3

Proportionality in Health Research Regulation

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3.1 INTRODUCTION

Proportionality in health research regulation can, at its broadest level, be understood as an attempt to balance two considerations that sometimes compete: the protection of individuals affected by research – especially, but not limited to, human subjects – and the promotion of socially valuable research. This chapter will explore the concept of proportionality through three sections: First, a clarification on what I mean by proportionality in this context and why it is important; second, an exploration of how particularly challenging it is to assess proportionality; and third, a proposal for a procedural approach to proportionality that may assist with those challenges. In particular, I will propose that adopting a facilitative attitude, undertaking rigorous justification, ensuring transparency and engaging with relevant stakeholders may be effective procedural means of overcoming the challenges of proportionality.[1]

3.2 WHAT IS PROPORTIONALITY?

The term 'proportionality' has several meanings even within the context of health research regulations. We can roughly distinguish between the first-order or study-level sense of the term, and second-order or policy-level sense.

First-order proportionality refers to the benefits *of a study* – inclusive of benefits to the subjects as well as society as a whole – being proportionate to its risks and burdens. It is interchangeable with 'favourable risk-benefit ratio' as found in the classic article 'What makes clinical research ethical?',[2] and a variety of authors have followed suit.[3] On this understanding, the benefits of a given study need to be of sufficient strength or magnitude to justify the risks individuals are exposed to. Research Ethics Committees (RECs), Institutional Review Boards (IRBs) or

[1] This chapter focuses on proportionality in human subjects research, though the analysis below should be applicable to other contexts as well (such as animal or basic science research).

[2] E. J. Emanuel et al., 'What Makes Clinical Research Ethical?', (2000) *JAMA*, 283(20), 2701.

[3] G. de Wert, 'Human Embryonic Stem Cells: Research, Ethics and Policy', (2003) *Human Reproduction*, 18(4), 672–682; G. Pennings, ESHRE Task Force on Ethics and Law Including, G. de Wert et al., 'ESHRE Task Force on Ethics and Law 12: Oocyte Donation for Non-Reproductive Purposes', (2007) *Human Reproduction*, 22(5), 1210–1213; F. G. Miller and S. Joffe, 'Limits to Research Risks', (2009) *Journal of Medical Ethics*, 35(7), 445–449; G. Hermerén, 'The Principle of Proportionality Revisited: Interpretations and Applications', (2012) *Medicine, Health Care and Philosophy*, 15(4), 373–382.

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TABLE 3.1 *Matrix of regulations' potential effects on research*

	Process (monetary/staffing costs, researchers' time, efficiency, and scientific validity)	Protection (relating to the interests of human subjects or other individuals directly affected by research)
Benefits (positive effects)	e.g. streamlining research review	e.g. data security protocols to protect confidentiality of subject data
Burdens (negative effects)	e.g. substantial time from researchers to ensure compliance	e.g. retaining sensitive study data for years, increasing risk of breach

equivalent are routinely tasked with making such assessments on a case-by-case basis for human subjects research.

I will set aside assessment of first-order proportionality in this chapter, as risk–benefit ratios will be covered elsewhere in this volume.[4] Instead, I will focus on second-order proportionality in health research, which operates primarily at the policy level (inclusive of national and institutional policies).

Second-order proportionality refers to whether the burdens of a given rule or policy governing research are proportionate to its benefits. The burdens and benefits can further be delineated along two axes: effects on the process of research including monetary/staffing costs, researchers' time, efficiency and scientific validity; and the effect on protection afforded to individuals affected by research (including, but not limited to, human subjects). As will be discussed below, this is not only limited to physical effects, but extends to other impacts such as the wrongdoing of privacy violations.

Proportionality assessments then, will involve evaluating the benefits of a regulation in terms of both protection and promotion, and weighing those against the burdens, also in terms of protection and promotion. While we might typically expect research regulations to impose burdens in terms of process while affording benefits in terms of protections, we should keep in mind that regulations can also have beneficial effects on processes, and deleterious effects on protections, as seen in Table 3.1.

