

# **The Ethics of Community Effectiveness Research in Developing Countries**

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## **Declaration**

I, Sapfo Lignou confirm that the work presented in this thesis is my own. When information has been derived from other sources, I confirm that this has been indicated in the thesis

# Abstract

The aim of the thesis is to explore and discuss the distinct ethical issues raised by the conduct of health-related cluster randomised trials in developing countries, in particular those related to informed consent and representation.

The thesis has four objectives: First, it seeks to identify ethical issues and their importance arising in CRTs and present how they are currently being addressed in published trial reports and papers on the ethics of CRTs. Second, it aims to discuss the limitations of addressing such ethical issues within the existing research ethics framework. Third, by relying on a human right to health, it aims to suggest a broader research ethics framework, beyond the existing clinical ethics paradigm, that takes into account the variety of health studies conducted in developing settings, as well as the broader socio-political context where collaborative health research takes place. Fourth, by examining the common moral features between cluster health studies and public health interventions, it aims to inform current research ethics guidelines and discussions on the ethics of cluster research by suggesting solutions to the problem of informed consent and cluster representation in developing countries, as well as to demonstrate the strength of the suggested research ethics framework in dealing with such complex issues.

I argue that under specific conditions a cluster trial is morally legitimate to proceed despite the absence of informed consent and that a decision regarding the conduct of research should be within the responsibilities of the legitimate political authorities of the host country. I conclude that collaborative health research, which aims to improve the health status of a developing population, should be part of a country's policy, similarly to decisions concerning the implementation of public health measures, and that human subjects should be protected at individual, social and institutional level.

For Iris, my closest companion and biggest distraction in this adventure...

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# Introduction

Cluster randomised trials (where intact social units or groups of individuals – rather than individuals themselves – are randomly allocated to intervention or control conditions) have become an increasingly important methodological tool in health research (Taljaard et al. 2009). However, the substantial methodological differences between cluster randomized trials and conventional randomized trials have ethical implications, which have not been thoroughly explored in the literature and addressed in current guidelines.

Ethical issues raised by these kind of studies are related to questions concerning informed consent and representation: for instance, from whom, how, and when must informed consent be obtained? Who are cluster representatives and what are their responsibilities? On methodology: Does clinical equipoise apply to CRTs? How do we determine if the benefits outweigh the risks of CRTs? And there are key justice issues, such as: How should the benefits and burdens of research participation be distributed between individual subjects and between clusters?

The aim of this thesis is to explore and discuss the distinct ethical issues arising in the conduct of health-related cluster randomised trials with a particular emphasis on their use in developing countries. The main issues that will be examined are related to questions on informed consent and representation. These include: whether consent is required from the clusters involved additionally to individual informed consent, if so how do we identify individuals – or groups – who can represent those clusters and how far can we say their guardianship extends to such a decision; whether a trial is legitimate to carry out when individual informed

consent is not possible; whether lack of individual informed consent violates the rights of the participants; the role and authority of cluster representatives; how to justify cluster research in which individual consent is not feasible in communities with no political structures, and others. For some of these questions, I will discuss the views of the participants of a cluster study in a complex society in Mumbai, where communities are usually amalgams of smaller communities and do not necessarily represent pre-existing political or sociocultural spaces (Osrin et al. 2009).

There are two main reasons for which the research topic has been selected. First, because informed consent and representation are particularly important in the ethics of cluster trials. Cluster trials present distinctive challenges relating to when consent is necessary and to alternative means of ensuring high ethical standards where consent from research participants is not an option (for instance for methodological reasons). Second, because of the significance of such issues in low-income settings; Not only consent can be a challenge in such settings (for instance for cultural reasons) but moral concerns about the ‘representativeness’ of community gatekeepers also arise. Taking into account that there is a pressing need for cluster studies in low income settings, guidance on whether and how a cluster study should proceed in developing countries seems particularly important.

To successfully tackle the research topic, the thesis has four objectives: First, it seeks to identify ethical issues in the conduct of health research related to informed consent and representation, and their importance arising in CRTs and present how they are currently being addressed in published trial reports and papers on the ethics of CRTs (chapters 1, 2 and 3). Second, it aims to discuss the limitations of addressing such ethical issues within the existing research ethics framework (chapter 4). Third, by relying on a human right to health, a principle grounded in existing widely respected law and conventions, it aims to suggest a broader research ethics framework, beyond the existing clinical ethics paradigm, that takes into account the variety of health studies conducted in developing settings, as well as the broader socio-political context where collaborative health research takes place (chapter 5). Fourth, by examining the common moral features between cluster health studies and public health interventions (chapters 6

and 7), it aims to inform current research ethics guidelines and discussions on the ethics of cluster research by suggesting solutions to the problem of informed consent and cluster representation in developing countries (chapter 8) as well as to demonstrate the strength of the suggested research ethics framework in dealing with such complex issues.

## **I.1 | Thesis Layout**

Chapters 1, 2 and 3 constitute a section of the thesis, which sets out and critiques the ‘standard view’ of research ethics. In these three chapters cluster randomised trials in developing countries are identified as a particularly interesting case in which the ‘standard view’ of research ethics is proved inadequate to provide ethical guidance.

The aim of the *first chapter* is to provide an introduction to cluster randomised controlled trials. First, important structural features, which distinguish cluster randomised controlled trials from ordinary RCTs, are presented. Then, I list the reasons for using CRTs in health research and finally, I briefly discuss the new ethical challenges that CRTs raise for researchers, research ethics committees and regulators.

In *chapter two* I discuss challenges that cluster design presents on the nature and practice of informed consent. Problems related to the inability of getting informed consent from all affected individuals are discussed in detail as well as solutions suggested in the literature on how a study may proceed if informed consent is not possible. I conclude that none of these solutions are sufficient and that a different perspective needs to be adopted from the one commonly taken in respect of conventional randomised trials.

In *chapter three* questions related to the role and authority of cluster representatives, known as ‘gatekeepers’, in CRTs are addressed. I first describe how the use of gatekeepers has been developed in the research ethics literature. I then explore the different roles that gatekeepers undertake in different CRT settings and discuss questions related to their authority to legitimately fulfil these roles. I conclude that the use of gatekeepers does not provide a solution to

challenges posed by informed consent especially when CRTs involve clusters, which lack organised structures.

Difficulties with obtaining informed consent from research participants in CRTs bring us to the question of whether and when it is acceptable to conduct a cluster research study when informed consent is infeasible to obtain. For this reason the aim of *chapter four* is to provide an ethical analysis of what is arguably the most challenging ethical issue health research in general: under what conditions we can morally accept the exposure of some individuals to research risks without their consent for social benefit. I present and discuss the main arguments for the justification of health research based on the moral approach normally taken in the research ethics literature. I then examine the implications for cluster research where individual consent is absent. I conclude that an alternative approach could better inform our understanding of cluster research and offer a new analytic insight in when it is legitimate to use a cluster design in health research.

In *chapter five*, I argue for an alternative approach to the moral justification of health research, which suggests that health studies, and in particular collaborative studies carried out in developing countries, should be considered within the broader social context in which they take place. I discuss the human right to health, an existing element of the widely respected practice and conventions, and argue that it should provide the moral basis according to which principles in research ethics should be interpreted and moral challenges related to health research (such as inability to obtain consent from the participants) should be addressed. I conclude that the proposed framework could provide better safeguards for the protection of participants in health research and at the same time it could support and encourage socially valuable research by taking into account a variety of health related studies that have not attracted much attention by existing guidelines and debates on research ethics.

The aim of *chapter six* is to explore and discuss the ethics of research interventions that involve populations or communities instead of individuals, and which often constitute the most effective ways of improving health in developing settings. By relying on Taylor and Johnson's (2007) definition of population-

based interventions, I present the ways in which such studies differ from conventional clinical studies and discuss the distinctive moral issues they present. I conclude that population based research is a distinct type of health research involving human subjects, because of its focus on populations rather than individuals, and that for this reason should not be considered within the current (clinical-based) research ethics framework. I then discuss the advantages of adopting a moral framework based on the human right to health when practical and moral challenges in the conduct of population-based research are presented. I conclude that a distinction between ‘population-based research’ and ‘disease-based research’, can help us better understand and address the ethical challenges raised in the cluster design and in particular the problem of informed consent (which I discuss in more detail in chapter 8).

Having argued in chapter six that *new* challenges concerning our inability to obtain consent in cluster trials are related to the distinct features of population-based interventions, one of the objectives in *chapter seven* is to examine the role of informed consent in public health settings. By reviewing the conditions under which it is morally legitimate to restrict personal freedom/autonomy for social benefit in different public health measures, I aim to explore whether the same justifications could defend similar interventions for research purposes. However, since cluster trials, due to their experimental nature, also inherit most of the ‘generic’ problems of health research (which have been widely discussed in the existing research ethics literature), as well as some of the specific problems investigators face in medical research when cluster trials involve clinical procedures, to successfully deal with the problem of informed consent in CRTs I also examine the role of informed consent in clinical ethics. Comparing different standards for seeking informed consent in clinical research and public health settings, I conclude that informed consent requirements in cluster trials should be adjusted to the level of risk involved.

The aim of *chapter eight* is to provide answers to the question: how should we proceed when informed consent in a cluster study is not possible? I first review examples of CRTs where informed consent is problematic because of the distinct features of population-based interventions. I discuss the conditions under which

seeking individual consent in such cases is not necessary and argue that a decision regarding the conduct of research should be within the responsibilities of legitimate political authorities of the host country. I then discuss cases where informed consent in CRTs may be problematic for reasons that investigators may encounter in other research designs. Based on the moral framework I presented in chapter 5, I discuss when seeking informed consent is necessary and when the consent requirement could be overridden by other competing moral values (such as respect for local culture). Finally, I review the role of research ethics committees and the importance of community involvement in ensuring that a research proposal is consistent with both the principles of research ethics and the local needs and interests of researched communities.

In the conclusion, I summarise the main arguments of the thesis and to discuss whether the main research questions raised in Chapters 1, 2 and 3 have been successfully addressed by the proposed research ethics framework.

The *Appendix* discusses the potential of an important moral issue that has not been included in current debates on the ethics of cluster research. By focusing on a cluster randomised trial in Mumbai, India, where clusters do not map on to collective units, I aim to examine whether defining communities for research purposes in collaborative health research may lead to a conflict between sponsor and host countries. The discussion in this chapter is based on collaborative empirical work with SNEHA (Society for Nutrition, Education and Health Action) in Mumbai, India. By presenting the views of research participants, we investigated whether residents' sense of community matches with the scientific notion of the cluster, defined by the investigator as a geographic area, and explored the extent to which the cluster trial answers their needs. We then examined whether the possibility of a conceptual mismatch is likely to have methodological implications for a study or to lead to potential social disharmony because of the research interventions. Following this analysis, I argue that it is important to take social factors into account as well as statistical efficiency when choosing the size and type of clusters and designing a trial. I conclude that one method of informing such design would be to use existing forums for community engagement to explore individuals' primary sense of community or social group

and, where possible, to fit clusters around them.

## **I.2 | Methodology**

A mixed-methods approach will be used incorporating both empirical and conceptual work.

### **I.2.1 | Literature review**

In the literature review, chapters: 1, 2 and 3 a series of ethical issues posed by cluster trials are defined and their importance is explained. Moreover contemporary principles of research ethics are reviewed as well as their limitations for successfully dealing with moral challenges in CRTs. Each of these issues will be addressed in detail in a subsequent chapter in the thesis. This necessary preliminary work, the literature review, is carried out to generate an initial framework of ethical issues arising in health research and cluster-randomized trials in particular.

### **I.2.2 | Empirical work**

Empirical work (chapters 8 and Appendix) includes in-depth interviews and focus group discussions with trial participants and gatekeepers (cluster level decision-makers) in a cluster randomised trial in Mumbai slums. The empirical work is aimed to inform the concurrent ethical analysis (i.e. the specific ethical issues to be addressed during the interviews and focus group discussions will be identified in the ethical analysis). The results of the empirical work are not presented wholesale in one chapter of the thesis but intersperse themes and quotes within the normative analysis for illustration and evidential support for claims.

### ***Setting***

Half of Mumbai's 12.5 million inhabitants live in slums (Officer of the Registrar General and Census Commissioner, Director of Census Operations Maharashtra: Census of India 2011; New Delhi: Ministry of Home Affairs, Government of India, 2011). Slum-dwellers are worse off with respect to most health, nutrition and population indicators. About one-fifth of slum homes have a private toilet, 31% of residents have completed 10 years of education, and the total fertility rate is below the replacement threshold at 1.9 (Government of India Ministry of

Health and Family Welfare: National Family Health Survey, India (NFHS-3 2005-06); Mumbai: International Institute for Population Sciences 2007). The city is divided into 24 municipal wards for administrative convenience. Of these, M East ward has the lowest literacy rate (66%), the highest infant mortality rate (66 per 1000), the poorest human development ranking (0.05), and a high proportion of slum settlements. L ward is ranked second lowest, with a human development index of 0.29, and both of these vulnerable wards have large migrant populations, low and insecure levels of livelihood activity, large-scale unauthorized housing, and poor education and health facilities (Lignou et al. 2016).

For these reasons, M East and L wards were selected for a cluster randomized controlled trial of an intervention to improve the health and nutrition of women and children in Mumbai's slums through Community Resource Centres. The trial involved 40 informal settlements, each having approximately 600 households. 20 areas were allocated to have community resource centres and 20 acted as controls. Allocation was done in three blocks of 12, 12 and 16 communities. Resource centres were set up in three phases, of 6, 6 and 8 centres, respectively, with six-month intervals between the start of each phase. The centres were set up to act as bases for collection and dissemination of health information, provision of services, and referral of individuals and families to appropriate services. The effects of the intervention were evaluated against indicators of maternal health and infant feeding, women's reproductive health, violence against women and children, and childhood nutrition (Lignou et al. 2016). Outcomes were compared with those in the 20 control settlements (More et al. 2013).

