLoS Med*. 2007;4(9):e273.

[122] Grill, Christiane. "Involving stakeholders in research priority setting: a scoping review." *Research involvement and engagement* 7 (2021): 1-18.

- How do non-human animals matter for research priority setting?
    - The suffering and death caused to non-human animals during research matters ethically and should be taken into account. It can be taken into account at two points. First, during priority setting. Here the harm to non-human animals matters when prioritizing among different research programmes that will involve different uses of animals. For example, one research programme might use a mouse model and another cultured human cells, or one might expect to use more and another fewer sentient animals. There are ethical reasons to give higher priority to research programmes that involve less animal suffering. For more discussion see Chapter 2 and Chapter 5 (Scenario 1).

      The other point at which harm to non-human animals should be taken into account is when researchers propose specific studies involving animals. Those should normally not be evaluated during priority setting but should be assessed by ethical and scientific review committees according to national regulations and international ethical and scientific guidance.

Existing priorities

- Research priorities for my country/topic/organization have already been set. Do I have to revisit them?
    - Before embarking on a new priority setting exercise, it is always important to check whether priorities have already been identified by another party. If so, careful thought should be given to whether additional priority setting is warranted. Duplicative priority setting is wasteful—using resources that could be better spent carrying out research. Following a consistent set of priorities can also assist with the coordination of research efforts among different research actors within a country or a topic. That said, where circumstances have changed or the priorities set do not clearly apply to your work, it may be valuable to carry out another priority setting exercise (possibly on a smaller scale).

- We're already setting priorities ethically. Why do we need to use this guidance?
    - Many countries and organizations already carry out ethically sensitive priority setting exercises. Some excellent examples can be found in Chapter 5. Even for those who believe that their process is exemplary, this guidance may be helpful in two respects as they plan their next exercise. First, it is valuable to critically reflect on one's process in order to ensure that it includes everything that matters. The framework offered by this guidance can facilitate thinking through an existing priority setting process in a systematic manner. Second, it is important to

be explicit about the values that underlie one's priority setting. Being explicit about values allows priority setters and also third parties—such as patients, researchers, policy makers, and the public—to understand where priorities came from and what justifies them.

Relationships

- What happens when the research priorities of an international funder differ from the research priorities that have been set by the nation where they are planning to conduct research?
    - Legitimate concerns have been raised about whether the priorities of international organizations, funders, and high-income countries are driving the global health research agenda to the detriment of the health needs of people living in LMICs. Whenever health research is planned in an LMIC whose government has already set its national priorities, those existing priorities should be taken into account. Research that plans to deviate from national priorities merits special attention. If it is not *responsive* to the country's health needs or if it is likely to *displace* higher priority research, it should not be conducted.[123] However, the fact that a topic or question does not appear on a list of national priorities does not automatically rule it out. First, some research questions might be locally important, but not make it onto a list of national priorities. Second, some research might be an international priority—that is, a topic that is collectively important—without being high priority for each individual country where people are affected by the condition or problem. Third, responsible priority setting includes looking at the activities and priorities of other funders and research organizations. National priorities may be set in the light of what international funders are already planning to do, so as to avoid duplication and fill gaps.

- How does the guidance address cases in which funding comes from a partnership with industry whose aim is profit?
    - For-profit actors also have ethical obligations with respect to priority setting. They should be carrying out socially valuable research consistent with their special obligations, assessing and justifying any harms to third parties, and following fair procedures. Where two entities with different ethical obligations are working in partnership, each should ensure that the joint activities are consistent with their own ethical obligations. For example, a government funder's obligation to optimize the social value of the research it supports should not be diluted by

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[123] CIOMS (2016): Guideline 2.

partnering with a for-profit company. The partnership should be entered into only if it will increase the overall social value of research the funder supports.

Using the guidance

- Should health research priority setting undergo ethics review?
  - Since priority setting exercises vary so much, no blanket statement can be made. At least *some* health research priority setting exercises appear to constitute *research involving human participants*.[124] These should undergo prospective review by a research ethics committee whenever that is required by the legislation governing research with human participants in the jurisdiction in which the priority setting exercise takes place.

- Does research priority setting discourage innovation?
  - Some may worry that insisting that research reflects the results of priority setting exercises will lead to more conservative science. They may think that the social value requirement, in particular, will emphasize applied research with more predictable benefits, over more fundamental science whose ultimate implications for human health cannot be known in advance. While this worry is understandable, ethical research priority setting should not stymie innovation. It is perfectly consistent with optimizing social value to take a long-term view of what is socially valuable science—accepting that the benefits will most likely be felt decades in the future. It is also consistent with optimizing social value to support research whose payoff is very uncertain, but where the payoff would be huge if it resulted. Nothing about the obligation to set research priorities explicitly, in a systematic way, and guided by ethical principles entails preferring low risk-low reward research over high risk-high reward research.[125]

- Does every research priority setting exercise have to follow all the steps described in the guidance?

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[124] "**Research involving human participants**: Any social science, biomedical, behavioural, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge in which human beings: (1) are exposed to manipulation, intervention, observation or other interaction with investigators, either directly or through alteration of their environment; or (2) become individually identifiable through investigators' collection, preparation or use of biological material or medical or other records." (World Health Organization. *Standards and operational guidance for ethics review of health-related research with human participants* (2011)).

[125] For example, 2024 Nobel Prize winner, David Baker, was supported in his research on computational protein design by, among others, Open Philanthropy—an organization that transparently sets its funding priorities on the basis of estimates of how much good it can achieve with its limited resources (Open Philanthropy. *Cause Selection*. 2024. Available at: https://www.openphilanthropy.org/cause-selection/)

  - Research priority setting exercises are varied—ranging from individual scientists planning their next lines of research to international bodies setting global research agendas. Any guidance that can apply to all these exercises has to be quite general. It aims to articulate shared ethical principles, but these principles have to be applied according to the individual context, which may look quite different from one situation to another. Many priority setting exercises will follow all of the activities described in Chapter 3. Some may not. Provided that decisions about what activities to include in a priority setting exercise are consistent with the ethical principles, no particular set of steps is prescribed.

- There are other guides to research priority setting available. Why should I use this one and not the others?
  - This guidance is unique in its focus on the ethical considerations that should govern health research priority setting. It is not intended to replace other guides that focus on other aspects of priority setting exercises (e.g., how to organize and analyse relevant data, how to carry out Delphi and other techniques, and so on). The relationship between this guidance and some of the more popular priority setting methods is described in Chapter 4. Some priority setters may wish to use an existing method; others can learn from these methods while designing their own process to fit their own context. In all cases, it is essential to reflect on whether the process is consistent with ethical principles.