Like first-order proportionality, there is a justificatory relationship: the benefits of a rule or policy must be sufficient to justify the burdens imposed. But unlike first-order proportionality, second-order proportionality is not evaluated on a case-by-case basis. Rather, it concerns the total effect a given policy has on the research enterprise. It is the responsibility of policymakers – including regulators and institutional leaders – along with institutional bodies like RECs and IRBs, to ensure that their policies are proportionate in this way.

Still, context will be important in assessing the proportionality of a given policy. Rules will have different impacts on different institutions, fields of study, countries and cultures. For example, a rule requiring written informed consent from subjects – which ensures consistent provision of information and ease of auditing – may be quite proportionate in societies with high literacy. But in societies with low literacy, the requirement would lead to the exclusion of many subjects, potentially endangering the scientific validity and depriving already-marginalised groups of potentially beneficial interventions. This could tip the rule from being proportionate to being disproportionate.

[4] See Coleman, Chapter 13 in this volume.

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3.3 PROPORTIONALITY OF REVIEW AND PROPORTIONALITY OF HARMS

Discussions around second-order proportionality typically focus on two related aspects: proportionality of review, and proportionality of harms. Proportionate review involves tailoring the degree of scrutiny to the amount of risk subjects may be exposed to.[5] Proportionality of harms defines those risks in terms of probability of physical or psychosocial harms.

In regard to proportionality of review, low-risk research may be reviewed under expedited or exempted pathways, where only one or two members of a REC are directly involved in assessing and approving a study. Higher-risk research would instead go to a full board.

Full board reviews take more time, potentially reducing the efficiency of research with potential social benefits. However, they also are more likely to pick up on potential ethical failings, due to both the larger number of eyes on a proposal, and the greater diversity of expertise brought to bear on it. This will be more proportionate for studies with higher risks to subjects, and so in need of closer attention. For low-risk studies, there may not be much reason to apply that extra scrutiny, as the marginal benefit to subjects of correcting a failing is relatively small. At the same time, the study will still consume resources, which may be separate grounds for some scrutiny.[6]

However, ethics review is just one component of research oversight. Many policies governing health research operate using different mechanisms, including rules that bind researchers directly, regardless of the scrutiny applied. These include policies delineating the contents of informed consent, confidentiality protections, documentation and authorisation. All these requirements have the potential to slow down research or increase its costs, and so must be justified in terms of the benefits they afford. Stratifying the stringency of a wider variety of rules is more common in Europe, while US regulations only stratify the review process.[7]

Additionally, approaches centred around proportionality of harms capture only part of the justifications for rules governing health research. The four principles approach can help illustrate this. Beauchamp and Childress identified four central mid-level ethical principles that underpin bioethics in general, and research ethics in particular: beneficence, non-maleficence, respect for autonomy and justice.[8]

Beneficence in this context relates to the impetus to ensure that socially beneficial research is conducted in an efficient manner; inefficiencies resulting from over-regulation increase the overall cost of research, in turn reducing the amount of research – and thus social benefits generated – that can be conducted on a given budget. Non-maleficence refers to the potential harms of research mentioned above. On the above understanding, proportionality would primarily involve balancing beneficence – in terms of promoting valuable research – against non-maleficence (avoiding harms caused by research).

This leaves out autonomy and justice, which are also relevant to proportionality assessments. Consider the following examples of informed consent – as an illustration of respect for autonomy – and subject selection (illustrating justice concerns).

[5] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 'Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans', (2018); NHS Health Research Authority, 'Proportionate Review: Information and Guidance for Applicants'.

[6] See Coleman, Chapter 13 in this volume for more discussion of efforts to streamline ethics review in this way.

[7] A. Rid, 'How Should We Regulate Risk in Biomedical Research? An Ethical Analysis of Recent Policy Proposals and Initiatives', (2014) *Health Policy*, 117(3), 409–420.

[8] T. L. Beauchamp and J. F. Childress, *Principles of Biomedical Ethics*, 7th Edition (Oxford University Press, 2013).