### ***Data collection***

As part of the empirical study, we collected qualitative data to understand participants' perception of community and the factors that shaped their views. Participants were also asked about preferred methods of consultation, representation and their satisfaction with methods actually employed in the study. Participants were recruited from across several intervention and control clusters in order to involve residents with different socio-economic and demographic backgrounds. Data collection took place between August and October 2012. Separate semi-structured questionnaires were designed to guide the focus group



discussions and individual interviews. They were developed iteratively through conceptual discussions between S. Lignou, S. Edwards, D. Osrin, S. Das and G. Alcock, a multidisciplinary team with backgrounds in medicine, research ethics, social sciences and both quantitative and qualitative research methods. Discussions focused on the general content, topics of interest and the structure of individual questions. With the help of J. Mistry (a local translator/research assistant conversant with the study objectives and underlying concepts) the team piloted and refined the questionnaires to familiarise themselves with the meaning and flow of questions, and to ensure that translations were comprehensible. The researcher-translator felt more comfortable verbally translating from questionnaires in English to local languages during data collection.

The questionnaires were divided into broad sections on respondent background, understanding of community, community health, perceptions of risk (associated with participation in a cluster trial), representation (by decision-makers), and understanding and acceptance of community-based research. Background information included age, gender, occupation, length of residence in the area, and the nature of local family and social networks. The section on community was designed to explore how respondents understood and described the concept and meaning of 'community', based on their experiential knowledge of living in a Mumbai slum area. Given their complexity, discussions about uncertainty and risk associated with participating in community-based research trials were developed more in interviews with decision-makers and group discussions with residents than in individual interviews with residents.

The aim of the focus group discussions was to obtain a broad sense of residents' understandings and views on community, health and community-based research, and the individual interviews to explore themes in more detail, drawing upon individuals' experiences of inclusion in the cluster trial. Potential respondents were identified by community organizers, word of mouth, or casually during fieldwork in their communities. S. Lignou and J. Mistry conducted all group discussions and individual interviews. The focus groups were held in SNEHA community centres, the in-depth interviews with residents in their homes, and the interviews with decision-makers in their homes or offices.

Two focus group discussions took place with local residents and 20 semi-structured interviews with different respondent groups. On average, ten participants took part in each focus group, most of them women aged 18-55. Semi-structured interviews with ten residents (nine women and one man) and seven individuals (five men and two women) identified by residents as local leaders or decision-makers were conducted. The interviews lasted approximately an hour each. In addition, two Municipal Corporators (locally-elected government officials involved in urban planning and development) were interviewed and one representative of a political party located in a slum community. Before giving verbal consent to participate, the purpose of the study was explained to the participants, who were also given a participant information sheet and assured of confidentiality. Data collection ceased once it was felt that no new themes were emerging or that concepts and categories appeared to be sufficiently explored.

Each interview was audio-recorded and subsequently translated and transcribed in English. Care was taken to minimise misinterpretation from changes in meaning or bias during the translation process (Easton et al. 2000). Interview transcripts included a paragraph describing the background, setting and process of the data collection activity.

### ***Data analysis***

Individual interview transcripts were reviewed by S. Lignou in order that key emergent themes could be identified. These were used to inform subsequent data collection and in the development of early analysis. Thematic data were entered into a spreadsheet in Microsoft Office Excel, and organized into columns of cases and rows of transcribed data excerpts. Given the relatively small number of participants, data were manually analysed using a thematic analysis approach (Lacey A, Luff D. *Qualitative Data Analysis*. 2007. The NIHR RDS for the East Midlands/Yorkshire & the Humber). Several drafts of the analysis were written up, providing the opportunity to further refine the themes and provide a fairly rigorous interpretative framework with which to conceptualize and present the findings (Lignou et al. 2016).

***Ethical approval***

The study was approved by the Multi-institutional Ethics Committee of the Anusandhan Trust, in March 2010 (Lignou et al. 2016).

**I.2.3 | Conceptual Work (chapters 4 to 8)**

Ethical analysis begins with the articulation of important questions (e.g. Under what conditions can we morally accept the exposure of some individuals to research risks without their consent, for the social benefit of such research? What is the role of informed consent in clinical ethics? When is it morally permissible to restrict personal autonomy in public health settings? (and others). For each ethical issue identified, an ethical analysis is presented based on political and moral philosophy. An extensive review of the scholarly literature documents and critical analysis of arguments is offered for and against ethical positions. The ethical analysis seeks to synthesize arguments in the literature into a coherent position and propose solutions to the moral questions identified in the literature review.

# Chapter 1

## Important structural features of CRTs

The aim of this chapter is to provide an introduction to cluster randomized controlled trials. First, important structural features, which distinguish cluster randomised controlled trials (CRTs) from ordinary randomised controlled trials (RCTs) will be presented. Then, I list the reasons for using CRTs in health research and finally I briefly discuss the new ethical challenges that CRTs raise for researchers, research ethics committees and regulators.

### 1.1 | Important structural features of CRTs

The cluster-randomized design is an increasingly important methodological tool in health research (Taljaard et al. 2009). It is used in a number of cases: in knowledge translation research, quality improvement research, community based intervention studies, public health research, and research in developing countries (Weijer et al. 2011). In cluster randomized trials (also known as group randomized or place randomized trials), intact<sup>1</sup> social units or groups of individuals, rather than individuals themselves, are randomly allocated to differing intervention arms (intervention or control conditions) (Taljaard et al. 2009). Clusters can be primary care practices, hospital wards, households,

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<sup>1</sup> In certain studies clusters may be created mainly for research purposes (see APPENDIX for a more detailed discussion) and thus the term ‘intact’ may not be appropriate to describe those groups. The reason, however, the term ‘intact’ is used here is to highlight the moral significance of considering group interests in the ethics of cluster research (an issue which will be discussed in Chapters 3 and 8).

neighbourhoods, schools, or entire communities or villages (Weijer et al. 2011)

There is a wide variety of CRTs, and many different levels and ways in which people are involved in them. The choice of the trial design depends on the question and hypothesis addressed by the trial. Research interventions in cluster trials may be delivered to an entire randomized group as a unit or to individuals within each group (to individual cluster members). All members of the group/cluster receive the same intervention (Weijer et al. 2011). Outcomes are then observed on individual cluster members (or subsamples of members) to evaluate the effect of the experimental intervention. Although outcomes are observed on individuals, they may be aggregated at the cluster-level, for example, percentage of X-ray requests by physicians (Taljaard et al. 2009).

In CRTs experimental units (the direct recipients of the intervention) may be different to the randomization and observation units; for instance the group that receives the experimental intervention may not be the same as the group from which data are collected. Moreover, the measurements chosen to evaluate the interventions might be available from routine records and the people might not need to be contacted directly. In such cases, we need to distinguish between consent to intervention and consent to data collection (this is not often explicit in RCTs) (Hutton 2001). The outcomes of interest might be measured on those directly receiving the intervention, or on those intended to benefit indirectly; for instance, a trial may assess practitioners' knowledge or the changes in their patients' health (Hutton 2001).

Compared with an individually randomized trial with the same number of individuals, cluster trials have lower statistical power (Donner and Klar 2000) This is a result of the fact that clusters tend to have various characteristics in common, and therefore show some intra-cluster correlation (the responses of individuals within a cluster tend to be more similar than the responses of individuals in differing clusters); "Since participants within any one cluster are more likely to have similar outcomes, the outcomes are not completely independent. Thus, the statistical power of a cluster randomised trial may be substantially less than that of a similar-sized individually randomised trial" (MRC

2002, p. 7). Even a small intra-cluster correlation can have important implications for statistical power if the clusters are large. However, some improvement in efficiency can be gained by using matched or stratified designs<sup>2</sup> (Hutton 2001). Therefore, the use of a cluster-randomised design must be carefully justified (Weijer et al. 2011). As a rule of thumb, it is more important to have an adequate number of clusters than a large number of participants in each cluster to enhance the potential of detecting true differences between study arms (Killip et al. 2004).

## **1.2 | Why randomize by cluster/ Reasons for using CRTs**

There are several reasons, scientific (methodological) and practical (due to logistical and political constraints), for the use of CRTs in health research (Hutton 2001). Some of the types of cases in which cluster randomized design is used are listed below:

### **1.2.1 | [A] Methodological reasons for doing a cluster randomised trial**

#### ***Cluster level intervention***

In recent years, there has been a growing interest in generating dependable evidence about the effectiveness of health policies, programs and practices, which cannot be rigorously tested through individual randomization. In health services implementation research for example, the intervention may be administered to the health professional or teams of health professionals or may involve changes to the health care organization (Taljaard et al. 2009). Cluster randomized trials in which entire medical practices or health care units are randomized, are ideal for this purpose.

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<sup>2</sup> Stratification of clinical trials is the partitioning of subjects and results by a factor other than the treatment given. Stratification can be used to ensure equal allocation of subgroups of participants to each experimental condition. This may be done by gender, age, or other demographic factors. Stratification can be used to control for confounding variables (variables other than those the researcher is studying), thereby making it easier for the research to detect and interpret relationships between variables. For example, if doing a study of fitness where age or gender was expected to influence the outcomes, participants could be stratified into groups by the confounding variable. A limitation of this method is that it requires knowledge of what variables need to be controlled (Paggio et al. 2001).

Interventions may also involve training or education of health professionals with the aim of improving patient care. The nature of the intervention in those cases may require it being administered at the cluster level. For instance, Lewin and colleagues studied the impact on patient outcomes of a cluster-level training programme for health workers caring for tuberculosis patients in South Africa. The study targeted primary care clinics in Cape Town that had tuberculosis treatment completion rates of less than 70%. In the intervention arm of the trial, nurse clinicians underwent an 18-hour in-service training program that focused on patient centred care and quality improvement. Study outcomes compared patient treatment completion and patient cure rates before and after the study intervention (Lewin et al. 2005).

Likewise, in public health there is a growing concern to improve policies and programs. Cluster randomization is often the only feasible approach to evaluate alternative policies and models of care (Taljaard et al. 2009). An example of that case is the Community Intervention Trial for Smoking Cessation (COMMIT). This cluster level intervention used mass education to target entire communities in an attempt to reduce smoking rates. Through a wide range of influences including public education, health care workers promoted smoking cessation. With such broad interventions, a conventional trial design would have been impossible (The Commit group, 1995).

### ***Cluster action of an intervention***

Cluster design is also used when investigators want to study both individual and group effects of an intervention. Trials of the impact of vaccines and some drug treatments (that act at individual and community level) cannot be evaluated in isolated individuals since their effectiveness is dependent on how many other people also have the intervention (Hutton 2001). Researchers by using a cluster design can measure the effectiveness of a vaccine for an infectious disease administered at the individual level but observed among those in the wider community (as a consequence of herd immunity) by detecting the likelihood of individuals becoming infected, the severity of the infection and the transmission of the disease (Hutton 2001).

### ***Treatment cluster contamination***

Another methodological reason for which randomization at the individual level may be undesirable is the need to avoid contamination. For instance, researchers studying the change of social behaviour or the transmission of knowledge may choose to randomise participants at the level of a GP practice or town to avoid social interaction between the participants in close proximity, which will contaminate the study (Taljaard et al. 2009). The study of Kennedy and colleagues is an example of such cases. They conducted an individual level intervention in which they studied the effect of patient-centered educational materials on patient knowledge, anxiety, and quality of life. Patients in the study were on long term follow-up for ulcerative colitis. Because patients interaction with each other was frequent, since they were attending the same clinic, the researchers randomised clusters of patients attending the same clinic to receive either the educational material or no intervention (Kennedy et al. 2003).

Cluster design may also be used to enhance subject compliance. Studies conducted in workplaces, schools or general practices could be enhanced by interaction between subjects; e.g. formal or informal discussions (Hutton 2001).

## **1.2.2 | [B] Practical reasons for conducting a cluster randomised trial**

### ***Administrative convenience***

Administrative convenience is another reason for using cluster-randomized design. As noted in the MRC guidelines: “If the intervention involves supplying equipment or staff to an administrative unit, then, by randomising these units rather than individuals, only a subset of the units would receive the equipment or staff. This may be administratively cheaper or more convenient.” (MRC 2002, p. 4) In cases where access to patients is only possible through professionals, a conventional design would require large numbers of individual professionals to be contacted and requested to pass on trial information. When researchers need to have access to routine data, cluster design is ideal as they only need to approach relevant administrative or archiving authorities, such as general practices or hospital trusts, and not a large number of individuals to pass on trial information (Hutton 2001). Moreover, using clusters makes the personnel more likely to



cooperate since professionals could concentrate in a few locations and do not need to change practice for each patient. Finally, a conventional design in developing nation settings where special equipment or personnel are required would make the trial organization and implementation very complicated (Taljaard et al. 2009).

### ***Political reasons***

A second pragmatic reason for doing cluster trials exists in cases where it is necessary to obtain permission from national and local governments or community leaders to conduct the trial. In developing countries, in particular, where there is no local tradition of individual informed consent, consent has been sought from the head of a village to use the village as a cluster before proceeding to contact individuals (Taljaard et al. 2009).

## **1.3 | Ethical issues in CRTs**

### **1.3.1 | Importance of the problem**

Although the basic principles reflected in international ethics codes underpinning the ethical conduct of research involving human subjects have become enshrined in the ethics review of biomedical research, their application in cluster randomized trials does not have a clear-cut interpretation. The fact that the cluster design involves groups of participants or patients has implications for both the science and the ethics of CRTs. Those ethical challenges have not been thoroughly explored in the research ethics and bioethics literature. Relevant international and national guidelines were designed to protect the welfare and liberty interests of individual participants. The only guidelines addressing cluster randomised trials are the UK Medical Research Council document (Cluster Randomized Trials: Methodological and Ethical Considerations 2002) and the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials (2013). However, neither the broad scope of the ethical issues in CRTs is addressed in the MRC documents (Taljaard et al 2011) nor the applicability of the Ottawa Statement guidelines in collaborative research in developing countries is clear. As a result, there is lack of authoritative guidance to help researchers design and conduct their trials according to the highest ethical standards.

Moreover, because of the absence of formal guidelines for CRTs, research ethics committees and regulators do not have an international standard to follow, which results in uncertainty and variety of interpretations to ethical standards and permissible practices that should be adopted (Weijer et al. 2011). Since research ethics boards (REBs) may be unfamiliar with this increasingly important study methodology, they may fail to consider all of the relevant ethical issues generated by a study protocol, resulting in inadequate subject protection and unequal treatment of subjects in different jurisdictions (Taljaard et al. 2009).