- How often should research priorities be revisited?
  - There is no fixed time period within which research priorities should be revisited. Nevertheless, it can be valuable to pre-specify a timeline, since that will affect the scale and scope of one's priority setting exercise. Whether to revisit priority setting outside of that timeline and how substantial any revision to priorities should be will depend on the situation of the priority setter *and* on external events. For example, a transformative discovery in a scientific field or a sudden outbreak of a novel disease might mean that priorities need to be reconsidered on short notice. In deciding whether to revisit priorities and how extensive subsequent priority setting exercises should be the following guiding questions might be helpful:
    - To what extent have the existing priorities been addressed?
    - Have changes in the field rendered many priority topics obsolete?
    - Does the priority setter need to respond to important external events, such as a disease outbreak, natural disaster, conflict, or change in government?

- Has a key decision point been reached [see Appendix X][126]? For example, a funder might receive an increase or decrease in funds to disburse, a research unit might hire new personnel, etc.

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[126] [Refer to appendix on key decision points for different research actors, if included.]

APPENDIX 1. THE RESEARCH ECOSYSTEM

Research priority setting does not happen in a vacuum. Each actor whose decisions affect what research gets done operates within the existing global health research ecosystem. This ecosystem comprises many other actors who conduct and influence research. They all operate against a background of health care systems that may use the products of research and legislation that shapes research. The following tables summarize key features of the research ecosystem relevant to priority setting: the actors who affect what research is conducted, the decision points at which allocation decisions are made, and the scarce resources that limit what health research can be conducted.

	Who sets priorities?		**When/how?**
	Categories	**Examples**	**Decision points**
FUNDERS	Academic and other research institutions	- All India Institute of Medical Sciences - Institut Pasteur - Kenya Medical Research Institute - Universities	• Establishing institutional priority areas • Designing funding schemes • Setting criteria for scoring grant applications
	Pharmaceutical and Biotechnology Companies	- Aspen Pharmacare Pfizer Inc. - Sun Pharmaceutical Industries Ltd.	
	Private sector philanthropic foundations, trusts, NGOs, corporate donors	- Bill & Melinda Gates Foundation - Médecins Sans Frontières - Wellcome Trust	

	Public sector institutions	- European Commission - Instituto Nacional de Salud Pública, Mexico - US National Institutes of Health	
	Public sector multilaterals	- Unitaid - World Bank - WHO	
	Categories		**Decision points**
Research Institutions	Universities		• Setting institutional priorities • Designing internal funding schemes • Allocating resources for personnel • Monitoring departments and activities • Rewarding employees for research outputs
	Hospitals and healthcare providers		
	Non-governmental organizations		
	Government agencies that directly conduct research		
	Pharmaceutical and biotechnology companies		
	Categories	Examples	Decision points
Policy Makers	Legislators and elected officials	• Ministers of Health • Parliamentarians	• Setting national priorities • Allocating funding to state agencies • Promulgating laws and regulations, e.g., intellectual property laws, tax breaks for research

	Multilaterals		- OECD - WHO - WTO	- Publishing guidelines and regulation
	Regulatory Bodies	Bodies responsible for the marketing approval of new drugs and devices	- South African Health Products Regulatory Authority - US Food and Drug Administration - European Medicines Agency	- Interpreting legislation - Issuing guidance
		Bodies responsible for the health technology assessments	- National Institute for Health and Care Excellence (NICE) - Health Intervention and Technology Assessment Program (HITAP)	
	Categories			**Decision points**
Individuals and Networks	Individual researchers			- Making decisions about areas of specialization - Identifying research areas and research questions - Applications for funding - Hiring decisions
	Research networks			
	Professional organizations			- Promoting certain research topics through conference and other activities - Providing forums for research exchange and networking on specific topics

	Categories	**Decision points**
OTHER ACTORS	Journals	• Encouraging certain topics for submissions. • Gathering editorial boards with certain areas of expertise • Publishing certain research findings
	Research Ethics Committees	• Stopping research that would violate participants' rights • Checking whether proposed research projects have sufficient social value to justify risks and burdens
	Patient organizations	• Advocating for more research on certain diseases • Rasing awareness in society on certain topics • Soliciting patient priorities

What is allocated?	
Types of Resources	**Scarcity in the ecosystem**
Funding	Money is essential for the success of almost every research project and is always in limited supply
Facilities and equipment	Facilities and technical equipment can be the limiting factors on what research gets conducted in an institution and so may have to be allocated as a scarce resource
Expert personnel and their time	The availability of qualified scientists, clinicians, grant administrators, grant reviewers, and other professionals is limited but required to enable health research
Research participants	For some types of research, especially studies of rare conditions, there are not enough willing, eligible participants to power all the studies that might be conducted

APPENDIX 2. BEST PRACTICES FOR INCLUSIVE PRIORITY SETTING

Including members of disadvantaged and marginalized groups

As discussed in Chapter 2, particular efforts should be made to ensure that participants who are members of more disadvantaged and marginalized groups have a meaningful say during the research priority setting process. If their valuable perspectives are to have an effect on what priorities are set, they must be included in ways that give them genuine representation and give their representatives genuine voice. Tokenistic inclusion will not change the prevailing practices by which those with power and social status ultimately make the decisions. Box 2 provides some guiding questions to help priority setters think through how to meaningfully include members of more disadvantaged and marginalized groups in health research priority setting. Further details can be found in in the Companion Document of *Sharing Power with Communities in Priority-Setting for Health Research Projects: A Toolkit*.[127]

Box 2. Including disadvantaged and marginalized groups in health research priority-setting: guiding questions[128]

1. Before priority-setting

- How will relationships with disadvantaged and marginalized groups be built or strengthened before priority-setting starts?
- How will members of disadvantaged and marginalized groups be supported to participate?

Who initiates and for what purpose

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[127] Pratt, Bridget. Sharing Power with Communities in Priority-Setting for Health Research Projects: A Toolkit (available online at https://www.researchforhealthjustice.com)

[128] Adapted from Pratt, Bridget. "Inclusion of marginalized groups and communities in global health research priority-setting." *Journal of Empirical Research on Human Research Ethics* 14.2 (2019): 169-181)) and Sharing Power with Communities in Priority-Setting for Health Research Projects: A Toolkit.

2. Leadership

- Will community partners be amongst those leading the health research priority-setting process? Ideally, community partners represent and can access communities that are considered disadvantaged or marginalised in their diversity.

3. Scope

- Will research priorities be solicited relating to *all* health problems experienced by disadvantaged and marginalized groups?

4. Empowerment

- Will the capacity of members of disadvantaged and marginalized groups to participate in research priority-setting be strengthened?