Informed consent may in part be aimed at harm mitigation, so subjects can avoid participating in trials whose risks are unacceptable to them personally. But it also aims at respecting the ability of subjects to govern their own lives – here, to ensure that participating in a study is in accordance with their values. This includes risks, but may also relate to other factors such as how much they identify with the aims of the study, trust researchers, or believe it will produce social benefits.[9]

Fair subject selection might also have a risk-mitigation aim, insofar as subjects particularly vulnerable to harm from a study may be excluded. But this must also be balanced by justice considerations in excluding certain groups from a study. A case in point is the routine exclusion of pregnant women from research. This is done in the name of non-maleficence, as fetuses are frequently thought to be at higher risk of harm from experimental interventions. But the result is a lack of evidence for the safety of a wide variety of drugs on pregnant women, forcing them into an uncomfortable dilemma: accept substandard care with a more proven safety record, or go for proven interventions that have an uncertain risk to their children. As such, a rule meant to protect pregnant women arguably perpetuates injustices against them.[10]

Assessments of proportionality should go beyond benefits and harms to incorporate considerations of justice and respect for persons. These considerations may factor in on both sides of the proportionality equation: the burden of regulation may be necessary to prevent an injustice and promote autonomy, or – as with the case of preventing research with pregnant women – a regulation's burdens may be shown to be unjustifiable by virtue of the injustice and disrespect that it promulgates.

3.4 THE CHALLENGE OF SOCIAL VALUE

From the preceding discussion, it should already be evident that assessments of proportionality of a given policy governing health research will be quite complex. Further challenges emerge upon closer analysis, one of which is how to integrate the social value of research into proportionality assessments.

Up until this point, it has been assumed that greater efficiency, lowered cost and improved scientific validity in health research are unquestionably valuable. This is predicated on a potentially contestable notion – that the outputs of research have substantial social value. If policies slow down research, then in turn society's access to valuable outputs – more effective treatments, better prevention of disease, mitigation of symptoms and side-effects, etc. – will slow down. Increased costs mean less research can be done, and thereby fewer valuable outputs are produced. Further, detriments to scientific validity – such as limitations on the use of placebo-controlled trials – may undermine the robustness of those outputs.

It is often held that all health research must contribute to social value in order to be ethically justified.[11] For present purposes, it is sufficient to note that if a given study really has no social value, proportionality is irrelevant – it should not be permitted in the first place.

[9] N. Hallowell et al., 'An Investigation of Patients' Motivations for Their Participation in Genetics-Related Research', (2010) *Journal of Medical Ethics*, 36(1), 37–45.

[10] F. Baylis and A. Ballantyne, 'Missed Trials, Future Opportunities', in F. Baylis and A Ballantyne (eds), *Clinical Trials Involving Pregnant Women: Missed Trials* (Switzerland: Springer, 2016), pp. 1–13.

[11] Emanuel et al., 'What Makes Clinical Research Ethical?'; Council for International Organizations of Medical Sciences and World Health Organization, 'International Ethical Guidelines for Health-Related Research Involving Humans', (CIOMS, 2016). See also Van Delden and Van der Graaf, Chapter 4 in this volume.

Meeting the minimal threshold of social value masks the larger, much more intractable issue of assessing the magnitude of that social value. This magnitude is important in proportionality assessments to get an understanding of how problematic a given inefficiency or other detriment really is. For low social value research, barriers to research may more easily be outweighed by ensuring protections for subjects; vice-versa for high social value research.

But there is no reliable formula for quantifying the social value of a given study. The results of all studies are by nature uncertain – if we knew the results ahead of time, there would be no need to engage in a study in the first place. Much health research is not directly translatable; it instead builds a base of understanding that over time, in combination with other studies, will eventually lead to improved practice down the road. It is also unclear how we should judge the impact of health research. Some measures like Quality-Adjusted Life Years are relevant here, but these have been disputed as too abstracted a way from patient experiences and values,[12] and being potentially discriminatory.[13]

Still, some reasonable estimates of possible social benefits of a given study must be possible. This is the routine task of agencies that disburse grants for research, after all. Moreover, research regulation can itself play a role in improving the social value of a study. For example, beyond risk assessment, a REC/IRB review of scientific validity and value can play a role in promoting sound knowledge generation from studies.[14]

3.5 COMPLEXITIES OF ANALYSIS

The evaluation problem is compounded at the policy level, where broad categories of research are being considered, rather than individual studies. Furthermore, the social value of research is just one piece of a proportionality assessment. We need to ascertain not only the social value of the research, but the extent to which a given policy will detrimentally impact this research. While it is routine for policymakers and academics to perform economic impacts of regulations, these analyses have been questioned in terms of their rigor and real-world validity.[15] In the research context, a full analysis would have to take into account the extent to which increased cost of research would crowd out further socially valuable studies, assuming total budgets for research are independent of regulatory policy.