To illustrate the serious challenges that CRTs pose to the current conceptual framework for research ethics, let us consider the following example. As I will later explain principles for the protection of the liberty and welfare interests of individual research participants, as laid out in the Belmont Report, cannot answer most of the ethical questions raised in this case:

*A study randomized villages in Nepal to provide nutritional supplements to women of childbearing age. Villages were randomized to one of four study arms: vitamin A supplements, -carotene supplements, both supplements, or placebo. The outcome of interest was mortality associated with pregnancy and childbirth. Community leaders agreed to randomization of communities, while individual women gave verbal consent to receive the supplements and provide data. A sample of women who became pregnant underwent further investigations, including blood sampling. Mortality and other variables were collected prospectively by study workers. Further information regarding fatalities was obtained from interviews with the families of any subjects who died (West et al. 1999).*

Some of the ethical issues raised by this kind of studies are the following: is consent required from the communities involved additionally to individual informed consent? If so, then who has the authority to speak on behalf of the community and based on what criteria? Do the researchers have special obligations towards the subjects of the study, for instance a duty to provide ancillary benefits to all study arms (despite the size of the cluster and the cost involved) because of the developing nation setting? How do we determine

whether the benefits outweigh the risks in this type of studies?

Before discussing in detail the ethical challenges presented in cluster randomized controlled trials, let us briefly consider the essential ethical principles of health research on humans to explain why the distinctive features of CRTs challenge our current understanding of research ethics.

### **1.3.2 | A standard view of research ethics**

International codes governing research on people are largely based on individually randomized trials. In those trials individual subjects are randomised to receive one of the differing treatment regimens and they are typically simultaneously the unit of randomization, the unit of experimentation, and the unit of observation (Weijer et al. 2011). Contemporary research ethics is viewed as governed by three principles laid out in the Belmont Report, a widely accepted governance code in research ethics. These three principles are the principle of respect for persons, the principle of beneficence (and its complimentary principle of non-maleficence), and the principle of justice.

The ethical principle of *respect for persons* means that choices of autonomous individuals (people who can responsibly make their own decisions) ought to be taken seriously. People lacking autonomy, such as young children or adults with advanced dementia, are entitled to protection. This principle is the source of the moral rules requiring informed consent from research subjects (researchers should obtain agreement from a research subject or their surrogate decision-maker to participate) and protection of confidential health information (Taljaard et al. 2009). Informed consent is valid when the research subject (or their surrogate decision maker) has adequate information about the study, understand what is at stake in the decision and freely decide to participate (Weijer et al. 2011).

The ethical principle of *beneficence* means that researchers have an obligation to protect subjects from avoidable harm and, where possible, to promote the good of research subjects. This principle is the source of a variety of moral rules that guide the analysis of benefits and harms of the study (Taljaard et al. 2009). The principle of beneficence is considered as complimentary to the principle of non-

maleficence, which requires that health research should not add to the burdens those participating in research already face. This principle rules out any research proposal that would make research participants worse off because of their involvement in research.

The ethical principle of *justice* means that researchers have an obligation to treat study subjects fairly and to ensure that the procedures for their selection are equitable. The researchers must also ensure that vulnerable groups (such as children, incapable adults, prisoners, or pregnant women) are not exploited (included as a population of mere convenience) or excluded without clear justification (Taljaard et al). This principle also requires that research subjects who are harmed as a result of research participation should be compensated (Childress 1976).

It is obvious that some of the questions raised in our example cannot be answered by relying on the ethical principles of our current system of research ethics (the Belmont Report Principles are assumed to form the basis of the standard position, which will be discussed in Chapters 2 and 3, and critiqued in later chapters). For instance, the principle of respect for persons does not provide any guidance on how we should answer the question “who has the authority to speak on behalf of the community and based on what criteria?” In Chapter 5 I suggest an alternative moral framework for research ethics where these questions can be better understood and addressed.

## **1.4 | Conclusion**

The aim of this chapter was to provide an introduction to cluster randomized controlled trials. I presented the important structural features, which distinguish CRTs from RCTs, the reasons for using cluster design in health research and the new ethical challenges CRTs present, which will be discussed in the following chapters.

# Chapter 2

## Consent and Cluster Trials

Informed consent is an important subject of discussion in the literature concerning the ethics of health research. The aim of this chapter is to set out and critique the ‘standard view’ of research ethics by discussing challenges that cluster design presents on the nature and practice of informed consent, and in particular: from whom, when, and how must informed consent be obtained in CRTs in health research, what kind of information should be provided, and the necessity and feasibility of obtaining individual consent. In the discussion section problems related to the inability of getting individual informed consent are presented as well as solutions suggested in the literature on how a study can proceed if informed consent is not possible. I conclude that none of these solutions are sufficient and that a different perspective needs to be adopted to that commonly taken in respect of conventional randomised trials.

### 2.1 | Informed consent in research ethics guidelines and regulations

Individual informed consent is widely considered an essential ethical requirement for study participation in health research<sup>3</sup>. As stated in the Nuremberg code: “The voluntary consent of the human subject is absolutely essential... The duty and responsibility for ascertaining the quality of the consent rests upon each individual

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<sup>3</sup> A detailed discussion on why the informed consent requirement has a central role in clinical ethics is presented in Chapter 7.

who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity” (Article 1). As a general rule, informed consent for study participation must be obtained from research subjects or their surrogate decision makers.

Criteria for informed consent for research participation are laid out in national and international research ethics guidelines (Department of Health and Human Services: Protection of Human Subjects Washington USA; 2005, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council, Social Sciences and Humanities Research Council: Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans Ottawa Canada; World Medical Association: Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects Ferney-Voltaire France; 2008 Council of International Organizations of Medical Science: International Ethical Guidelines for Biomedical Research Involving Human Subjects Geneva Switzerland; 2002). Those include disclosure requirements: an explanation of the purpose of the study; a description of the study interventions; a description of the risks and potential benefits to subjects from research participation; a description of alternatives available to potential subjects should they choose not to participate; a description of confidentiality protections; a statement assuring potential subjects that participation is voluntary, that they may withdraw at any time, and that their quality of care will not be affected should they choose not to participate or to withdraw; and, information on whom they may contact with questions (McRae et al. 2011).

A number of these guidelines allow for a waiver of consent under certain conditions. For instance, in the Helsinki Code, although similar principles to those in the Nuremberg code are stated, informed consent is not given the prime position, and the possibility of situations in which a “physician considers it essential not to obtain informed consent” is presumed (Hutton 2001)<sup>4</sup>.

Cases where individual informed consent may not be feasible are also considered

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<sup>4</sup> Exceptions to the informed consent requirement in clinical context are discussed in Chapter 7.

in the case of ‘Community-based research’. WHO/CIOMS guidelines state: “Where research is undertaken on a community basis - for example by experimental treatment of water supplies, by health services research or by large-scale trials of new insecticides, of new prophylactic or immunizing agents, and of nutritional adjuvants or substitutes - individual consent on a person-to-person basis may not be feasible and the ultimate decision to undertake the research will rest with the responsible public health authority. Nevertheless, all possible means should be used to inform the community concerned of the aims of the research, the advantages expected from it and any possible hazards or inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated, in every possible respect, in the community context.” (Howard-Jones 1981, p. 1447).

## **2.2 | A moral foundation of informed consent**

In the introduction I referred to the ethical principles of research ethics: respect for persons, beneficence and justice.

The requirement for informed consent for research participation is often argued to stem from the principle of respect for persons. According to this principle, the wishes of autonomous individuals should be respected. Autonomous individuals are those who are capable of self-government and who can make responsible choices for themselves. Autonomous individuals should be free from coercive influences and decide about their participation after being adequately informed about the study. The principle of respect for persons also requires that individuals with diminished autonomy should be protected.

The ethical principle of respect for persons may be viewed as deriving from deontological moral theory, which suggests that people have intrinsic moral worth by virtue of their capacity for rational decision making about their ends (McRae et al 2011). It also suggests that each of us has a duty to recognize and respect the capacities for personhood in others (Freedman 1975). As Freedman explains informed consent arises “from the right which each of us possesses to be treated as a person, and in the duty which all of us have, to have respect for persons, to

treat a person as such, and not as an object. For this entails that our capacities for personhood ought to be recognized by all – these capacities including the capacity for rational decision and for action consequent upon rational decision” (Levine 1988, p. 145). Respecting the worth of others suggests that people can only legitimately be involved in other people’s projects or activities if they can adopt other people’s ends as their own. By providing informed consent a competent person demonstrates that they freely give agreement to participation, based on an adequate understanding of information related to that decision (Sim and Dawson 2012).

The purpose of human research is to generate knowledge for social benefit and in order for this to be possible human subjects will be put at risk primarily (or merely) for the benefit of others<sup>5</sup>. According to the principle of respect for others, this practice can only be morally legitimate if research subjects can adopt the ends of the study as their own. Informed consent constitutes the giving of permission to researchers to act in this way; i.e. it (partially) justifies research subjects to be exposed to risk for social benefit. By obtaining informed consent researchers (partially)<sup>6</sup> fulfill their duties to respect research subjects’ autonomy and treat them as ends in themselves (McRae et al 2011).

Although empirical data suggests that informed consent is often difficult to achieve, because of difficulties related to understanding and recollection of research information (de Melo-Martin and Ho 2008; Faden and Beauchamp 1986; Lignou and Edwards 2012), and thus it could be argued that research does not and need not aim to respect autonomy (see discussion in Chapter 4 where the view that the purpose of informed consent is to protect personal autonomy is critiqued as inadequate) to facilitate the discussion, I will assume in this part that informed consent is a necessary requirement in human research.

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<sup>5</sup> Although in certain cases participants might get direct benefits from the study (beneficial research).

<sup>6</sup> As I explain in Chapter 4, a researcher’s moral duty to respect the autonomy of their research subjects is not exhausted in obtaining informed consent.



### 2.3 | New issues regarding informed consent in CRTs

Informed consent is the main subject of discussion in the literature concerning CRTs. As already mentioned, the ethical principle of respect for persons suggests that researchers are generally obligated to obtain informed consent from the individuals that participate in their research. However, because of their design i.e. cluster randomization, cluster level interventions, and cluster size, CRTs present challenges in obtaining individual informed consent.

In conventional clinical trials (RCTs) the process of obtaining informed consent is straightforward. “In the RCT, consent is generally viewed in terms of a dyadic relationship and is construed in terms of the agreement, or otherwise, of the individual patient or participant” (Sim and Dawson 2012). In most cases the research subject is simultaneously the unity of randomization, the unit of experimentation and the unit of observation. Therefore, researchers can obtain individual informed consent from prospective research subjects before randomization, the intervention they will receive and data collection (McRae et al. 2011).

In CRTs clusters may be randomized before researchers identify or approach cluster members. As a result, it is often not possible to get individual informed consent for random assignment (McRae et al. 2011). Moreover, the different levels of randomisation and intervention mean CRTs raise important ethical issues on the levels at which consent can be sought and the reasons for which it can be sought. In CRTs there are many cases in which it is either impossible, or extremely difficult to get informed consent from the individuals to whom the intervention will be applied, while there are also cases where, even though it is possible to get individual informed consent, some researchers argue that it is not necessary to do so<sup>7</sup>. In short, CRTs raise new issues on the nature and practice of informed consent in health research (Hutton 2001). Some of these challenges are listed below:

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<sup>7</sup> These cases are discussed in detail in Chapter 8.

### **2.3.1 | Levels at which consent might be sought**

In RCTs consent operates at the level of the individual person (participant). In CRTs there are further levels to consider. In CRTs we randomize at the level of the intact social group (cluster) and not at the level of the individual, as a result, there is another layer of consent that, it could be argued, should be obtained for the entry of the cluster into the trial. Thus, additionally to individual informed consent, it is claimed that consent should also be sought by a cluster representative for the trial to go ahead (I explain this further in the section: feasibility of consent).

### **2.3.2 | Consent to what?**

In CRTs consent might be sought for the use of routinely held data, additional data collection (with or without the use of invasive procedures) or administration of an intervention (Hutton 2001). It is generally argued that consent should be considered and obtained at several levels and at no level responsibility can be delegated with impunity (Hutton 2001).

### **2.3.3 | Information**

The information provided, when consent is sought in CRTs, might be more complicated than that required for RCTs. For instance, a practical difficulty that researchers face in CRTs is to explain the trial to those allocated to a control arm, since consent is often sought after randomisation (Hutton 2001). In CRTs if a cluster member refuses the allocated intervention (i.e. routine care) they usually cannot get their preferred alternative. However, this is not a new issue in CRTs. In RCTs individuals who decline participation cannot necessarily get their treatment of choice (Hutton 2001). According to Hutton, trial information should be provided even in the cases where a member of a cluster cannot opt out of the intervention (for instance, when an insecticide is sprayed throughout their village). Although providing information in those cases could either increase goodwill or subjects' concern, a failure to inform a research subject might result in a sense of violation (Ashcroft 1998; Snowdon et al. 1999).

### **2.3.4 | Timing of informed consent**

Another issue in CRTs is the timing of informed consent. Klar and Donner raise

this issue by comparing two studies examining the impact of administration of vitamin A on early childhood mortality. The first study used households as units of randomization and sought informed consent before randomization. The second study used the community as unit of randomization and researchers obtained consent after randomization. Klar and Donner expressed their concern by noting that: “the relative absence of ethical guidelines for cluster randomized trials appears to have created a research environment in which the choice of randomization unit may determine whether informed consent is deemed necessary before random assignment... It seems questionable, on both an ethical level and a methodological level, whether the unit of randomization should play such a critical role in deciding whether informed consent is required [before randomization]” (Weijer et al. 2011).

### **2.3.5 | Necessity and Feasibility of informed consent**

The necessity and feasibility of obtaining individual informed consent from research subjects depends on the nature of the study and the intervention (Hutton 2001).

Considering the necessity for seeking individual informed consent, it is often argued that we should distinguish between experimental and epidemiological research (Hutton 2001). In epidemiological research data is collected from patient records. According to MRC guidelines, when the intervention is at the level of a practice and it does not affect patient care, then explicit consent from individuals is not necessary (Hutton 2001)<sup>8</sup>. Different standards for seeking consent also apply in RCTs where the difference between routine and experimental care is discussed. However, even if we consider consent necessary for all epidemiological studies, in the context of health services research this distinction is more difficult; in areas where there is continuous innovation it is not easy to determine where research begins and thus in which stage researchers should seek consent (Hutton 2001).