Who participates

5. Representation

- Who are the disadvantaged and marginalized groups within your project or program's research setting or population?
- Which of these groups will you engage during priority-setting and for what reasons?
- Do organizations or individuals exist who can represent those groups?
    - For organizations, do you have evidence that their memberships reflect the group's diversity and are regularly consulted about their health needs and priorities?
    - For individuals, do they collectively reflect the group's diversity and share lived experience with those they are representing?
- Given the answers to the previous three questions, how will participants be chosen?

6. Mass

- Will the number of participants drawn from disadvantaged and marginalised groups equal or exceed the number drawn from higher status groups in your project or program's research setting or population? If not, what are your reasons?

How they participate

7. Stage of participation

- Will members of disadvantaged and marginalized groups be involved from the start of the priority-setting process? If not, what are your reasons?

8. Level of participation

- Will members of disadvantaged and marginalized groups be involved as decision-makers? Is this level of participation acceptable to them?

9. Space

- What spaces exist in the host community that are not imbued with norms that silence disadvantaged and marginalized groups?
- Will you involve disadvantaged and marginalized groups in selecting the space for priority-setting? If not, what are your reasons?

10. Ground rules

- Will disadvantaged and marginalized groups be involved in developing and approving the ground rules for the priority-setting process? If not, what are your reasons?
- What ground rules will you include to ensure disadvantaged and marginalized groups aren’t silenced during priority-setting?

11. Facilitation

- Will you have a locally-based person facilitate consultations and deliberations? If not, what are your reasons?
- How will the facilitation give participants an equal opportunity to speak at focus groups and deliberations?
- How will the facilitation make disadvantaged and marginalized groups feel comfortable sharing relevant, personal stories about their community’s health concerns?

12. Listening

- How will the research team ensure disadvantaged and marginalized groups' ideas are listened to during consultations and deliberations?

13. Being heard

- Will the voices of disadvantaged and marginalized groups have equal or greater weight than other participants’ voices? If not, what are your reasons?

Compensation and follow-up

14. Resources and compensation

- How will disadvantaged and marginalized groups be compensated for participation?

15. Accountability

- What will be done to ensure that the final research priorities are acted upon?
- How will the final research priorities be fed back to disadvantaged and marginalized groups who participated in priority-setting?

APPENDIX 3. OPERATIONALIZING SOCIAL VALUE ASSESSMENTS

Health research priority setting should aim at two broad goals: maximizing the benefits of health research to patients and populations, and reducing inequity. These goals are encapsulated by the principle that health research priority setting should optimize the *social value* of research. As discussed in Chapter 2, social value is a function of: (1) the likelihood that the research will produce generalizable knowledge that will ultimately benefit human health and well-being, (2) the magnitude of those benefits if they were to result, *and* (3) the extent to which providing those benefits would reduce inequity.[129] These benefits cannot usually be directly measured. Instead, social value assessments must be operationalized through proxy indicators. This appendix provides some further points to consider and examples to guide priority setters in operationalizing social value assessments.

1. Defining social value

The first step is to clarify exactly what social value means in your context. This includes thinking about what counts as a benefit, who counts as a potential beneficiary, and how to conceptualize equity.

Points to consider:

a. **Health research does not only lead to health benefits.** Health research typically aims to (ultimately) improve health. Yet, health, narrowly conceived, is not the only thing that matters to people and it is not the only benefit that can result from health interventions. For example, a study comparing a home-based intervention with an intervention that can only be administered in a health care facility might be valuable in part because the former intervention would reduce disruption in patients' lives and lead to lower out-of-pocket costs. In line with the WHO's expansive definition of health as "a state of complete physical, mental and social well-being",[130] dimensions of well-being that are not always thought of as components of health are still relevant to social value. Such dimensions might include protection from financial shocks, reduction in stigma, or an increased ability to engage in

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[129] Barsdorf, Nicola, and Joseph Millum. "The social value of health research and the worst off." *Bioethics* 31.2 (2017): 105-115.

[130] Constitution of the World Health Organization (1948). https://www.who.int/about/accountability/governance/constitution

meaningful work and social activities. Where non-health benefits are *likely to be substantial*, consideration should be given to how they can be captured in assessments of social value.

b. **The effects of health research go beyond patients and beyond humans**. The health care interventions that are developed as a result of research can have indirect effects on individuals other than the recipients. For example, a treatment that improves patient mobility may also benefit carers. Where these indirect effects are *predictable* and *substantial* they should be considered when judging the social value of research.[131] Health research can also lead to benefits and harms to non-human animals and the environment. For example, health research can generate information on how health-related sectors can mitigate their climate change impacts. On the other hand, new health technologies may have substantial and potentially deleterious effects if they are energy and resource intensive.[132] Again, where such effects are *predictable* and *substantial*, they should be taken into account. How much weight should be given to effects on non-human animals and the environment versus humans is contentious; this guidance does not take a stance on that question.

c. **Equity is multidimensional.** According to WHO, "equity is the absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g., sex, gender, ethnicity, disability, or sexual orientation)."[133] This encompasses not only health-related differences, but also differences in other factors relevant to well-being (Box 3). For example, research into interventions to treat or prevent "neglected diseases" in LMICs may have high social value because the magnitude of the potential benefits are large *and also* because the people who suffer from these diseases are among the most disadvantaged worldwide.[134] In most cases, this disadvantage is not just a matter of worse health, but also higher rates of poverty, stigma and discrimination, and the like.

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[131] Du Toit, Jessica, and Joseph Millum. "Are indirect benefits relevant to health care allocation decisions?." *Journal of Medicine and Philosophy* 41.5 (2016): 540-557.

[132] Bhopal, Anand, and Ole F. Norheim. "Priority setting and net zero healthcare: how much health can a tonne of carbon buy?" *bmj* 375 (2021).

[133] World Health Organization. *Health Equity*. 2024. Available at: https://www.who.int/health-topics/health-equity.

[134] Sharp, Daniel, and Joseph Millum. "Prioritarianism for global health investments: identifying the worst off." *Journal of Applied Philosophy* 35.1 (2018): 112-132.

Box 3. Types of inequity

The causes of inequity in health and well-being are multiple and interacting. Inequities may be experienced by groups defined in terms of age, race or ethnicity, gender, sexual identity, disability, immigration status, geography, and more. A group may be worse off—and so deserving of greater consideration on equity grounds—due to disparities in any of the following:[135]

- Health outcomes (including morbidity and mortality)
- Access to health systems and services
- Education
- Income and wealth
- Access to social protection (e.g., sick pay, unemployment protection, pensions)
- Access to nutrition
- Housing and transportation
- Their physical environment (e.g., air quality, sanitation, clean water)
- Access to financial and judicial services
- The social environment (e.g., discrimination and stigma)
- Public safety

2. Operationalizing the definition: choosing criteria

The second step is to identify criteria for comparing research options that will optimize social value according to your definition. These criteria will vary according to context. Below we give three examples of how this can be done. You may also add other criteria, corresponding to the other ethical principles or to other constraints on what research options can be chosen.