There are similar uncertainties and complexities in relation to assessing protections. Only a few policies will be relatively easy to assess: prohibitions of activities that would almost certainly harm or wrong participants. Failure to obtain informed consent from competent adults for interventional research may be an example, insofar as it would be a clear violation of autonomy.

But often, harms or wrongs are probabilistic, with the probabilities themselves unknown or uncertain. Policies may only reduce the likelihood of such harms or wrongs, rather than prevent them entirely. For example, a requirement that researchers provide their CVs to review boards has some use – ethics board members can ensure that they have the relevant qualifications to carry out the study procedures. At the same time, it would be difficult to articulate exactly how much harm (qua adverse outcomes) is actually prevented by such a policy. In theory, one could perform a comparative analysis of researchers with different qualifications and assess correlations

[12] P. J. Neumann and J. T. Cohen, 'QALYs in 2018—Advantages and Concerns', (2018) *JAMA*, 319(24), 2473.
[13] B. Davies, 'Bursting Bubbles? QALYs and Discrimination', (2019) *Utilitas*, 31(2), 191–202.
[14] A. Binik and S. P. Hey, 'A Framework for Assessing Scientific Merit in Ethical Review of Clinical Research', (2019) *Ethics & Human Research*, 41(2), 2–13.
[15] R. W. Hahn and P. C. Tetlock, 'Has Economic Analysis Improved Regulatory Decisions?', (2008) *Journal of Economic Perspectives*, 22(1), 67–84.

with adverse study outcomes. But such analyses have not been done for the wide array of subfields and procedures that ethics committees may encounter, so those setting policies on the matter must instead rely on personal judgment.

Finally, there is the question of how to bridge the two sides of proportionality, namely, burdens and benefits. That is, how to determine if a given burden on research is justified by the benefits it affords? A potential approach is to leverage decision theory, where the gains and losses to individuals' well-being from a regulation are quantified and aggregated, and a determination is made as to whether a given regulation or policy overall improves expected utility.[16]

Here, incommensurability is a particular issue. Even if one side or the other can be somehow defined and explicated, the values on either are likely not commensurate – they are not easily compared and weighed up against each other. Perhaps the burden of requiring informed consent for some secondary data research can be quantified in terms of the increased cost, delays and potential bias of only including those who would consent. But those measures are of an entirely different nature from the autonomy interests of individuals to maintain control over data about them, one of the main values being protected by informed consent requirements. Unfortunately, again, there is no formula to make such assessments, and a good deal of individual judgment on the part of policymakers is necessary.

3.6 PROCEDURAL APPROACHES TO PROPORTIONALITY ASSESSMENTS

There is an old joke that philosophers like to kick up dirt in front of their eyes, then complain they can't see. The above may appear to be like so much dirt, pointing out all the difficulties in doing a proper proportionality assessment of health research regulations. So, at this point, I will be somewhat more constructive and propose some ways that proportionality assessments can be made more reliable and legitimate.

The following will primarily be procedural proposals. That is, they are not explications for how to determine whether a given regulation is proportionate. Rather, they are a series of structures and systems governing the process of assessing proportionality that should have two desirable features: they will improve the reliability of proportionality assessments, by prompting systems that are better able to assess whether a given rule's protections really justify the burdens imposed; and they will help engender legitimacy in those assessments, by adopting systems that can earn the confidence of stakeholders – including researchers and participants – in the proportionality of rules that are ultimately produced.

At the most general level, it is important for those involved in regulation to have a **facilitative attitude** towards proportionality. A view that their role is solely to protect subjects may engender the perception that they are there to get in the way of valuable research.[17] This will not only engender hostility towards regulations and regulators but is also fundamentally mistaken. It ignores the crucial consideration of proportionality; to ensure that any burdens are adequately justified by the benefits they bring about. As a result, proportionality requires consideration of both the positive and negative sides of the research enterprise.