Another problem related to the feasibility of obtaining informed consent relies on

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<sup>8</sup> Some advocates of the informed consent requirement object to this view– I discuss this further in Chapter 7.

methodological reasons. As stated in Helsinki Code II, some studies would be vitiated if participants were asked to consent. When a cluster trial studies a behavioural intervention, the informed consent process may lead to treatment contamination (Eldridge et al. 2005, Glanz et al. 1996). As explained by Edwards and colleagues: “Informing the controls fully about the experimental arm(s) is likely to produce the very effect that randomizing by cluster was designed to avoid – that is, prompting controls to adopt the treatment(s) under investigation. One option is to withhold information about the novel treatment from controls, on the grounds that they are getting conventional care and are therefore in the same position as people outside the experiment” (Edwards et al. 1999). In those cases, an independent committee would assess the validity of the reasons for not seeking consent and whether a waiver of consent could be justified for the trial to go ahead (Hutton 2001). However, it is important to consider whether withholding information about the study from participants in the control group can be consistent with the principle of respect for persons and the moral duty of the researchers to respect participants’ autonomy (I discuss this issue in detail in chapter 8).

The major discussion on feasibility of obtaining informed consent in cluster randomized trials, though, relates to the suggested classification of CRTs into ‘individual-cluster’ and ‘cluster-cluster’ trials (Edwards et al. 1999) and is discussed in the following section.

## **2.4 | Feasibility of getting informed consent and the nature of clusters**

### **2.4.1 | Cases where it is possible to get individual informed consent**

The potential to obtain individual informed consent is often linked to the ‘level’ of the intervention. Generally, in individual-cluster trials it is feasible to get individual informed consent. In individual-cluster trials we randomize at the level of the cluster but the intervention is directed at the individuals within the cluster. Examples of individual-cluster trials are vaccination studies, patient-centered educational brochure studies and training and educational programmes for health workers. Within each cluster it is (in theory) perfectly feasible to obtain consent

from the cluster members who will receive the intervention and given that individual informed consent is possible, it is generally argued that there is a moral duty to obtain it.<sup>9</sup> To this extent CRTs are very similar to RCTs.

However, there is one additional complication; although research subjects can consent to the intervention, since it occurs at the level of the particular patient, they cannot consent to the trial-taking place (because the unit of randomization is the cluster). For this reason, there will typically be another layer of consent required. There will be a ‘gatekeeper’, a ‘guardian’ or ‘cluster representative’ whom we must approach before we are allowed to enter a given cluster into the trial, for instance a school director, a village leader and others (Edwards et al, 1999). As summarised by Sabin et al (2008) “the consensus position is that some form of representative mechanism can be allowed to consent for entry of the cluster into a study, but the process requires careful safeguards and should be conducted in a transparent manner. Insofar as the [Cluster Trial] is studying an experimental agent like a new vaccine, if informed consent at the level of the individual cluster member is feasible, then it should be asked for.” (Sabin et al. 2008, p. 42).

Although individual informed consent is in theory possible in individual cluster trials, the use of a representative mechanism for the entry of a cluster into the trial may present moral challenges. As it will be discussed later, in many cases it will be unclear who, if anyone, has the right to speak for a given cluster. Moreover, although, in the case of individual-cluster trials the individuals in the cluster have the opportunity to decline participation, their refusal does not necessarily mean that alternative interventions or treatments will be offered to those who wish to opt out (because of the nature of the trial) (Sim and Dawson 2012). In addition, when a gatekeeper refuses to give consent for cluster randomization, cluster members are denied access in the trial, despite their willingness to participate.

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<sup>9</sup> Although individual consent is possible in individual-cluster trials, in certain cases it should be avoided for methodological reasons, e.g. to avoid contamination (see 2.3. Necessity and Feasibility of informed consent). Suggested solutions to the problems with obtaining individual informed consent in individual-cluster trials are discussed in Chapter 8).

Issues related to the rights of individuals to make their own decisions about research participation and the obligations of researchers to ensure that the procedures for their selection are equitable need also to be taken seriously into account.

#### **2.4.2 | Cases where it is impossible to get individual informed consent**

There are cases where it is not feasible or meaningful to obtain individual informed consent. In cluster-cluster trials the intervention is delivered at a cluster rather than an individual level and thus it may be very difficult for cluster members to avoid the intervention if they do not wish to participate in the trial (although individual consent may feasibly be given or withheld for outcome assessment or access to health records). In environmental interventions for instance, such as water fluoridation or when an insecticide is sprayed throughout a village, it might be impossible for the experimental subjects to withdraw, even if adverse events associated with the intervention were reported (Hutton 2001). The fact that individual refusal of informed consent may be, in effect, rendered meaningless undermines the very purpose of consent (UK Medical Research Council 2011).

The practical difficulties in obtaining individual informed consent are illustrated in a CRT reported by Rowland and colleagues:

*Falciparum and vivax malaria are important health problems in Pakistan and indoor spraying of insecticide is the major preventive method used. The CRT sought to test the effectiveness of a new insecticide – alphacypermethrin – in controlling malaria rates in rural Pakistan. The primary outcome measures were the annual incidence rates of falciparum and vivax malaria. The 180 km<sup>2</sup> study area in Punjab province was divided into nine sectors and each was randomized to spraying with one of two preparations of the insecticide or a no spraying control. In the two intervention arms of the study, all living quarters, storage rooms, and animal quarters were sprayed once with the insecticide. Survey teams visited 400 houses in each district every two weeks to identify new cases of malaria by symptom report and, when indicated, a blood smear to look*

*microscopically for the parasite. Additionally, a cross-sectional survey collected blood smears from 200 to 300 school children in each sector before and after the intervention period. Village elders were informed of the study and gave their permission for the study to be conducted. The study concluded that the new insecticide reduced the annual incidence of falciparum malaria by 95% and vivax malaria by 80%. (Rawland et al. 2000).*

In this CRT, all residents within the study area were deliberately intervened upon via manipulation of their environment and, hence, are human research subjects. However, it would have been impossible to obtain the informed consent of all research subjects in this study. As the study involved spraying all living quarters, storage rooms, and animal quarters within a geographic area, it would have been difficult for cluster members to avoid the intervention. Even if one refused to allow one's own home to be sprayed, one could not practically avoid all the treated buildings in the community (the insecticide proved to have an effective half-life of about six months). As a result, the refusal of informed consent in this study would have been meaningless. Second, requiring investigators to obtain the informed consent of research subjects would have rendered the study infeasible. Each of the nine study sectors contained approximately 2000 people living in 400 homes. The practical impossibility of obtaining informed consent in such cases presents a serious ethical challenge to CRTs (McRae et al. 2011).

According to Edwards and colleagues, in such studies, “the autonomy principle is lost except insofar as the individual has any democratic choice of who the guardian is and some right to consultation by the guardian” (Edwards et al. 1999). They suggest that when informed consent is not feasible, the decision to undertake the research is to be made by a ‘guardian’, a ‘gatekeeper’ or ‘cluster representation mechanism’ (a person or body charged with making decisions on behalf of the entire cluster) (Edwards et al. 1999). This authority must take the responsibility for the consequences of research and also inform the community/cluster on the research, although the people charged with this responsibility might not themselves be directly exposed to the interventions

(Hutton 2001)<sup>10</sup>. In other words, it is considered that “the role of the guardian is key to the ethical conduct of cluster trials” (Edwards et al. 1999).

This view is adopted by the MRC guidelines: “Individual level interventions generally do allow individual choice” while cluster level interventions “do not allow individual choice” (UK Medical Research Council 2002). It is suggested that in individual randomized trials, cluster consent should be obtained for the individuals to be approached, while in cluster-cluster trials cluster consent would be consent on behalf of the individuals (UK Medical Research Council 2002). In this document it is also recognized that both individual and cluster interventions may be included in a single trial. In this case informed consent should be obtained where it is possible: “The fact that individual choice does not exist for a [cluster level] intervention (or for cluster randomisation) does not, for instance, prevent individual consent being sought for giving a complementary [individual level] intervention which is part of the intervention package, or for taking samples, recording information, or extracting data from records” (UK Medical Research Council 2002).

Based on the above suggestions, in cluster-cluster trials and CRTs that involve large clusters, it is essential to consider whom researchers should approach to provide consent on behalf of the cluster; who ought to have the power to deliver the cluster? The selection of a cluster representative is more important and complicated in cluster-cluster trials than in individual-cluster trials, because individual autonomy seems to be lost while a gatekeeper’s decision could substantially affect cluster members’ interests.

When communities are chosen as clusters, things are more straightforward. In CIOMS guidelines it is stated that in community-based research, researchers should seek consent from their community leaders. When communities are randomized as clusters, their gatekeepers/community leaders are likely to be

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<sup>10</sup> The authority of gatekeepers in fulfilling this role will be discussed in the following chapter.



affected by the decisions they make.<sup>11</sup> However, even in that case cluster consent may be problematic; as a Nigerian study indicates, community leaders' consent is cheaper and easier to obtain and their views should not be assumed to be identical with the views of their community as a whole (Onwujekwe et al. 1999)<sup>12</sup>. There are also further ethical issues related to community consent that should be considered, i.e. how a community is defined, how its representatives are chosen, how we should proceed if a community leader is not willing to accept the role of advocate, to whom should responsibility for the decision to enter the cluster be passed, and others.

Although cluster consent has been proposed as a solution to overcome difficulties in obtaining individual consent in cluster-cluster trials, it is important to consider further ethical problems associated with this solution and decide whether and when the moral conduct of a CRT is justified when individual consent is not possible.

## **2.5 | Discussion**

The ethical principle of respect for persons generally requires that researchers obtain informed consent from research subjects. As mentioned above, informed consent plays a key role in the ethical justification of human participation in research. By providing informed consent research subjects state they adopt the ends of the study as their own and also permit researchers to expose them to risks for other people's benefit. However, in some CRTs seeking individual informed consent is either impossible or would undermine the scientific validity of the trial (e.g. when there is high risk of contamination). If informed consent cannot be obtained, then it seems reasonable to argue that a study cannot proceed. This, however, would lead to undesirable consequences, from the point of view of scientific research, since it would significantly restrict the conduct of CRTs (especially of cluster-cluster trials and trials involving large clusters).

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<sup>11</sup> However, it is not clear in these statements how communities are defined and whether all communities have leaders who are recognised as such.

<sup>12</sup> Further problems with this approach are discussed in Chapter 8.

It is important therefore to decide whether we should consider consent from research subjects as an absolute ethical requirement, and thus judge such CRTs unethical, or whether we believe that CRTs can still be morally justified in the absence of individual consent because of their importance for health or other research (e.g. poverty solutions).

One way to deal with this problem is to argue for a waiver of consent (individual and cluster consent). Weijer et al. (2011) argue that there are cases where informed consent is not necessary in cluster trials. In particular, one of those cases is when patients or community members are only indirectly affected by the intervention; in other words when they are not considered research subjects (regulatory and ethical requirements for informed consent only apply to research subjects).

Another case in which Weijer et al (2011) argue that informed consent should not be required is when a research involves no more than minimal risk and when the rights and welfare of the subjects are not adversely affected. Along these lines McRae et al (2011) claim that a partial solution to the problem of obtaining informed consent in cluster trials can be found in international regulatory provisions, where conditions for a waiver of consent are described. For instance, as stated in International Ethical Guidelines for Biomedical Research Involving Human Subjects “when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects’ records), the ethical review committee may waive some or all of the elements of informed consent” (Eckstein 2003, p. 472). According to this statement exposing research subjects to risks for the benefit of others without their consent can only be justified if those risks are insignificant. In contrast, when informed consent is not feasible and the study involves more than minimal risk, the research subjects are treated as means only and thus the study cannot be considered ethical.

Following McRae et al., we can easily argue that if a study is considered to have major social benefit and involves only minimal risk for the participants, individual

consent can be waived. In contrast, if a study involves risky procedures for the participants then overriding consent should not be allowed. In other words, it can be argued that although the moral requirement for informed consent is very important in medical research, it can be overridden without violating the principle of respect for persons, if specific moral safeguards are established.

Although McRae and colleagues seem to resolve the problem of justifying cluster trials when informed consent cannot be obtained, there are still several critical questions that need to be answered. In particular, how do we determine the social value of a study? How should we define minimal risk in collaborative health research? Is the moral duty to respect the subject's autonomy still fulfilled when the risk involved is minimal but the subjects do not adopt the ends of the study as their own or when they are not given the option to opt out of the trial? Should individual consent be overridden when a study involves more than minimal risk but informed consent processes are not compatible with the values and customs of the host country?<sup>13</sup> In certain studies, such as community-based research, researchers may be familiar with the needs and values of the researched populations by consulting a cluster representative or a community leader about the community and community members' values and interests<sup>14</sup>. However, when clusters include less cohesive social groups, it is more difficult for the researchers to know in advance whether potential participants would agree with the aims of the study.

Another case in which individual informed consent is not considered necessary in cluster-cluster trials is when the research cannot be practically carried out otherwise and when appropriate, the research subjects are informed (45 Code of Federal Regulations). However, this suggestion is not helpful, since we will still need to clarify how the requirement that a trial could not practicably be conducted otherwise should be considered and also provide practical guidance to researchers and research committees (Weijer et al. 2011). In addition, another point that still

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<sup>13</sup> I discuss these questions further in the following chapters.

<sup>14</sup> However, as mentioned earlier, community leaders should not always be assumed to represent community values.

needs to be clarified is why researchers should inform subjects about their participation in a study, in which they have been deprived the right to opt out; and in the case there are reasons to provide this information, how this should be done.

As previously discussed, Edwards and colleagues (1999) suggest that the decision to participation in cluster-cluster trials should be decided on a higher level, when individual consent is not possible and this view is adopted in the MRC guidelines. According to this suggestion, a person or representation mechanism should serve as guardian and provide proxy consent on behalf of cluster members.