Points to consider:

a. Fundamentals

- *Choice of criteria*. There should be criteria that capture each component of social value: (1) the likelihood that benefits result from conducting the research, (2) the magnitude of those benefits if they result, *and* (3) the extent to which providing those benefits would reduce inequity. In addition, for project-level priority setting exercises, the relative costs of research options should ideally be estimated (for thematic priority setting exercises this may not make sense). For many priority setters, costs will be monetary. But the relevant

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[135] Based on: National Academies of Sciences, Engineering, and Medicine. *Communities in Action: Pathways to Health Equity. Chapter 3: The Root Causes of Health Inequity*. Washington, DC: The National Academies Press (2017); World Health Organization. Health equity and its determinants (2021). https://www.who.int/publications/m/item/health-equity-and-its-determinants.

scarce resource ("the cost") could also be the time of experts who would carry out the research, number of research participants, biospecimens, space in health care facilities, or access to specialized technologies.

In principle, it would be possible to assign numerical values to each of these components. A score could then be assigned to each research option with higher scores indicating higher overall priority (Figure 4). Such a calculation would parallel the use of *cost-effectiveness analysis* in health care systems deciding which interventions to prioritize and the RICE method for product development.[136] In practice, this is not always practical. Nevertheless, it is valuable to keep the relationship among the components of social value in mind when deciding what criteria will be used for scoring research options and how the scores will be compiled.

$$\text{Priority score} = \frac{P \times B \times E}{C}$$

P: Probability that research project is successful
B: Magnitude of benefit if successful
E: Improvement in equity if successful
C: Cost of carrying out the research project

Figure 4. The social value equation

Insofar as direct indicators are available, they should be used. For example, it is often possible to estimate the cost of a research project (in monetary terms, staff time, etc.). Where direct indicators cannot realistically be measured, proxy indicators should be used. These might include:

- *Objective proxy indicators*, e.g., the prevalence of a condition can be a partial proxy for the potential magnitude of benefit from successful research (see Chapter 5, Case Study 2 for an example).
- *Subjective proxy indicators*, e.g., asking scientists to estimate the probability of success (see discussion of the CHNRI method in Chapter 4).

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[136] Jamison, Dean T. "Cost-effectiveness analysis: concepts and applications" in Roger Detels et al. (eds), Oxford Textbook of Public Health. Oxford: OUP (2009); McBride, Sean. *RICE: Simple prioritization for product managers*. https://www.intercom.com/blog/rice-simple-prioritization-for-product-managers/

Even subjective proxy indicators should be informed by data as much as possible. So, for example, there is no agreed measure of equity nor accepted view of how equity improvements should be weighted. At some point, subjective judgments will have to enter the picture. Yet, the people making judgments about how to score alternative research options on the basis of equity can still be provided with relevant data (such as information on how different diseases are distributed among socio-economic groups in a population). This makes their subjective judgments better informed.

- *Different types of research*. The paths to social benefits are extremely varied (Box 4). For more basic biomedical science, there might be multiple possible paths to social benefits. For example, there might be many possible uses for information about how different parts of the nervous system communicate or what happens when a particular gene is switched on. Whether any particular study ultimately benefits humans will depend on future research that itself cannot be easily mapped out. Basic science therefore poses particular challenges in estimating social value. This fact does not imply that it lacks social value; neither, however, does it mean that choices among basic science projects are arbitrary. The criteria used for comparing basic science projects can still usefully be mapped to the components of social value. Indicators for the likelihood of success may include factors that improve the probability that the research leads to generalizable knowledge (e.g., experimentalist skills, statistical soundness of study designs, recruitment plans, institutional support, and so on) and factors that improve the probability of uptake (e.g., external validity, plans for publication and dissemination, coordination with other research groups, and so on). Sometimes plausible paths to social benefits can be identified (Box 4). Otherwise, indicators for magnitude may have to be more indirect, such as considering whether a topic is neglected, whether the results are potentially transformative, or the significance of knowledge gained for other scientific questions. Even when the ultimate beneficiaries cannot be known, equity can be considered (e.g., focusing on diseases and environmental factors that affect worse-off populations, requiring that female animal models be used as well as male, pushing for the collection and use of biological samples to be representative of a population, and the like).

  For research that is closer to patients, the paths to social benefits can be relatively predictable. For example, a drug going into phase 3 trials will be expected to benefit the population suffering from the disease that it treats. Of course, even in these cases nothing is certain. The drug may not be effective or it may turn out to be effective for a different disease in the end. Nevertheless, for clinical and public health research it often makes sense to capture magnitude through criteria such as prevalence and severity and equity through measures of how disadvantaged potential beneficiaries are. The likelihood of success can be evaluated through looking at include factors that improve the probability that the research leads to generalizable knowledge and factors that improve the probability of uptake, just like for basic biomedical research. In addition, likelihood will be increased where research has clear relevance to practice, will generate results that are usable by clinicians, and/or has actionable policy implications.

Comparative judgments are easier the more similar the projects being compared. It is particularly difficult to compare high-quality research of different *types*, e.g., comparing the social value of laboratory science with health systems research is extraordinarily hard. This is an important challenge for funders with broad portfolios, including many national funding bodies. It might be the case, for example, that social value would be optimized by investing in a mixture of basic and more applied research. More work is needed on the question of how to allocate resources across different types of health research.

- *Waste*. Research that has no realistic prospect of generating benefits even in the long-term has no social value. Such research is wasteful and should be eliminated. Wasteful research is presumptively unethical because it uses up resources that could otherwise be put to better use. In addition, if it involves human or animal subjects, it may expose them to risks without justification. Wasteful research includes studies that ask questions whose answers are already known, research that will never be disseminated, "seeding trials" that are funded by companies just to promote an approved product, and studies that are underpowered or so poorly designed that they will not generate knowledge.[137] In general, for a research project to have non-zero social value there must be at least one plausible path to social benefits. Consideration should be given to actively identifying and eliminating wasteful research. For example, this might include requiring prior reviews of the existing evidence base to reduce the risk of unnecessary duplication or a study being predictably underpowered, ensuring that clinical trials are registered and their results reported even if negative, and so on.[138]

b. The process for developing criteria

- *Fair procedures*. As discussed in Chapter 2.4, both the selection of criteria themselves and their use in a research priority-setting process may be helpfully informed by *fair procedures* that *include* other parties. Patients, carers, community members, clinicians, policy makers, scientists, and other groups often have insights into what constitutes social value in a particular context and how it might be measured or compared.