A more useful way for regulators to frame their role would be as facilitators of responsible research. This is not to say that they are there to make research easier than it might otherwise be; almost any regulations will have some costs in terms of efficiency, expense or validity, and

[16] R. D. C. Bernabe et al., 'Decision Theory and the Evaluation of Risks and Benefits of Clinical Trials', (2012) *Drug Discovery Today*, 17(23–24), 1263–1269.

[17] S. Pinker, 'The Moral Imperative for Bioethics', *Boston Globe* (1 August 2015).

regulators should be up front about that. However, enforcing reasonable rules that are proportionate to the burdens they accrue is a means to ensure that the research that does occur is responsible in terms of the benefits to those affected. The term 'facilitation' gives explicit emphasis on the need to ensure that the regulations are as minimally intrusive as necessary to achieve a given protective aim.

This framing has both inward-facing and outward-facing benefits. Looking inwards, regulators are reminded of the need to consider burdens of regulation along with benefits, and the balancing effort between the two in the proportionality assessment. This will help avoid blatantly one-sided approaches to regulation. Also, looking outwards, expressing this attitude in engagement with stakeholders can help assure them that their interests are being adequately accounted for. Such engagement is not merely limited to top-down communication of regulatory decisions, but active engagement as will be discussed further below.

A related procedural approach is actually doing the work of a proportionality assessment – that is, providing **rigorous justification** of a rule or policy's proportionality. It may be tempting to give up in the face of the uncertainties and ambiguities discussed. Nevertheless, responsible regulation must proceed. Ignoring proportionality can lead to one-sided policies, which either produce overly protective regimes with unacceptably burden research, or overly permissive regimes that do not adequately provide protections out of fear of inhibiting research.

And it will be work, indeed. When a given rule is under consideration, a non-trivial amount of research and analysis will be needed. Is there evidence on the magnitude of the harms or wrongs being prevented? What about the effectiveness of the proposed rule? And on the flip side, what effects will it have on the research enterprise? What are the quantifiable and non-quantifiable costs? Finally, when all those considerations are taken into account, can the regulation's protective effects truly justify the burdens imposed? And if not, can it be refined so that it does?

The final justificatory step may be the most uncertain and challenging. In some ways, it is an ethical or normative question relating to the values promoted and inhibited by a given policy. Regulators are not typically trained in philosophical analysis that may assist here, but some features of decision-making can be highlighted. These include articulation of the competing values at stake; scrutiny of any empirical evidence adduced; consistency between different judgments; clarity in terms of the reasons a given rule is justified, or not.

There is not space to elaborate here on such analytical tools. Indeed, no single article could adequately do so. Instead, it may be that regulators – or at least, some individuals in the regulatory process – should receive training in these analytical tools. As it stands, many relevant degrees like Masters of Public Policy or Masters of Public Administration do not routinely integrate such analytical training into their curriculums, focusing instead on social sciences. Reform of these curriculums might help boost competence in performing proportionality assessments. Alternative educational systems should also be considered, such as short courses, blended learning modules and ad hoc training workshops that may be more practicable for working professionals.

Especially because of the difficulty of making proportionality assessments, **transparency** in justificatory analyses will be crucial. Transparency here refers to some public promulgation of the reasoning process behind the decision that is reached. This would not only be easily accessed by stakeholders, but promulgated to relevant stakeholder groups so they are aware it exists in the first place.

Almost any rule will involve some trade-offs between protection of individuals and minimising burdens on research. As such, criticism from some affected stakeholders is inevitable. Having the reasoning and evaluation of a proportionality assessment will not eliminate that criticism, but it

can go some way towards blunting suspicion that such an assessment was one-sided or ignored their concerns.