However, there seem to be many reasons for which such decision cannot be decided on a higher level (by a cluster representation mechanism). In cluster-cluster trials in particular, things may be very complicated as a high level of confidence is needed and it is also important to consider issues such as conflicts of interests (between cluster representatives and cluster members). For some of these problems, it may be easy to find solutions; for instance overcoming certain practical difficulties, such as making sure that the decision for a cluster to participate in research is done in a transparent way and that there will be cluster representatives who will responsibly fulfil their role. Edwards et al. (1999), for instance, suggest that gatekeepers should sign a consent form in which they clearly state their duties towards their cluster, before they undertake the role of volunteering their cluster into trial.

Yet, other problems are more difficult to deal with. In particular, the selection of the person or body to represent cluster members' interests is not straightforward and there is no guidance on how a cluster representative should be identified. Especially in developing settings, in which trial access may be people's only chance to get medical benefit, the selection of gatekeeper is critical, since their refusal to involve their cluster into the trial would substantially affect cluster members' interests and rights.

Moreover, the solution of using gatekeepers as proxy decision makers to justify the conduct of cluster-cluster trials is problematic. As I will explain in the next chapter, a gatekeeper's consent cannot serve as a substitute of individual consent,

because the standard reasons for justifying proxy consent do not apply in CRTs.

Some proposals have been made to overcome this difficulty. Hutton (2001) for instance has proposed the use of multiple guardians/gatekeepers. Edwards et al. have suggested opinion polls, focus groups, citizens' juries, and referenda (Edwards 1999). I discuss those in more detail in chapter 8, but for now, I will claim that none of these suggestions really constitute a form of consent parallel to the individual informed consent in RCTs.

Apart from the use of gatekeepers, some alternatives to the traditional model of informed consent have been suggested by the advocates of informed consent (those that believe that the requirement of informed consent is essential in health research) so that the conduct of cluster-cluster trials can be ethically justified. However, these strategies raise further concerns, as they seem to be inadequate for different moral reasons.<sup>15</sup>

One proposal is to presume individual consent by invoking some sort of social contract, in which individuals as citizens are presumed to have a duty to contribute to public benefit by taking part in research (John 2009). However, this is a controversial proposal and there are also some main differences between presumed and actual consent that should also be considered as well as the criteria that a study should fulfil to fall under this category (given the risk of exploitation, the interests of pharmaceutical companies, and others).

An alternative suggestion is to rely on hypothetical consent: to consider what a person would consent to if she were able to do so. However, this suggestion is also problematic in the case of CRTs since it would be extremely difficult to gather sufficient evidence from all cluster members to ensure that their participation is according to their wishes (Sim and Dawson 2012). Hypothetical consent would also be problematic in CRTs in which there is no option to opt out of the trial.

Sim and Dawson (2012), however, have suggested a different way of considering

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<sup>15</sup> I revisit these views in Chapters 4 and 8.

hypothetical consent. According to them, what we should consider is whether a rational person could adopt the ends of the study in question. They believe that this question could be answered by relevant experts, institutional review boards, that could act as guarantors, as the key decision-making body in evaluating the ethical conduct of a study. By providing overall ethical scrutiny of a study, IRBs can evaluate arguments related to both the ethical and the scientific aspects of a research protocol. IRBs can consider the welfare of the participant, the privacy or confidentiality of his or her medical data and other ethical related considerations that consent is designed to protect and then weight them against the scientific value of the study, in order to judge whether a particular study can ethically proceed.

They also note that their solution is different to the solutions suggested by the advocates of informed consent, since the role of IRBs is not to provide consent on behalf of cluster members (which in most cases is problematic) (Sim and Dawson 2012). They also argue that their solution does not present the same difficulties with comprehension and disclosure requirements that traditional informed consent strategies and their varieties present. The advantage of IRBs (over gatekeepers or other cluster representation mechanisms) is that they do not purport to give a form of consent as a permission on behalf of a community. Rather, they provide overall ethical scrutiny of a study from perspectives that include but extend beyond those of the participants in the study. In more moral terms, according to this suggestion, IRBs can focus on those ethical concerns that consent is designed to protect. Therefore, although individual consent is not feasible, the values/goals it is supposed to protect are still protected by this mechanism (Sim and Dawson 2012).

Although we can recognise Sim and Dawson's solution as preferable to any reliance on proxy consent, we should note that only objective values can be protected by IRBs, since individual participants' personal values and goals cannot be taken into account. Evidence has shown that people have different ways of weighting the moral values and personal interests that may be at stake by their participation in a research study (Bolvin et al. 2009). This means that in contrast to what Sim and Dawson argue, not all goals that individual informed consent was supposed to protect can be respected by IRBs calculations.

Despite the fact that the distinction between individual-cluster and cluster-cluster trials reflects what it is followed in practice (meaning that researchers usually obtain consent from participants in individual cluster trials and not in cluster-cluster trials (Eldridge et al. 2005, McRae 2011)), important ethical questions still haven't been answered, (i.e. there is no conclusive resolution in the literature). Considering the moral foundation of informed consent, I will later argue that a different perspective needs to be adopted on this issue from the one commonly taken in respect of the conventional randomised trials. When individual informed consent is not possible, we should make sure that sufficient justification is given for its omission and not seek solutions that take us away from the essential purpose and notion of informed consent (for instance by relying on hypothetical consent to resolve all difficulties with obtaining explicit consent in cluster trials<sup>16</sup>). Moreover, as I later explain (chapter 7) informed consent does not constitute an absolute requirement. Inability to obtain individual consent is not only present in CRTs; in emergency medicine, for instance, requirements for individual informed consent cannot be fulfilled (Largent et al. 2010). Considering the lack of individual consent as acceptable in such cases and thinking of CRTs as a valuable research tool in health research, we can argue that research ethics guidelines and regulations should allow sufficient flexibility to permit the use of CRTs when appropriate. This of course leads us to the question of when it is appropriate to use the cluster design, which will be discussed in the following chapters.

Difficulties in obtaining individual informed consent and inability to opt out of the trial are not the only problems associated with informed consent in CRTs. Questions such as: "Do health professionals have a moral obligation to participate as subjects in CRTs designed to improve professional practice?" are also important, however they will not be the focus of this thesis.

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<sup>16</sup> As I explain in Chapter 8, although hypothetical consent may (partially) justify a cluster study where individual consent is not possible, it does not provide a straightforward solution for all cluster trial interventions.

## 2.6 | Conclusion

The aim of this chapter was to critique the ‘standard view’ of research ethics because of its limitation in addressing moral challenges related to the conduct of cluster trials in developing countries. After briefly discussing the moral purpose of informed consent and its place in international regulatory provisions, I explored the new issues that the CRT design raises regarding consent information, timing, levels at which consent should be obtained, necessity and feasibility of obtaining informed consent. I concluded that suggestions found in the literature do not meet those challenges and that a different perspective needs to be adopted on this issue from the one commonly taken in respect to the conventional randomised trials.



# Chapter 3

## **The role and authority of gatekeepers in CRTs**

In the previous chapter, I discussed the new issues that the CRT design raises on the nature and practice of informed consent and argued that suggestions found in the literature do not meet those challenges and that a different perspective needs to be adopted on this issue from the one commonly taken in respect to the conventional randomised trials. In this chapter, I also critique the ‘standard view’ of research ethics by addressing questions related to informed consent and representation. First, I describe how the use of ‘gatekeepers’ (cluster representatives) has been developed in the research ethics literature. I then explore the different roles that gatekeepers undertake in different CRT settings and discuss questions related to their authority to legitimately fulfill these roles. I conclude that the use of gatekeepers does not provide a solution to challenges posed by informed consent, especially when CRTs involve clusters that lack organised structures.

### **3.1 | Representatives in CRTs: Who are gatekeepers and what are their responsibilities?**

Difficulties in obtaining individual informed consent in CRTs (because of cluster randomization, cluster-level interventions, and cluster size) have led to the practice of using gatekeepers (also referred as guardians or cluster representation mechanisms). As Edwards et al. (1999) suggest: “the decision about whether a particular cluster participates in the trial is taken by an agent who has the power to

‘deliver’ that ‘cluster’ and who acts as an advocate on behalf of cluster interests. Guardians may be democratically elected or appointed, though not necessarily with this specific role in mind” (Edwards 1999, p. 1408).

Gatekeepers are considered to play a prominent role in CRTs in protecting group and individual interests; this role however differs depending on the features of the study. In cluster-cluster trials (as previously discussed) the role of the gatekeeper is more expansive to the role gatekeepers usually take in individual cluster trials, as they “must consent to or decline both trial entry and the intervention as a single package” (Edwards et al. 1999). According to Edwards et al. (1999) the gatekeeper will provide proxy consent for the members of the cluster for both cluster randomization and the intervention they will receive. In individual-cluster trials, in which it is feasible to obtain consent from research subjects for the intervention they will receive and data collection procedures, gatekeepers only provide permission to enter the cluster into the trial.

Donner and Klan also consider the role of gatekeeper as cluster advocate, who can decide about research participation or cluster randomization on behalf of cluster members: “it may be permissible in some studies that the decision regarding random assignment and implementation of an intervention comes from community leaders or decision-makers” (Donner and Klan 2000, p. 49). Hutton expresses a similar view, as she describes gatekeepers as “people in either political or administrative positions who are able to give consent for those within a cluster to be randomised” and whose consent may occur on ‘multiple levels’. (Hutton 2001, p.476).

According to Edwards and colleagues (1999), a gatekeeper should advance the interests of the cluster and preserve its trust<sup>17</sup>. They argue that the decision to enroll their cluster in a trial will depend on whether the study in question is in the interests of the cluster. Hutton (2001) adds that a gatekeeper would agree to a set of duties towards their cluster before serving as a representative. She also argues

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<sup>17</sup> As however I later explain this does not prevent a gatekeeper rejecting to undertake the role of an advocate and refuse to consent to the entry of their cluster into an otherwise beneficial research (Hutton 2001).

that a gatekeeper may inform cluster members about research and also provide information to researchers about special considerations in the cluster. In contrast, Gallo and colleagues (2012) claim for a more restrictive understanding of the role and authority of gatekeepers (which will be discussed in section 3.2.).

The view that gatekeepers should act as cluster advocates and decide on behalf of cluster members considering the interests of the cluster, is also reflected in the MRC Guidelines: “the ethical principle here is that the [gatekeeper] must act in good faith, and in this regard only in the interests of the cluster represented” (MRC 2002). It is also stated that the gatekeepers should be informed advocates throughout the trial and avoid any conflicts of interests, as well as disclose any unavoidable conflicts (MRC 2002). Although in MRC guidelines it is acknowledged that gatekeeper’s consent is not truly equivalent to individual consent, it is stated that it may be the best strategy to protect the interests of research subjects. To ensure then that gatekeeper’s agreement is analogous to individual informed consent, several safeguards are proposed, such as documentation as evidence that the gatekeeper understands the interests and values of the cluster. By this way a gatekeeper’s consent could reflect what research subjects would endorse if they had the opportunity to decide by themselves (MRC 2002).

Finally, the view that gatekeepers should act as proxy-decision makers for research participants has recently been discussed in CIOMS (Council for International Organizations of Medical Sciences). As it is stated, interactions between researchers and representatives should be “aimed at obtaining the views of people who are in effect proxies for the potential subjects” (CIOMS 2009).

Despite these descriptions, however, it is unclear how a gatekeeper should be identified, especially when a trial includes clusters with no administrative or political structures or where more than one authority may be in charge. Because of the diversity of groups participating in CRTs (athletic organizations, communities, health centres, nursing homes, schools, workplaces and others) there is no guidance on how a gatekeeper should be chosen and how group characteristics may influence who should take the role of the representative in each case (Weijer

et al. 2011).

## **3.2 | Roles of gatekeepers**

Gatekeepers have undertaken a variety of roles in CRTs (Gallo et al. 2012). Moreover, because of the diversity of groups participating in CRTs, people in different positions have served as gatekeepers. For instance, in trials in which communities are involved, medical leaders, community leaders, government authorities, and community advisory boards have undertaken the role of gatekeeper. In trials in which schools are involved as clusters, local governments, school districts and principals have filled this role (Gallo et al. 2012).

### **3.2.1 | Gatekeeper roles relevant to the protection of individual interests**

Many of the roles that gatekeepers undertake aim to primarily protect the interests of cluster members. In health research, both autonomy interests (i.e. the right of the potential subject to freely decide to participate in a trial after being adequately informed) and welfare interests (i.e. the right of the potential subject to be protected from undue research risks) may be at stake. Gatekeepers have undertaken different roles to protect those interests. In particular, they may provide proxy consent for research subjects, when individual informed consent is not possible (usually in cluster-cluster trials or trials that involve large clusters). They may give permission for cluster randomization before cluster members are identified by the researchers or when individual consent to randomization is not possible. They may give permission to approach cluster members, determining in this way, which individuals researchers may contact. Finally they may help researchers to identify potential research subjects in studies that involve clusters whose members are not easily identifiable (Gallo et al. 2012).

The role that a gatekeeper will fulfill depends on the type of the study; for instance, providing proxy consent for the intervention that cluster members will receive is usually a role that gatekeepers in cluster-cluster trials or trials that involve large clusters undertake. Moreover, the role that a gatekeeper will undertake also depends on the type of cluster (i.e. on whether the cluster is a community, a sports team, a school etc.) and the position/ profession of the person

who is called to represent it. For instance, in a health-centre study, researchers may ask a gatekeeper to give permission to approach cluster members. This role can only be undertaken by a physician, who can also be responsible for the welfare of the patients – members of the cluster (i.e. someone who can ensure that research will not be against their best interests and that their privacy would be respected). Similarly, in a study aiming to evaluate different strategies for smoking cessation, researchers may need a gatekeeper to identify potential research subjects. This role can be fulfilled by a member of the cluster (a smoker visiting the clinic) and not necessarily a professional, since the gatekeeper in this case is not responsible in regard to cluster members, only helps researchers to identify other members of the same group (Gallo et al. 2012).