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[137] Macleod et al. 2014.

[138] Chalmers, Iain, and Paul Glasziou. "Avoidable waste in the production and reporting of research evidence." *The Lancet* 374.9683 (2009): 86-89.

- *Epistemic injustice*. In developing criteria, care should be taken to minimize the risk of epistemic injustice. Epistemic injustice occurs when individuals or groups are treated wrongly as potential sources of knowledge. This may be because they are treated as less credible (*testimonial injustice*) or because their experiences are not recognized in the dominant conceptual schemes used by science (*hermeneutical injustice*).[139] More general information should not automatically be preferred to more locally relevant information; concepts from dominant Western ways of understanding the world—such as racial/ethnic categories, paradigms of mental illness—should not simply be assumed. Appropriate *inclusion* (see Chapter 2, Principle 4.3 and Appendix 2), especially of disadvantaged or marginalized groups, can help reduce the risk of epistemic injustice.

Box 4. Paths to social value

The path to social value for drug and vaccine candidates going into clinical trials is usually clear. But this is not the only path by which health research predictably leads to improvements in health and well-being. The following examples illustrate a small number of the many types of health research and myriad paths to social value that they can take.

Basic biological research. Widely used molecular biology techniques that have revolutionized the development of diagnostics, treatments, and vaccines are derived from basic biological research.[140] Notably, though the discovery of the underlying mechanisms might be the result of so-called "curiosity driven" research, possible applications are often posited before or by the time the biological mechanism is identified. For example, decades before mRNA vaccines against Covid-19 proved so successful, researchers explored whether mRNA could be delivered into human cells as vaccines for treatment or prevention;[141] Kary Mullis, widely credited as the inventor of the polymerase chain reaction (PCR) knew immediately the practical importance that PCR would have if it worked.[142]

Post-marketing drug studies. Studies of drugs that are already approved and prescribed to patients may reveal rare side effects. These studies may be phase 4 randomized controlled trials (such as the SCOUT trial that showed sibutramine increased the risk of myocardial infarction and stroke[143]). They may also be database studies that review case reports from prescribing physicians (such as the reports of liver

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[139] Fricker, Miranda. *Epistemic injustice: Power and the ethics of knowing*. OUP Oxford, 2007.

[140] Ronai, Isobel, and Paul E. Griffiths. "The case for basic biological research." *Trends in Molecular Medicine* 25.2 (2019): 65-69.

[141] Dolgin, Elie. "The tangled history of mRNA vaccines." *Nature* (2021): 318-324.

[142] Mullis, Kary B. "The unusual origin of the polymerase chain reaction." *Scientific American* 262.4 (1990): 56-65.

[143] James, W. Philip T., et al. "Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects." *New England Journal of Medicine* 363.10 (2010): 905-917.

toxicity leading to Canada withdrawing approval for nefazodone[144]). If the drugs are withdrawn or contraindications are added to the label, patients are protected from risks.

Behavioral science. Concerns about rising rates of obesity in many high- and middle-income countries has led governments to look for policy solutions. Interventions ranging from sugar taxes[145] to restrictions on advertising to children[146] to the content and design of nutrition warning labels[147] have been informed by social science research. Importantly, it was often clear ahead of time which policies were likely to be under consideration and so on what topics data from qualitative and quantitative research would potentially be sought.

3. Three examples

The tables below summarize three attempts to set out indicators for estimating the social value of research. They are presented here to illustrate how the concept of social value could be operationalized in a way that allows comparative judgments to be made. It may be valuable to consider how they could be adapted to your own priority setting context, including—where appropriate—adding effects on non-human animals and the environment.

Table 3. Social value indicators from “Research Priority Setting Checklist”[148]

Criterion (general)	Criterion (specific)
Magnitude of health problem	• Prevalence: the number of people affected by a disease • Severity: how bad a disease typically is for a given patient • Economic and social costs: the non-health burdens a disease imposes on patients, their families, communities, and society at large
Equity	• Medical disadvantage: will the research benefit sicker patients? • Social disadvantage: will the research benefit patients who are socially disadvantaged?

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[144] Stewart, Donna E. "Hepatic adverse reactions associated with nefazodone." *The Canadian Journal of Psychiatry* 47.4 (2002): 375-377.

[145] Hagenaars, L. L., et al. "Effectiveness and policy determinants of sugar-sweetened beverage taxes." *Journal of Dental Research* 100.13 (2021): 1444-1451; Popkin, Barry M., and Shu Wen Ng. "Sugar-sweetened beverage taxes: lessons to date and the future of taxation." *PLoS medicine* 18.1 (2021): e1003412.

[146] Buckingham, David. "The appliance of science: The role of evidence in the making of regulatory policy on children and food advertising in the UK." *International Journal of Cultural Policy* 15.2 (2009): 201-215.

[147] Corvalán, Camila, et al. "Structural responses to the obesity and non-communicable diseases epidemic: the Chilean Law of Food Labeling and Advertising." *Obesity reviews* 14 (2013): 79-87.

[148] Pierson, Leah, and Joseph Millum. “Health Research Priority Setting: Do Grant Review Processes Reflect Ethical Principles?” *Global Public Health* 17.7 (2022): 1186-1199, at 1190.

	• Priority for users: is the research considered a priority by potential beneficiaries, e.g., patients with the condition being researched?[149]
Likelihood of meeting scientific aims	• Scientific merit of the research proposal • Quality of investigators • Quality of institutions: whether they are well equipped to host the proposed research • Likely adoption: whether the research findings are likely to be translated into practice or policy
Cost of proposed research	• Economic costs • Human resources • Utilization of facilities

Table 4. Social value indicators for controlled human infection studies[150]

	Consideration	Explanation or illustration
	1. Magnitude of health benefits (at the time the research results could lead to health benefits)	
Benefits	*1.1. Magnitude of health-related harm from the disease*	"Loss in health-related quality of life or life expectancy per affected patient or individual at risk of infection,"
	1.2. Magnitude of health-related benefit from the research	"Potential gains in health-related quality of life or life expectancy that an affected patient or individual at risk of infection might make"
	1.3. Number of potential beneficiaries	
Equity	*1.4. Priority of potential beneficiaries as a matter of justice*	"e.g., level of disadvantage experienced over their lifetime."
	2. Likelihood of health benefits	
Probability	*2.1. Novelty and innovation of research question(s)*	"Possibility of addressing the research question(s) based on existing or expected future evidence, as summarized in complete and systematic reviews"
	2.2. Quality of research question(s)	"Maturity of the research question(s) given the existing evidence"

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[149] This is also potentially a magnitude criterion.