Moreover, there is good reason to suppose that stakeholders are owed this sort of transparency. For researchers, regulations have coercive force – failure to abide by them will result in penalties, whether criminal, civil, or – in the case of instructional policies – professional. It is a matter of respect to those individuals who are liable to such punishments that the reasoning process behind the rules is laid out in full. Other individuals like research subjects have a different relationship with regulations; while regulations do not directly bind them, they are carried out in their name. And if a regulator decides against enacting a given protective rule, that regulator is deciding to permit a certain degree of risk of harm to accrue to participants or others. Those affected individuals deserve to know the reasoning process behind this decision, as they may well be harmed by it.[18]

Another benefit of transparency is that it can prompt regulators to ensure their reasoning is truly defensible. Behind closed doors, there may be a temptation to wave away concerns that are too difficult or complex. By making their reasoning public, they are compelled to seriously reckon with all the considerations that stakeholders may find relevant. If not, they will be open to – legitimate – scrutiny and critique for inadequate analysis that will undermine confidence in the rules that are put forth.

Promulgation of reasoning and justification from regulators to stakeholders is important, but limited insofar as it is top-down and one-way. A more thoroughgoing and robust way to ensure adequate consideration of competing interests and earn public trust in proportionality assessments is **to directly engage** with those groups, to allow the co-creation of rules and collaborate assessment of the thorny issue of proportionality.

There are a myriad of ways that stakeholders can be engaged in proportionality assessments. For more details on approaches to and justifications for public engagement, see Aitken and Cunningham-Burley, Chapter 11 in this volume (on public engagement and access), and Burgess, Chapter 25 in this volume, (on public engagement and health research regulation).

These approaches are especially valuable for complex and uncertain issues like proportionality assessments. A small group of regulators may have parochial approaches or biased analyses that can be avoided by the involvement of a larger body of stakeholders. It may also relieve some of the pressure to make such complex judgments on their own, by soliciting assistance from a wider group.

This engagement should not be seen as one-off, or only occurring prior to rulemaking. A truly proportional approach to regulation must recognise the potential fallibility of initial judgments, and the fact that the situation on the ground may change. Protections previously seen as adequate could become threatened. For example, DNA profiles have recently been shown to be re-identifiable, which means previous protections merely stripping names and other extraneous information from such profiles are no longer sufficient to guarantee anonymity.[19] Previously burdensome compliance can be made easier by new technologies, as arguably occurred with the advent of digital compilation of ethics review documents allowing for more rapid collation and assessment.

For this reason, engagement should be a continual process, with the proportionality of a given rule periodically up for review and re-evaluation. Regulators may not be equipped to maintain

[18] N. Daniels, 'Accountability for Reasonableness', (2000) *BMJ*, 321(7272), 1300–1301.

[19] Y. Erlich et al., 'Identity Inference of Genomic Data Using Long-Range Familial Searches', (2018) *Science*, 362(6415), 690–694.

such active review, so instead being open to updates and comments from stakeholders may be optimal. This both relieves regulators of some burden to keep regulations' proportionality up to date, and ensures stakeholders have a continued ability to positively impact the rules that affect them.

To be sure, there are limitations on how much engagement can do. It was noted earlier that regulators may need additional training to adequately undertake proportionality assessments. This would already be practically difficult with regulators; with broader stakeholder groups, it is probably impossible. As such, there may be some limit on the extent to which co-creation is achievable for matters as complex as proportionality assessments. Still, we should not allow the perfect to be the enemy of the good; engagement has substantial value, as explained, that can supplement the deep analysis that regulators are responsible for.

3.7 CONCLUSION

In this chapter, I have explored the notion of proportionality in the context of health research regulation. Proportionality was defined in terms of a justificatory relationship: the benefits afforded by a given rule must serve to justify the burdens imposed by it. Assessing proportionality is no easy task; it is beset by uncertainties and challenges of analysis at a variety of levels, and involves weighing of different values – relating to beneficence, non-maleficence, justice and autonomy – that are non-commensurate and often non-quantifiable. The task of proportionality assessment is not impossible, however. Indeed, it is a necessary part of responsible regulation of health research. I have suggested several procedural approaches that can help improve the reliability and legitimacy of those assessments: a facilitative attitude; rigorous justificatory analysis; transparency in reasoning; and engagement in decision-making. These procedures recognise that we cannot formulaically produce an answer as to whether a given regulation is proportionate, and judgement is required. Hopefully, the contents of this chapter – in conjunction with the other material in this volume – can go some way to assisting those involved in regulation in understanding the nature, importance and practice of proportionality assessments.