### **3.2.2 | Gatekeeper roles relevant to the protection of cluster interests**

Gatekeepers may undertake roles related to the protection of the interests of the cluster. Because of the heterogeneity of the social groups participating in CRTs (ranging from very cohesive communities to sports teams), cluster interests are not as well understood as the individual interests and thus lack definitive characterization (Gallo et al. 2012); for instance, in certain cases it would be difficult to determine how cluster interests differ from individual interests especially when clusters do not reflect predefined groups. Moreover, cluster interests are more complex and thus the morally relative interests at stake in research may potentially conflict. In general terms, in health research by cluster interests we mean the identity interests of the group (i.e. the values and beliefs of the group, its group reputation, social practices and traditions) and the social structures of the group (i.e. shared economy, the provision of social services, communication, mechanisms for decision-making). Based on this definition it could be argued that when clusters are created solely for research purposes and thus non-coherent groups are involved in cluster research, such clusters do not have interests qua clusters. Gatekeepers protect cluster interests when they consent on behalf of the cluster, when they provide protocol approval or when they are involved in cluster consultation (Gallo et al. 2012).

According to MRC guidelines, gatekeepers are asked to provide consent for

cluster randomization in both individual-cluster and cluster-cluster trials. Cluster permission should be based on cluster interests and is commonly provided by an authority in the cluster, for instance a community leader, a mayor, etc. Although the gatekeeper's decision to permit cluster randomization in individual-cluster trials is independent of individual informed consent (cluster members can still refuse to receive research intervention), it is a precondition for individuals in the cluster to be approached and asked to participate in a study. In other words, a gatekeepers' refusal will preclude cluster members' access to a trial (Gallo et al. 2012). In cluster-cluster trials, the gatekeepers' role is more expansive, as they are called to provide cluster consent for randomization and intervention.

Gatekeepers may also provide feedback and advice to researchers on the design and conduct of a study, for instance providing insights as to the cultural appropriateness of different intervention activities. Cluster consultation may be given in all stages of the research process and may involve cluster representatives or community advisory boards (members from communities). In cluster consultation gatekeepers do not consent on behalf of the cluster (Gallo et al. 2012). Moreover, cluster representatives may provide protocol approval, after it has been approved by a research ethics committee, to ensure that the study is in line with the values and needs of the cluster (Bolton et al. 2003).

Finally, gatekeepers may undertake the role to protect organizational interests, when a CRT involves organisations such as hospitals, nursery homes and others. When organisations are identified as clusters, cluster interests and organizational interests may overlap. However, there are cases where organizational interests may conflict with the interests of the cluster (for instance when the trial has implications on the hospital staff or when financial costs should be considered) (Gallo et al. 2012). Similarly, gatekeepers may offer permission on behalf of an organization to participate in a study (for instance a school). In those cases again, the gatekeeper should consider the interests of the organization, for instance availability of staff and others (Gallo et al. 2012).

### **3.3 | Gatekeeper authority to undertake these roles**

Gatekeepers have undertaken a number of roles in CRTs to protect individual,

cluster and organisational interests. These roles are very important because of the consequences they have for other people. Consider for instance proxy consent in cluster-cluster trials. A gatekeeper has the power to expose other individuals to research risks without their informed consent or exclude them from potential benefits by declining cluster participation. It is therefore, very important to consider whether gatekeepers have the authority to fulfill the roles they usually undertake in CRTs.

### **3.3.1 | Gatekeeper authority to protect individual interests**

Edwards et al. (1999) argue that the role of guardian is key to the ethical conduct of CRTs. Although individuals in the clusters do not have the opportunity to freely decide whether they want to be enrolled in a study, their autonomy is not lost: “In the longer run, individual autonomy could be strengthened by considering the rights of individuals vis à vis the selection and behaviour of cluster guardians” (Edwards 1999, p. 1408). However, as Hutton (2001) notes, a gatekeeper’s role to protect individuals under their care from research risks does not necessarily suggest them acting as advocates. For instance, a hospital chief executive may protect patients under their care from harm, but that does not necessarily mean that they also should seek to offer them alternative treatments.

Edwards et al. (1999) in contrast argue that a gatekeeper’s role to provide permission for the entry of their cluster into a trial entails a moral duty to act as an advocate on behalf of cluster members. To ensure that gatekeepers will fulfil their roles as advocates, they suggest before they volunteer a trial to sign a consent form in which they clearly state their duties towards their cluster. However, a problem still remains if a gatekeeper refuses to take the role of an advocate, since it is often unclear to whom this role should pass so that individuals in the cluster are not denied access to a potentially beneficial trial.

Although difficulties in obtaining individual informed consent in CRTs have led to the practice of using gatekeepers (Edwards et al. (1999), Hutton (2001), Donner and Klar 2000), their authority in providing proxy consent on behalf of cluster members (as suggested in MRC 2002 and CIOMS 2009 guidelines) can be questioned. This is because the circumstances in which proxy consent is required

and justified in RCTs and medical practice in general do not apply in CRTs. First of all, in most cases cluster members are competent adults (and not incompetent participants) who can freely decide whether research participation is according to their interests. Moreover, in CRTs gatekeepers are usually asked to provide proxy consent for individuals with whom they do not have a close personal relationship and thus do not know their personal values and interests. It is therefore reasonable to argue that the gatekeepers' role to protect individual interests by providing proxy consent can only be morally justified when those individuals have autonomously authorized them to act in this way. However, as Gallo et al. (2012) note this is rarely the case.

Since, conditions that confer legitimacy on a proxy decision maker do not apply in CRTs, gatekeepers who provide permission to randomization and cluster intervention without being authorized by cluster members violate cluster members' autonomy (Gallo et al. 2012)<sup>18</sup>. As gatekeepers are rarely authorized by cluster members to consent on their behalf (Gallo et al. 2012), Weijer and colleagues (2001) have argued for a restricted authority of gatekeepers in protecting individual interests. Criticizing the moral legitimacy of using proxy decision makers in CRTs, they claim that to respond to the challenges posed by the difficulty of obtaining individual consent, we do not necessarily need to invoke gatekeepers.

First of all, they argue for a restricted role in providing permission to randomise cluster members. According to Edwards et al (1999) and Hutton (2001) in individual-cluster trials the role of gatekeeper is to provide consent for the entry of the cluster into the trial. As we mentioned above, although gatekeepers' permission for randomization does not exclude individual consent (cluster members can still agree to or decline participation), it can however exclude an individual from potential benefits if a gatekeeper refuses to permit cluster randomization. A gatekeeper, who undertakes this role, without being authorized

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<sup>18</sup> However, it should be noted at this point that although gatekeepers do not normally meet the standards for proxy consent in CRTs, there are cases outside the research context where one individual is empowered to make decisions on behalf of others, for instance in representative democracy.



by cluster members, violates the interests of the individuals that he is supposed to protect.

According to the principle of justice (one of the ethical principles in medical research ethics discussed in Chapter 1) risks and benefits of research should be fairly distributed. In the Nuremberg code, it is clearly stated that “unjustifiable exclusions, and unjust and irrational uses of resources” should not be accepted (Ashcroft 2000). Past practices in which certain groups i.e. children or pregnant women were denied the opportunity to participate in a trial that could provide them benefits for their own protection have strongly been condemned (Ashcroft 1998). Although in CRTs exclusion is not related to discrimination, a gatekeeper’s power to exclude cluster members from access to research benefits should be seriously taken into account. According to Edwards et al. (1998) there is evidence that research participants on average fare better than those who do not participate because of improvements generated by the trial (although it is unclear whether this is due to additional care provided during the study or the selection of participants). In developing countries research access may be even more important, since trial participation may be the only opportunity for some individuals to receive medical care.

A gatekeeper’s power to involve or exclude individuals from research participation is not new to CRTs; in conventional randomized trials doctors often decide to offer their patients a chance to participate in research (Taylor et al. 1984; Ashcroft et al. 1997). However, in CRTs this issue may be more complex. First of all, the people who serve as gatekeepers in CRTs are not always appropriate for the role they undertake (Gallo et al. 2012) and therefore their decision to deny cluster randomisation may be based on wrong criteria, for instance lack of understanding of the aims of the study (note that Edwards et al (1999) argue that gatekeepers should not necessarily be elected to undertake this specific role). Moreover, even if we accept that doctors sometimes have conflicts of interests and are potentially capable of using the role of a gatekeeper against their patients’ best interests, the fact that in CRTs often doctors rather than patients are the focus of the study, may suggest that this is likely to happen more

often.<sup>19</sup>

However, these problems do not suggest that the conduct of CRTs should generally be prohibited. As Weijer et al (2012) and Gallo et al. (2012) argue, there are cases in both individual-cluster and cluster-cluster trials, where consent from a gatekeeper is not necessary.

First of all, they argue that a gatekeeper's role in individual-cluster trials to offer consent to randomization is unnecessary, when researchers seek individual consent from cluster members at the earliest opportunity and before the start of intervention or start data-collection procedures (Weijer 2012). By this way, cluster members can still adopt the ends of the study as their own (agree or deny to be exposed to risk for other people's benefit) and thus the moral purpose of informed consent is fulfilled.

Moreover, they argue that proxy consent on behalf of cluster members is not required in cases where a waiver of consent is appropriate. These are the cases when a CRT involves no more than minimal risk to individuals in the cluster. Under these conditions (and similarly to RCTs) a research ethics committee may approve a waiver of consent. Since, informed consent is not required (research subjects are only exposed to negligible risk for the benefit of others) there is no need for a gatekeeper to consent on behalf of cluster members.

Gallo et al (2012) argue that although gatekeepers do not generally have the authority to provide proxy consent for the members of the cluster, there are certain circumstances under which they can legitimately protect individual interests in CRTs. When the relationship between gatekeeper and cluster members is fiduciary in nature, for instance when there is a physician-patient or teacher-student relationship, the gatekeeper has a moral obligation to protect the interests of cluster members by providing or refusing to provide permission to researchers to approach those individuals. A gatekeeper's authority thus to refuse researchers

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<sup>19</sup> There are of course other morally relevant questions that should be answered in this case, such as whether a doctor has a moral obligation to enroll their patients when a CRT aims at improving patient care (Hutton 2001), however I will not focus on such issues in this chapter.

to approach individuals in their cluster is morally legitimate, because of their obligation to protect those individuals (Gallo et al. 2012). However, even in a fiduciary relationship between a gatekeeper and cluster members, it is still important to ensure that gatekeepers have no conflicts of interests and that they use their authority considering cluster members' best interests. An important question, however, that still needs to be answered is how a gatekeeper's role in permitting researchers to approach individuals in their cluster may differ from the role of permitting their cluster to be randomized in individual-cluster trials. A possible explanation (which is however not given by Gallo and colleagues) is that by giving permission to approach individuals in their cluster, gatekeepers can consider the best interests of each individual in the cluster separately.

Although Gallo and Weijer's suggestions on a restricted role of gatekeepers for the protections of individual interests in CRTs seem to resolve some of the problems presented in CRTs, there are still some moral challenges that haven't be met. In particular, we still need to consider how a CRT may proceed when informed consent is not possible and a waiver of consent is not appropriate, i.e. when cluster members cannot be approached before interventions or data collection begin and the study involves more than minimal risk.

### **3.3.2 | Gatekeeper's authority to protect cluster interests**

In certain cases, participation in cluster- randomized trials may substantially affect the interests of the cluster. According to Edwards et al. (1999) a gatekeeper's decision to permit or refuse cluster participation in a trial may be paternalistic, i.e. depend on whether research participation is in the cluster's best interests. A gatekeeper's decision to consent should rely on the belief that the cluster is expected to benefit more by the trial intervention than by a non-trial option. Although this criterion is widely acceptable in conventional trials (for instance when parents have to decide whether research is in their children best interests) in CRTs this calculation is more complicated. Questions on how to quantify the best interests of a group remain, not only because more than one person's interests should be taken into account, but also because other criteria should also be considered e.g. whether the trial is culturally controversial, whether it can answer the needs of the cluster, and others.

Cluster interests may include the preservation of the identity of the group and the maintenance of the integrity of social structures (Gallo et al. 2012). The role of the gatekeeper has been considered essential in protecting those interests (Edwards et al. 1999; Klar and Donner 2007; Hutton 2001). However, although a variety of functions are ascribed to gatekeepers for the protection of cluster interests, it is important to consider when the gatekeeper has the authority to protect those interests and what are the sources of their authority.

As already mentioned, issues related to the protection of cluster interests are more complicated. One reason for this is because the moral status of the groups that participate in research is not well characterized (Weijer et al. 2011). CRTs may involve a variety of groups (primary care practices, villages, communities, classrooms, sports teams and others) with varying degrees of cohesiveness and a variety of interests that may be at stake (which are not defined or addressed in current guidelines). In addition, the degree to which the interests of different groups will be affected by research participation will vary. For instance, the interests of a cohesive community studied in a genomic research may substantially be affected despite the anonymity of its members (the study may lead to perceptions that a particular community is more susceptible to a particular disease) (Weijer and Emanuel 2000). In contrast, in knowledge translational studies<sup>20</sup>, few group-based interests may be affected, especially when clusters are a number of individuals that do not have other things in common, except from the fact that they use the same services.

Protecting cluster interests in CRTs may also be difficult, because it is often not easy to determine who has the legitimate authority to protect and represent group-based interests. Often CRTs involve clusters that lack organized structures or legitimate authorities that could represent them<sup>21</sup>. In other cases, although clusters have organized structures, these structures haven't been established for making

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<sup>20</sup> Knowledge translation studies aim to inform and assist clinicians to deliver best practice to improve the outcomes of their patients.

<sup>21</sup> For instance see the example of a cluster randomised study in Mumbai slums discussed in the Appendix.

decisions about research (Edwards 1999). There may also be cases where a cluster representative refuses to serve as a gatekeeper (Hutton 1999) and researchers need to decide to whom the responsibility on cluster representation should be passed. Finally, gatekeepers may have potential conflicts of interests, for instance they may receive financial incentives or be interested in both the scientific result and the welfare of their cluster (Edwards 1999).

In community-based research most of these issues have been addressed. First of all, in the research ethics literature, community interests are generally recognized as very important (because of community's moral worth), and it is also recognised that researchers have a moral obligation to protect and promote those interests (Weijer et al. 2011). Moreover, the principle of respect for communities, which has recently been proposed by Weijer and Emanuel (2000) as an additional moral principle to the principles of justice, benevolence and respect for persons, is generally well accepted. According to this principle, the relationship between community and researcher is described as a partnership in which community consultation and negotiated agreement are key features (Ross et al. 2010). Moreover, according to this principle, when a community has legitimate authority to represent its members (a mayor, a legislative assembly or tribal council), researchers have a duty to obtain community consent additionally to individual consent (Weijer and Emanuel 2000).