[150] Adapted from Rid, Annette and Meta Roestenberg, "Judging the social value of controlled human infection studies" *Bioethics*. 2020;34: 749–763, at 754; see also Rid, Annette, et al. "Ethics of Controlled Human Infection Studies With Hepatitis C Virus." *Clinical Infectious Diseases* 77. Supplement_3 (2023): S216-S223.

	2.3. Rigour of research design and data analysis	"Suitability of the given human challenge model for addressing the research question(s)" "Generalizability of findings from CHI studies to larger clinical trials and the field (external validity)"
	2.4. Feasibility and rigour of research conduct	"Consistency of the research with national research priorities (if any)" "Quality and timeliness of community and public engagement" "Quality of the research team (e.g. training, prior experience, conflicts of interest, institutional support, access to wider research community)" "Quality of the research sites (e.g. equipment, management)"
	2.5. Quality of reporting and dissemination of results & scope of data, sample and challenge strain sharing	
	2.6. Influence on future research with the potential to lead to health benefits	
	2.7. Influence on clinical or public health practice	"Feasibility of implementing the interventions" "Acceptability of the interventions"

Table 5. Child Health and Nutrition Research Initiative (CHNRI) method criteria[151]

	Criterion	Explanation
Probability	Answerability	"Likelihood that research option would be answerable in ethical way"
	Effectiveness	"Likelihood that resulting intervention would be effective in reducing disease burden"
	Deliverability	"Deliverability, affordability and sustainability of resulting intervention"
Benefit	Disease burden reduction	"Maximum potential of intervention to reduce disease burden"
Equity	Equity reduction	"Effect of disease burden reduction on equity in population"

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[151] Rudan, I., et al. "A systematic methodology for setting priorities in child health research investments." *A new approach for systematic priority setting. Dhaka: Child Health and Nutrition Research Initiative* (2006): 1-11, at 5.

APPENDIX 4: USEFUL RESOURCES

Coordinating research efforts:

The WHO's *Global Observatory on Health R&D* is a source for information on what health research is being conducted globally.[152] In addition, several international organizations coordinate health research and identify gaps. These include:

- ESSENCE on Health Research, which promotes coordination among donors and funders of health research.[153]
- The G-FINDER project, which tracks investment into "R&D for new products and technologies to address priority global health challenges,"[154] including by industry.
- The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), which focuses on pandemic preparedness and response.[155]

Collaborative research projects:

Tools and expert assistance on developing equitable research partnerships, especially in collaborations between research institutions in high-income countries and research institutions in low- or middle-income countries can be found through the Research Fairness Initiative.[156]

Research ethics:

Resources relating to the ethics of research with human participants can be found through the WHO's Health Ethics and Governance Unit.[157] Two canonical sources of guidance are:

- World Medical Association, Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013)[158]

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[152] World Health Organization. *Global Observatory on Health R&D*. https://www.who.int/observatories/global-observatory-on-health-research-and-development

[153] TDR. ESSENCE on Health Research. https://tdr.who.int/groups/essence-on-health-research

[154] Policy Cures Research. G-FINDER. https://www.policycuresresearch.org/g-finder/

[155] Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). https://www.glopid-r.org

[156] Research Fairness Initiative. https://rfi.cohred.org

[157] World Health Organization. *Health Ethics & Governance*. https://www.who.int/teams/health-ethics-governance/governance/research

[158] World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013) https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

- Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Health-related Research Involving Humans* (2016)[159]

Two nuanced discussions of the ethics of research with non-human animals are:

- Nuffield Council on Bioethics. *The ethics of research involving animals* (2005).[160]
- Beauchamp, Tom L., and David DeGrazia. *Principles of animal research ethics* (2019).[161]

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[159] Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Health-related Research Involving Humans* (2016) https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[160] Nuffield Council on Bioethics. *The ethics of research involving animals* (2005). https://www.nuffieldbioethics.org/publications/animal-research

[161] Beauchamp, Tom L., and David DeGrazia. *Principles of animal research ethics*. Oxford University Press, 2019.

APPENDIX 5: TOOLS

The following flowchart illustrates the key activities involved in research priority setting exercises and the ethical considerations that are particularly relevant for each. For more details on each activity and how the ethical principles apply, consult *Chapter 3: Putting the principles into practice*.

Incorporating the ethical considerations into each activity will be facilitated by answering the *Guiding Questions for Ethical Research Priority Setting* listed on the following pages.

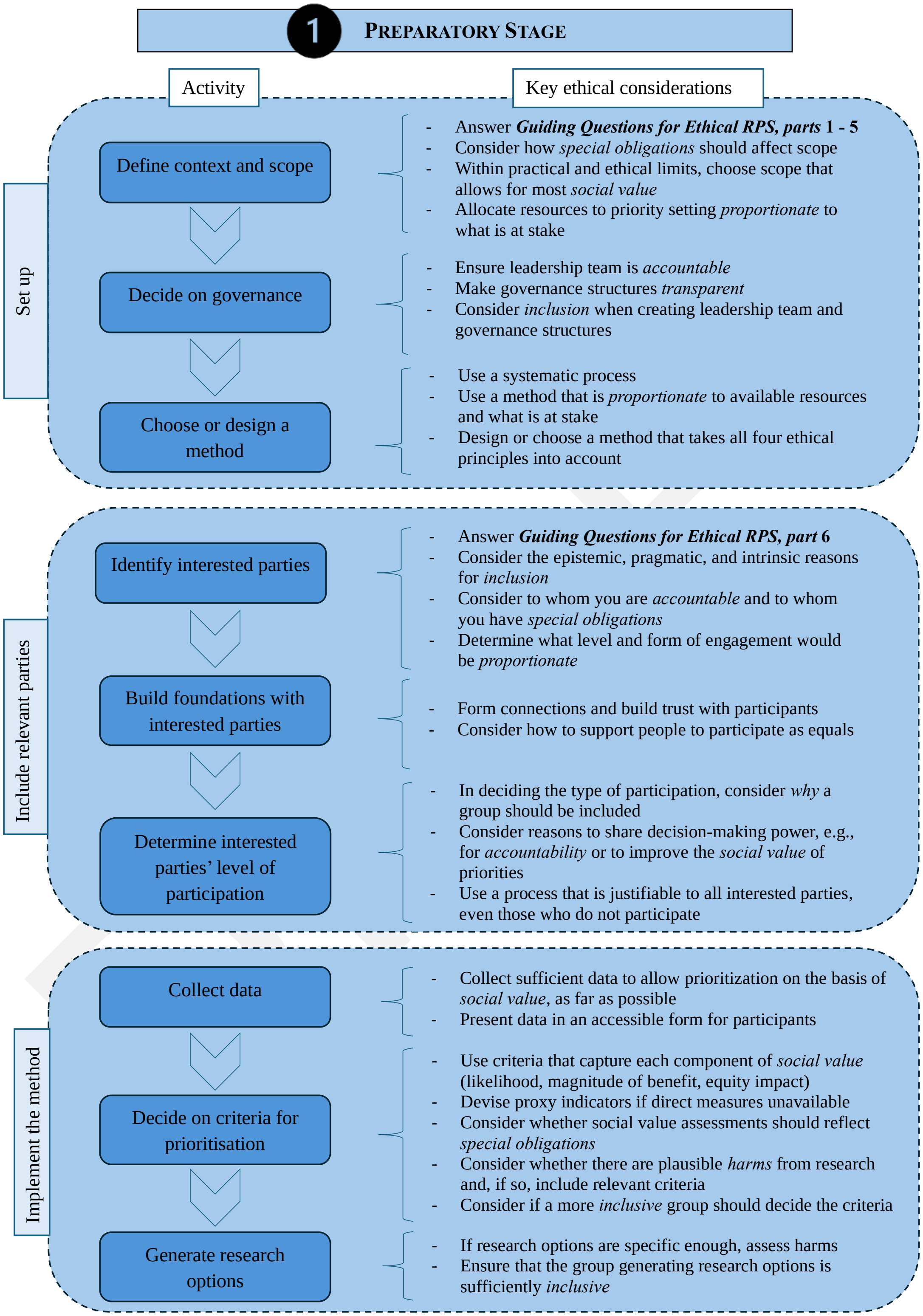


Figure 5. Flowchart of key activities and associated ethical considerations

Set up

Define context and scope

- Answer ***Guiding Questions for Ethical RPS, parts*** **1 - 5**
- Consider how *special obligations* should affect scope
- Within practical and ethical limits, choose scope that allows for most *social value*
- Allocate resources to priority setting *proportionate* to what is at stake

Decide on governance

- Ensure leadership team is *accountable*
- Make governance structures *transparent*
- Consider *inclusion* when creating leadership team and governance structures

Choose or design a method

- Use a systematic process
- Use a method that is *proportionate* to available resources and what is at stake
- Design or choose a method that takes all four ethical principles into account

Include relevant parties

Identify interested parties

- Answer ***Guiding Questions for Ethical RPS, part*** **6**
- Consider the epistemic, pragmatic, and intrinsic reasons for *inclusion*
- Consider to whom you are *accountable* and to whom you have *special obligations*
- Determine what level and form of engagement would be *proportionate*

Build foundations with interested parties

- Form connections and build trust with participants
- Consider how to support people to participate as equals

Determine interested parties' level of participation

- In deciding the type of participation, consider *why* a group should be included
- Consider reasons to share decision-making power, e.g., for *accountability* or to improve the *social value* of priorities
- Use a process that is justifiable to all interested parties, even those who do not participate

Implement the method

Collect data

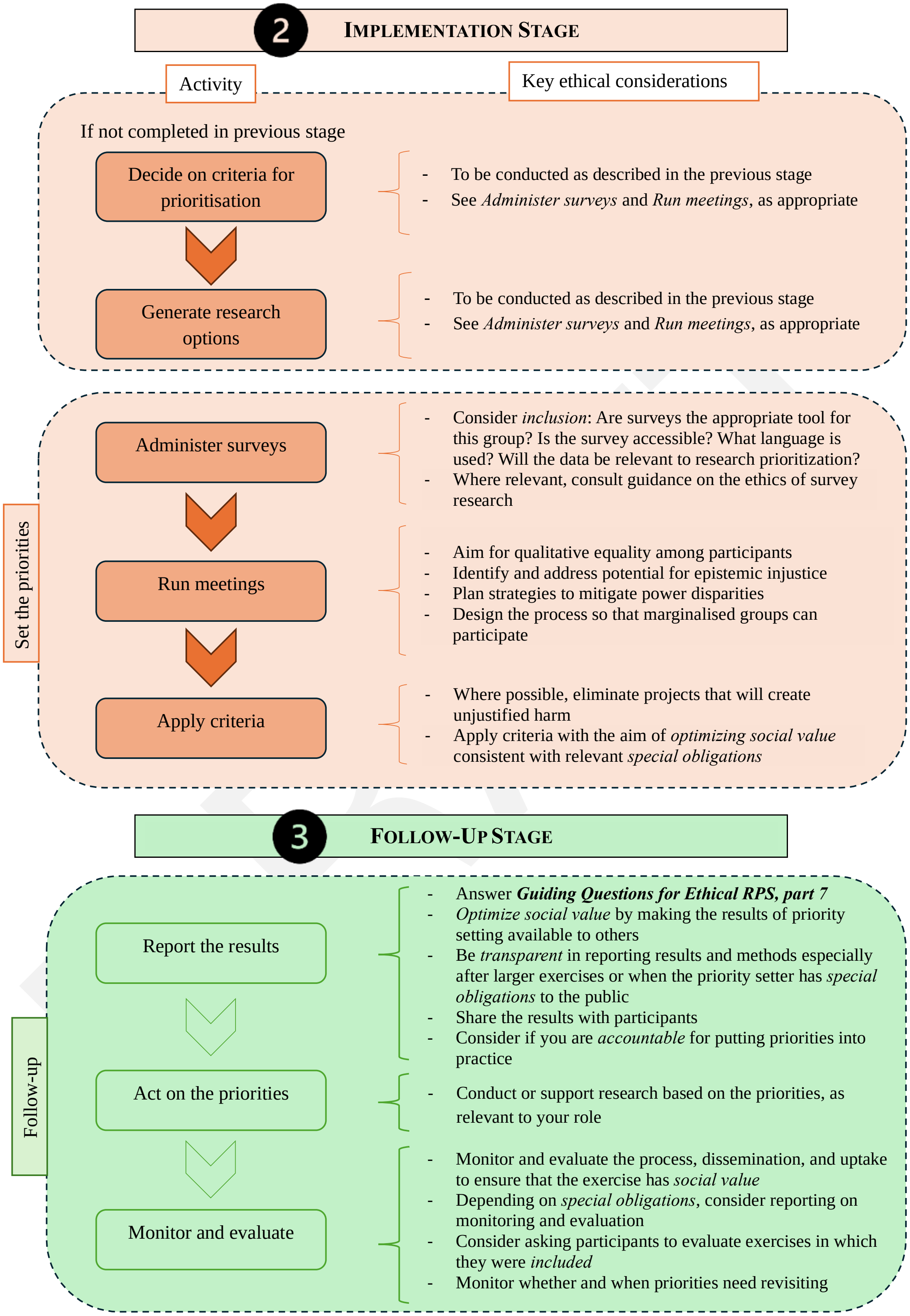
- Collect sufficient data to allow prioritization on the basis of *social value*, as far as possible
- Present data in an accessible form for participants