Gallo and colleagues (2012) believe that to meet the challenges raised by the protection of cluster interests and the authority of gatekeepers in fulfilling their role, we should consider the ethical principle of respect for communities and the mechanisms of community consultation and permission. In particular, they argue that in cluster clinical trials, similarly to community-based research, a gatekeeper can protect and promote the cluster's interests by giving permission for a cluster to participate in a trial, only if they have legitimate authority to represent the individuals involved and only if this authority extends to the decision at hand.

To decide whether a gatekeeper has a legitimate authority to make such decisions, they argue that it is important to consider whether the individuals who are affected by these decisions are satisfied with the gatekeeper's ability to make such

decisions (Gallo et al. 2012). Researchers can understand the social dynamics of the group by consulting with the members of the cluster and their leaders and by asking them questions about the gatekeeper's role. Researchers should ensure that group members understand and acknowledge the gatekeepers' role to make such decisions and acknowledge their authority to do so. Moreover, they should consider whether there is largely individual satisfaction with the institutions involved that are used to select those representatives (since the legitimacy of the institutions involved depends on whether the individuals who they supposed to represent are satisfied with them). To assess group members' satisfaction with the institutions researchers must consider not only past decisions but also the decisions at hand (Gallo et al. 2012).

These questions to assess whether a gatekeeper has a legitimate authority to protect cluster interests, however, may not be as easy to answer as Gallo et al. (2012) claim. In many cases there will be more than one authority that can take responsibility for the enrolment of the cluster into the trial. In particular, there may be cases in which both political and public health authorities have to be consulted but the boundaries of their jurisdiction are not the same. There are also may be cases in which more than one authority should be consulted and agreement between them cannot be achieved. In those cases, it will not be clear which authority should take priority. Examples of these cases are large-scale trials involving villages to test new insecticides. In those trials researchers have to get permission not only from a representative of the village-cluster but also from national and regional government (Helsinki II).

As it is obvious from the above, although some protections concerning the interests of a community may straightforwardly apply to CRTs, in which clusters are well-defined communities, in other cases these suggestions may not be helpful. When CRTs involve communities, in order to protect the interests of the clusters, researchers are usually required to seek community consent before approaching the cluster members. In CRTs, however, in which diverse groups (hospital wards, households, neighborhoods) or non well-defined communities are randomized, the applicability of community-based protections may not be appropriate. When gatekeepers are not legitimate representatives of the cluster,

the conduct of a trial should not be morally justified on the grounds that consent on behalf of the cluster has been obtained (Gallo et al. 2012).

Gallo et al. argue that when cluster permission is not appropriate, gatekeepers may usefully and legitimately protect cluster interests in other ways. Cluster consultation has been considered an important mechanism for the protection of group interests. It is considered as a partnership between researchers and cluster members. By cluster consultation researchers can understand whether their research addresses local health needs and respects the values of customs of the groups involved. Cluster consultation can be provided from research design to publication (i.e. consultation over protocol development, involvement in the conduct of research, dissemination of information, and publication of results) (Weijer and Emanuel 2000, Ross et al. 2010). However, as Weijer and Emanuel (2000) note, the degree of this participation will depend on the characteristics and the cohesiveness of the group (whether it has a common history and common culture that should be protected).

Although it is difficult to provide a general definition of what effective cluster consultation is, Dickert and Sugarman (2005) have given a description of what the goals of consultation should be. These include enhanced protection, enhanced benefits, legitimacy, and shared responsibility (Dickert and Sugarman 2005). Although group-based interests may be usefully protected by cluster consultation, when cluster consent is not legitimate, the aim of cluster consultation is not to give permission to researchers on whether their study should be conducted but on how it should be conducted. Possible means that can be used for that are meetings with opinion leaders, presentations at religious or civic organizations, the use of media and others (Gallo et al. 2012). However, it should be noted that although recommendations from cluster consultation are not binding, in cases in which there is strong negative reactions on the study proposed or the consultants believe that certain modifications should be made, those recommendations should be carefully taken into consideration. As Dickert and Sugarman comment: “it would be disingenuous to enter into a consulting arrangement where the consulting party does not intend, *ex ante*, to take the consultants advice. If relevant consultants have strong negative reactions or endorse particular modifications, those reactions

or modifications have significant moral force and warrant respect and careful consideration” (Dickert and Sugarman 2005, p. 1124).

However, for cluster consultation to take place (meetings with opinion leaders, presentations at religious or civic organizations and others) clusters would also need to have organized structures. When CRTs involve non well-defined groups, not only cluster consent but also cluster consultation may be difficult to achieve. In such cases, we still need to consider how the decision for trial participation should be taken and how those groups can be protected in health research.

Finally, we should note that in CRTs the role of gatekeepers in protecting various interests could be particularly challenging. Gatekeepers are called to protect various sets of interests, community interests, individual interests and, often, institutional interests as well (when gatekeepers hold administrative positions such as hospital chief executive officers and others). Since group interests and individual interests are separable and may even conflict in certain cases (Weijer and Emanuel 2000; Marshall and Rotimi 2001), it is important to consider how a balance can be achieved.

### **3.4 | Conclusion**

The aim of this chapter was to set out and challenge the ‘standard view’ of research ethics because of its limitation in addressing issues arising in the conduct of cluster research in developing countries, and in particular, those related to lack of informed consent and cluster representation. I discussed the role of gatekeepers in protecting individual, cluster and institutional interests in CRTs. I concluded that although their use has primarily emerged in response to the difficulties in obtaining informed consent in CRTs, challenges related to the identification of people to fulfil these roles and their authority to do so are not met especially when CRTs involve clusters that lack politically organised structures.



# Chapter 4

## **Justifying health research: The ethics of exposing individuals to research risks without their consent**

Difficulties with obtaining informed consent from research participants in CRTs brings us to the question of whether it is acceptable to conduct a cluster study when informed consent is infeasible to obtain. The aim of this chapter is to provide an ethical analysis of what is arguably the most challenging ethical issue in health research in general: under what conditions we can morally accept the exposure of some individuals to research risks without their consent for the social benefit.

The norms governing the scientific method of health research mandate that the interests of some individuals will be compromised or at least risked for the benefit of others (Miller and Weijer 2006; Rothman 2000). Health research, thus, because of its nature, introduces the possibility of exploiting research subjects for the social benefit. This is more obvious especially in medical research where research subjects, even very sick ones, are systematically exposed to potentially new medicines, so that new and more effective therapies can be widely available. It seems then that the main ethical concern raised in health research, generally, is how to justify the practice of exposing a group of people to risks for the benefit of others or society in general. In the case of cluster research, this problem becomes even more complex because the individuals, whose interests may be

compromised<sup>22</sup> for the general benefit, are mandated to serve as research subjects, since their enrolment is not based on their personal choice and they usually have no option to opt out of the trial. In the following paragraphs I present and discuss the main arguments presented in research ethics debates for the justification of health research<sup>23</sup> based on the moral approach in which they rely on. I then examine their implications for cluster research where individual consent is absent. I conclude that an alternative approach could better inform our understanding of cluster research and offer a new analytic insight on when it is legitimate to use cluster design for health studies.

## 4.1 | The Precautionary approach

The main aim of medical research (and health research in general) is to gain knowledge that will benefit people/society in the future: “The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)” (WMA Declaration of Helsinki, paragraph 6). In other words, health research has social value because of its ability to collect information that might be useful to identifying advanced methods to treat conditions and improve human health and well being.

Despite its value there is a general presumption in research ethics guidelines that health research is potentially harmful, or at least burdensome, for the participants. “In medical practice and in medical research, most interventions involve risks and burdens” (WMA Declaration of Helsinki, paragraph 16). Since research participation can lead to negative consequences for the individual (there is the

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<sup>22</sup> Some ethicists have disputed this view. What is considered to be in the interests of a research subject and under what conditions those interests may be compromised is debatable, as I discuss in this chapter.

<sup>23</sup> Although the discussion is mainly focused on ‘medical research’, I use the term ‘health research’, when appropriate, to refer to all types of research that may be employed by cluster design.

potential to result in their being harmed)<sup>24</sup> research guidelines and regulations state that it is permissible to expose research subjects to risks only when doing so can be justified by the value of the study<sup>25</sup> in question, restricting in this way the types of research in which research subjects, even competent adults, can participate.

The main focus, however, of current guidelines regulating health research is the protection of the interests of research participants; this is known as the ‘precautionary approach’. A widespread recognition of research abuses and scandals in the past led to the view that there is need for extensive regulations ruling research activity. For this reason, the importance of limiting the risks in which researchers can pose to their subjects are articulated in all current research regulations and guidelines (The Declaration of Helsinki and CIOMS guidelines, for instance, aim primarily at protecting participants from the risks<sup>26</sup> of research and ensure that their consent is respected). Moreover, central part of almost all current regulations and guidelines is that the interests of research participants should be given much greater weight than the interests of people who might benefit from the research in the future; for instance WMA Declaration of Helsinki states: “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (WMA Declaration of Helsinki 2013, paragraph 8)<sup>27</sup>.

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<sup>24</sup> To decide whether it is morally legitimate to expose others to risks we need to define what we mean by harm (i.e. whether we refer to physical harm, psychological harm, the time one spends when participate in research and so on). Since most guidelines require that all different risks to which subjects are exposed should be taken into account (Wendler 2012) this issue will not be discussed further in this chapter.

<sup>25</sup> Different views on how this value should be defined are discussed later in this chapter

<sup>26</sup> Although central part of the precautionary approach is that research risks should be restricted, there is generally no agreement on how to determine which risks are acceptable.

<sup>27</sup> Though research participants may be harmed from their participation, the potential of benefit should not be ignored; the standard of care for instance may be better within a funded research project.

In sum, the exposure of research subjects to risks of research according to current research ethics regulations is acceptable only when the study has the potential of being socially beneficial and when the interests of the individuals are sufficiently protected. Satisfaction of these conditions suggests that the interests of research subjects are not undermined in the pursuit of obtaining scientific information and therefore the main ethical concern raised by health research (the potential of them being exploited) is being addressed.

The importance of protecting research subjects from harms is also highlighted in Hans Jonas' essay "Philosophical Reflections on Experimenting with Human Subjects", one of the most widely reproduced philosophical essays in the field of medical ethics. Jonas claims that the interests of participants should always take priority over the interests of people who will benefit from the outcomes of research in the future. According to Jonas, although the progress offered by health research is normatively optional, the need to protect those exposed in research risks is mandatory: "Our descendants have a right to be left an unplundered planet; they do not have a right to new miracle cures. We have sinned against them if by our doing, we have destroyed their inheritance not if by the time they come around arthritis has not yet been conquered (unless by sheer neglect)"(Jonas 1969, p. 230–231).

This view raises several questions: First, should the interests of research subjects always take priority, as requested in the precautionary approach? How can we ensure that the interests of research subjects are sufficiently protected? Is Jonas right to argue that the conduct of health research is normatively optional? What does he mean by 'sheer neglect'?

#### **4.1.1 | Is health research normatively optional?**

Let us first consider the view that health research is normatively optional. The main difficulty with accepting this view is that it considers the status quo as satisfactory. In particular, in order to agree with Jonas's position, we must admit that today, compared to the past, we have sufficiently advanced medicine that permits individuals to lead adequately flourishing lives. As Wendler (2012) notes, the example of arthritis, cited by Jonas, reflects the view that the benefits of

health research are the ones that make an acceptable state in life even better. One could then argue that conditions, such as minor pains or aging, are not profound problems in our life. Indeed, exposing individuals to considerable risks with the danger of exploiting them seems difficult to be defended for such goals.

However, the health problems that Jonas identifies are not the only problems in our society. While significant medical improvements have been made compared to the past, there are many diseases that kill over a million people every year against which there is no adequate treatment. Moreover, there are no effective treatments for many chronic diseases, such as stroke, that significantly affect people's wellbeing. The suffering from life threatening diseases or painful conditions provides a good reason to argue that health research has a more important role than Jonas believes. Moreover, people who might be benefited by future research (as well as those who care about them or are likely to suffer from the same conditions or diseases in the future) would most likely not accept Jonas' view (whether however these people have a right to health research being conducted and thus that their lives being improved is a different issue that will be discussed later).

Another reason for which health research (and medical research in particular) is important is that it offers the benefit of discovering medical therapies and medicines, which cause less harm to the patients than current ones. A recent study (Lazarou et al. 1998) found out that the approved and properly prescribed use of medications is probably the 5<sup>th</sup> leading cause of death in the US. According to Wendler (2012) this suggests that, in contrast to what is commonly believed, in reality investigators are not harming some individuals in order to make others (more people) better off, beyond some already acceptable status quo. Rather, the real dilemma is to decide which is the less harmful practice; either allow physicians to expose patients to increased risks of harm, while treating them, or allow investigators to expose their subjects to risk of harm, while trying to find improved methods to cure other patients. To argue that there is a normative difference between these two cases, we need first to explain why harming individuals in the context of research (for this kind of studies) potentially involves

a significant moral wrong that harming patients in the context of care does not (Wendler 2012).

Rhodes (2008) gives another reason for which health research should not be considered as normatively optional (which will be discussed in more detail in the contractarian approach). She states that the conduct of health research is a way to correct social injustices. By focusing on the status quo being intolerable by many Americans who have no equal access to health care, she argues that the conduct of health research contributes to the fair distribution of health care in the near future. Rhodes notes that the aim of health research (e.g. preventive medicine research, health policy research, quality assurance research) is to help everyone with similar health needs, without excluding anyone.

The aim of all previous arguments has been to prove the importance of health research. It could be argued, however, that not all of them are equally convincing<sup>28</sup>. What seems easier to accept is that society should at least support and promote research aiming to reduce painful or fatal conditions that significantly affect people's wellbeing; therefore, that (at least) certain types of health research should not be considered normatively optional. As the norms governing the scientific method of health research mandate the compromise of the interests of some individuals for the benefit of others (Miller & Weijer 2006), it is consistent to argue that (at least in certain circumstances) the exposure of some individuals to research risks for the social benefit can be justified by the moral duty<sup>29</sup> of our society to promote health research.