Decide on criteria for prioritisation

- Use criteria that capture each component of *social value* (likelihood, magnitude of benefit, equity impact)
- Devise proxy indicators if direct measures unavailable
- Consider whether social value assessments should reflect *special obligations*
- Consider whether there are plausible *harms* from research and, if so, include relevant criteria
- Consider if a more *inclusive* group should decide the criteria

Generate research options

- If research options are specific enough, assess harms
- Ensure that the group generating research options is sufficiently *inclusive*



2 IMPLEMENTATION STAGE

Activity | Key ethical considerations

If not completed in previous stage

Decide on criteria for prioritisation
- To be conducted as described in the previous stage
- See *Administer surveys* and *Run meetings*, as appropriate

Generate research options
- To be conducted as described in the previous stage
- See *Administer surveys* and *Run meetings*, as appropriate

Set the priorities

Administer surveys
- Consider *inclusion*: Are surveys the appropriate tool for this group? Is the survey accessible? What language is used? Will the data be relevant to research prioritization?
- Where relevant, consult guidance on the ethics of survey research

Run meetings
- Aim for qualitative equality among participants
- Identify and address potential for epistemic injustice
- Plan strategies to mitigate power disparities
- Design the process so that marginalised groups can participate

Apply criteria
- Where possible, eliminate projects that will create unjustified harm
- Apply criteria with the aim of *optimizing social value* consistent with relevant *special obligations*

3 FOLLOW-UP STAGE

Follow-up

Report the results
- Answer ***Guiding Questions for Ethical RPS, part 7***
- *Optimize social value* by making the results of priority setting available to others
- Be *transparent* in reporting results and methods especially after larger exercises or when the priority setter has *special obligations* to the public
- Share the results with participants
- Consider if you are *accountable* for putting priorities into practice

Act on the priorities
- Conduct or support research based on the priorities, as relevant to your role

Monitor and evaluate
- Monitor and evaluate the process, dissemination, and uptake to ensure that the exercise has *social value*
- Depending on *special obligations*, consider reporting on monitoring and evaluation
- Consider asking participants to evaluate exercises in which they were *included*
- Monitor whether and when priorities need revisiting

Guiding Questions for Ethical Research Priority Setting

The prompts below are intended to help ensure that ethical considerations are incorporated into the design of your priority setting exercise. Answers to these questions will help determine which activities should be included in the exercise and how. Parts 1 – 6 are essential to addressing ethical considerations during the preparatory stage. Part 7 is essential to the follow-up stage. Ideally, these questions should be considered throughout the design and implementation of the exercise.

1. Scope	• How should we set the scope of this priority setting exercise (taking into consideration the practical *and* ethical aspects)? Consider: o What themes, subject areas, or types of research could realistically be included? o Within the limits of what *could* be included, do any of our ethical obligations affect the scope of what we *should* do? ▪ To whom are we accountable (e.g., the public, specific communities, funders)? ▪ What is our mission? ▪ Are there specific populations we should prioritize? (See, also, "Other special obligations" below)
2. Proportionality	• What time and resources will be devoted to priority setting? Consider: o How is the exercise likely to be used (e.g., how many and how important are the decisions that will be informed by the results, how urgently are priorities needed)? o What resources are available for priority setting? o What is needed to carry out priority setting well in this context?
3. Social value	• Within the scope we've identified, how are we defining *social value*? Recall that social value is a function of the likelihood that research leads to benefits, the magnitude of those benefits, and their impact on equity. Consider: o In what ways might our research lead to benefits? What type of benefits? o In what ways might our research lead to benefits that improve equity? o What would make these beneficial impacts more likely?

	• Given the answers to the previous questions—What criteria will we use to assess the social value of alternative research options? The criteria should be chosen with the aim of *optimizing social value*. Consider: o *Likelihood criteria*, e.g., scientific merit, novelty, answerability, likelihood of adoption of findings into practice. o *Magnitude criteria*, e.g., burden of disease, potential benefit from successful intervention, potential for broad application or transformative findings o *Equity criteria*, e.g., expected affordability of intervention, disadvantage of beneficiaries, consideration of gender, race/ethnicity, etc. o *Cost criteria*. Will this priority setting exercise consider the relative costs of different projects (in money, time, personnel, etc.)? If so, include criteria to estimate and compare the costs of research options. o *Appendix 3* provides more guidance and examples of criteria appropriate to different types of research • Further considerations: o What *process* should be used to generate and compare research options using these criteria? o Do we need to coordinate our activities with others? (e.g., for funders—what are other funders doing?) o Might the criteria for social value or the process by which they are selected reinforce epistemic injustice? If so, how can this be addressed?
4. Harms	• Are there harms to non-human animals or third parties that plausibly might result from any of the research options under consideration? • If harms are likely, consider for each case: o What would minimize the harms? o What would justify the harms?
5. Other special obligations	• In addition to scope restrictions, are there other ways we should take special obligations into account? o *Substantive considerations*, e.g., Should the process give greater weight to the health problems of specific groups (such as a national population or particular patient groups)?

	○ *Procedural considerations*, e.g., Are there specific groups who have a right to be included and in what way? (See "Inclusion" below)
6. Inclusion	• Why might we involve other parties in this priority setting exercise? Reflect on: ○ *Epistemic* reasons (including others to increase *accuracy*, e.g., because they have knowledge or expertise) ○ *Pragmatic* reasons (including others to increase *impact*, e.g., build trust, get buy-in) ○ *Intrinsic* reasons (including others because they have a *right* to be involved) • Based on this reflection: ○ Who should be involved? ▪ Aim for sufficient range and number so they can collectively represent the diversity of interested parties who should be included ○ How should they be involved? ▪ Structure the process so that everyone has a fair opportunity to contribute and to influence the results ▪ Check that the design will ensure meaningful participation from marginalized and disadvantaged individuals who are included (see *Appendix 2*)
7. Follow-up	• How will the process and results of priority setting be communicated and to whom? Consider: ○ To whom are we accountable? ○ Who participated? ○ Who might put the results into practice? • What other steps can be taken to ensure that the results of priority setting are acted on? • When or under what conditions will priorities be revisited?