#### **4.1.2 | How can we ensure that participant interests are sufficiently protected?**

An important reason, however, for which one may question the acceptability of a research study despite its potential social value is the absence of informed consent. It could be argued that the suffering (or even death) of some people from unfortunate conditions does not provide a sufficient reason to justify exposing

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<sup>28</sup> For instance, as I discuss later, Rhodes' argument is considered very controversial.

<sup>29</sup> Whether this should be considered as a perfect or imperfect duty will be discussed later.

some individuals to research risks (no matter how serious they are), if those individuals are deprived the right to decide whether they want to participate or not, as in the case of many cluster randomised trials. Moreover, a further argument can be made that permitting the exposure of research subjects to risks without their consent for the benefit of others might lead us to a slippery slope with serious abuses throughout society.

Several questions related to the absence of consent could be raised: Does the inability to obtain consent from research participants suggest that they are not treated fairly and thus that their interests have been compromised (irrespective of the kind and level of risk involved)? Should health research in which informed consent is not feasible always be prohibited despite its value (for the protection of research subjects)? Why the absence of consent is more problematic in the case of health research compared to other domains of life e.g. tax policy? The answers to all questions above will depend on the ethical approach we adopt. In chapter 7, I discuss the moral significance of informed consent in health research and political life and examine different approaches to the consent requirement; for now let us return to the discussion on how and when the exposure of some individuals to research risks can be justified based on the precautionary approach.

I have discussed so far that in contrast to Jonas' view, at least in certain circumstances (i.e. when alleviating the society from painful and fatal diseases) the conduct of health research should not be considered optional. Let us now return to the question of whether giving priority to the protection of the interests of research subjects is a necessary and sufficient condition for a health research to be justified.

The main concern in exposing some individuals to risks of research for others' potential benefit (even when the expected social benefit is significant) in the first place is the risk of their potential exploitation; the risk that investigators may treat their subjects as means to their (scientific) goals. The precautionary approach suggests that individuals' interests should always take priority over the interests of society. A necessary condition to ensure that subjects' interests are well protected is to confirm that research participants share the aims of the study. As Jonas notes,

when subjects adopt the aims of the study as their own they are acting in their own interests<sup>30</sup> despite the fact that they may be exposed to risks involved in procedures aiming to collect information to benefit others (Jonas 1969, p. 236). How to assess, however, whether a research subject has shared the aims of a study is controversial.

Some argue that there are objective conditions under which individuals can share the goals of a given research study. This objective view of what may be in someone's interest is considered very restrictive, as it generally rejects non-beneficial studies, non-therapeutic procedures involved in many beneficial studies and regards as problematic the involvement of healthy volunteers in phase 1 trials<sup>31</sup>. Despite these restrictions, however, the objective view provides a persuasive justification for the exposure of research subjects to risks of harm for the benefits of other people; as Wendler notes, the fact that individuals' participation is objectively in their interests suggests that there are less concerns for their exploitation (Wendler 2010) and leaves little room to potential participants to consent to studies that may be against their interests.

Does the fact, however, that a study is objectively in someone's interests constitute a sufficient condition to justify enrolling a competent adult in a study when individual consent is not feasible (provided that protective measures are taken as the precautionary approach demands, i.e. the risks are minimised and their interests are given priority over the potential social benefits)? In particular, in the case of a cluster trial, in which informed consent is not feasible, could we argue that when the aims of the study are objectively compatible with cluster members' interests, research subjects are sufficiently protected against exploitation and the trial is morally justified despite the lack of individual consent?

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<sup>30</sup> Although this view seems to confuse interests with consent (e.g. one may consent to an intervention which is against their interests), in Jona's account, as I later explain, this is not morally problematic for the protection of research subjects.

<sup>31</sup> In Phase one trials researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects (Norfleet and Gad 2009).



An alternative, broader interpretation contends that research subjects can share the aims of a study even when they do not have the condition it examines. For instance, individuals might decide to participate in a study and endorse its aims out of purely altruistic motives (for instance healthy volunteers in phase 1 trials) or because they have relatives or friends suffering from the condition which investigators examine or because they adopt the discovery of treatment for a specific disease as their personal goal. This view is based on standard preference satisfaction account of human interests, which states that “what is in a given individual's interests depends on what the individual happens to want or prefer, or the goals the individual happens to endorse, or the goals the individual would endorse in some idealised state scrubbed clean of the delusions, misconceptions and confusion which inform our actual preferences” (Griffin 1986). Thus, in order for subjects to endorse the aims of a study and in order research to promote participants’ interests, research subjects need to be well informed and willing to participate, irrespectively of whether their condition is relevant to the aims of the proposed research<sup>32</sup>.

An implication of this interpretation for the case of cluster research is that the enrolment of cluster members may not be easily justified when consent is not obtained (even if the aims of the study are in the subjects’ interests narrowly conceived). In order for a cluster study to be justified, researchers should at least find a way to ensure that participants endorse the aims of the study if their individual informed consent is not feasible to obtain<sup>33</sup>.

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<sup>32</sup> A main problem with this interpretation is that by identifying interests with preferences (even informed preferences) it does not take into account that potential participants may be willing to consent to studies that are not in their interests (e.g. non-beneficial studies where high risk is involved). Yet, compared to other approaches in research ethics that I discuss in this chapter, this interpretation does not necessarily entail the risk of research subjects’ exploitation; based on the ‘precautionary approach’ an essential condition for a study to proceed is that the interests of research participants be given much greater weight than the interests of people who might benefit from the study in the future.

<sup>33</sup> Defining whether a study should be in individual subjects’ interests and how these interests should be defined are morally relevant issues in the justification of cluster research. As I discuss later, cluster interests may differ to the interests of individuals in the cluster and even conflict. In the chapter 8 I examine this issue in more detail and suggest a solution in the case of conflict.

It seems then that irrespectively of the reasons for which someone might have accepted the aims of a given research study (either because the study is objectively in their health interests or because one has endorsed its aims for other personal reasons), there is an important question that needs to be addressed by the precautionary approach. Assuming that the protection of the interests of a research subject is a necessary condition for the moral acceptability of a health study, is informed consent an essential requirement in order for a research subject to be adequately protected? Should for instance, a cluster study in which individual consent is not feasible be prohibited even when very strict measures and protections have been adopted to preclude any concern for subjects' exploitation?

The precautionary approach has been criticised as restrictive because its focus on the interests of research subjects often prohibits valuable research (for instance see discussion below on the libertarian approach, the consequentialist approach and the arguments against "research exceptionalism"). This approach, however, takes into account a very important factor that other moral approaches neglect: exposing some individuals to risks of research is not only problematic to the extent that there is a potential of harm for the participants. By giving priority to research subjects' interests, current research ethics guidelines implicitly state that the behaviour of the researchers should reflect that their study is conducted in a moral manner. In other words, what the precautionary approach implies is that to assess a health study as morally acceptable, investigators and by implication society who are the agents exposing participants to research risk, should never be benefited in the expense of those individuals.

## **4.2 | The Consequentialist approach**

In contrast to the precautionary approach, which requires that dangers to research subjects should be considered more serious than social benefits, some ethical perspectives would give equal weight to the interests of all those potentially affected. The Consequentialist approach, for instance, focuses on the outcome of our actions. The fact that some of the studies that the precautionary approach prohibits would likely have important social value provides for the consequentialists a normative reason to eliminate those restrictions. To assess

whether a research study should be morally justified, according to the consequentialist approach, we must consider the benefits and harms to both research subjects and future patients/ society. Therefore individuals who will potentially be benefited from health research should equally be entitled to protection, concern and respect with those who serve as research subjects.

#### **4.2.1 | The strengths of the consequentialist approach**

In its utilitarian form this approach holds that the morally right course of action in any situation is the one that produces the greatest balance of benefits over harms for everyone affected. The consequentialist approach makes direct trade-offs between the harms and benefits of the participants and future patients or society in general. In contrast to the precautionary approach, utilitarians believe that the balance should not be by default loaded in favour of the interests of the research subjects; Harms to potential participants should be balanced against the harms of not conducting research, which in some cases may be the massive loss of life. Utilitarians notice that although presumptions for potential abuses in the future are justified, they should not always restrict the benefit a society may gain from valuable research. John Harris summarises: “we are, however, I believe, in real danger of allowing fear of repeating one set of atrocities to lead us into committing other new atrocities” (Harris 2005, p. 242).

For a research study to be socially beneficial it should be well designed, have valuable aims, and offer a reasonable hope of concrete benefits to future patients. Harris for instance defines as ‘serious research’ the research that aims to prevent serious harm or provide significant benefits to humankind (Harris 2005). If these conditions do not apply, research should be rejected, not only because it would be harmful for those who participate but also because it would be unlikely to benefit people in the future. Therefore, contrary to the libertarian approach (which I discuss later) the consequentialist approach would raise a high standard for the social value of a research study in order to justify the exposure of research subjects to risks irrespectively of their willingness participate. This view is

partially<sup>34</sup> compatible with research ethics guidelines, which state that it is permissible to expose research subjects to risks only when by doing so can be justified by the value of the study in question.

#### **4.2.2 | Problems with the consequentialist approach**

However, if we were simply to carry out actions ‘for the greater good’ as the utilitarian approach demands, the focus would shift towards overall benefits and actions would eventually overlook and outweigh the interests of research participants. What is sometimes deemed for the greater good could entirely be the opposite in regard to the individual participant (since utilitarianism focuses on the outcomes, it is not concerned with how these outcomes can be achieved). Perhaps the greatest ethical concern with utilitarianism is that it fails to take into account considerations of justice. We can imagine instances where a certain course of action would produce great benefits for society and at the same time clearly unjust for the research subjects who will bear its burdens (for instance, a potentially valuable study which involves risk of death for the participants). This could be a dangerous route to take; research participants could be merely exploited for progression of human knowledge. This is why the utilitarian approach is considered as controversial by many ethicists. The consequences of adopting a utilitarian approach is the reason that health research is often treated with suspicion; the aftermath of Nazi doctors’ atrocities, examples of extreme medical arrogance and paternalism such as the Tuskegee Study of Untreated Syphilis (1932-1972) as well as more recent examples such as the UK major scandal with the unauthorized and deceitful post-mortem removal and retention of organs and tissue from children (The Royal Liverpool Children’s Inquiry Report 2001) are all examples of abuses and violations of research subjects’ integrity. Considerations of justice provide an apparent reason for which utilitarianism should not be the sole principle guiding our decisions.

Thoughts such as when one should be able to overrule another individual’s wishes are relevant when discussing the ethics of cluster research. The argument that an

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<sup>34</sup> As mentioned earlier, guidelines also insist on the consent requirement and mandate that the interests of research participants should be given priority over the interests of people who might benefit in the future.

action is for the greater good is often used when overriding autonomy. As an individual's right to choose does not often result in positive benefit for the largest number of people, a participant's prior wishes and liberty could be ignored. The argument thus put forward for not gaining consent in regards to health research is that ultimately research studies, in which individual consent is not feasible, could be used to benefit the lives of a great number of people. Thus, cluster studies with the potential to offer significant benefit to society are morally justifiable in utilitarian ethics even if the risks involved are not minimal and participants are deprived of the right to decide whether to be involved or withdraw from the study.

Another problem with the utilitarian approach is that it demands that many different factors are considered in the assessment of whether an activity should be permitted, particularly in the realms of consent. Yet, a weakness of utilitarian thought is that it does not make it practical to weigh out different consequences with clarity and ease. As we can never be really certain about all of the consequences of our actions, especially in the context of research, utilitarianism may present a serious problem; If, adhering to a utilitarianism framework research investigators were to constantly overrule the wishes of research subjects, arguably for the greater good, a knock on effect of mass decrease in population satisfaction may occur, as a result of people fearing what could happen to their own bodies despite their desires. This would limit the number of research studies taking place, since the public might refrain from supporting research<sup>35</sup>. As the aim of health research is to improve people's health and public support is essential for this aim to be realised, utilitarianism cannot be used as a default justification of denial of individual consent in health research even when the expended outcomes are important<sup>36</sup>.

It seems that it may be hard to draw a line at whether something can be done for the greater good. By relying on a utilitarian approach to assess whether a cluster

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<sup>35</sup> Financial support and participation are both essential for a health study to be conducted.

<sup>36</sup> Additional reasons for which public support is important in health research are discussed in Chapter 8 (see for instance discussion on how public involvement may improve the quality of a study).

trial should be morally acceptable, we are faced with a dilemma; should we allow the conduct of cluster research with significant social value, despite the absence of individual consent or should we permit only the studies in which individual consent is possible? In cluster trials in which consent is impractical to obtain, it could be argued that research subjects have to endure an additional burden/harm: they are denied the freedom to decide whether they want to participate or not (the degree of this burden of course would depend on the nature of the intervention involved – i.e. how individuals' freedom is being compromised and their ability to opt out of the trial if they do not wish to participate). A problem then with the utilitarian approach is that by focusing on the outcomes of an action irrespectively of means used to produce these outcomes, it only takes into account the potential harm involved in the research intervention. To decide however whether a cluster study in which consent is not feasible can be justified, a consequentialist approach should both consider its potential social value and the net effect of the infringement's consequences for research participants based on both the risk involved in the intervention and the degree of which participants' freedom has been compromised. Utilitarians argue that concerns for the abuse of research participants have created a barrier preventing human knowledge and progression by placing much emphasis on the protection of human subjects. Yet, the challenge they need to face is to find a way to promote valuable research and ensure public support by permitting studies, which deprive research subjects from making their own decisions regarding their participation.

Another difficulty with the utilitarian approach is that it does not take into account all the interests that may be affected by one's participation when possible harms to the participant are balanced against potential social harms. Individuals have clearly an interest to avoid physical harms posed by research. However, by contributing to a particular project their interests may be implicated and thwarted even in the absence of physical harm. For instance, let us consider the case of an individual who offers blood sample for a particular project. When the project is over the researcher uses the stored sample for future research, which aims are opposed to the subject's beliefs. Is the subject harmed if he or she never found out about the aims of the future study? According to research ethics guidelines, which

mandate that the potential participant should understand and voluntarily agree with the aims of the study, this person is harmed although not personally affected by the practice. It could be then argued that to assess whether a research study is permissible or not more factors than those considered by a utilitarian approach should be taken into account.

Let us now consider the social value of health research. The benefits that society enjoys as the result of some individuals' participation in research, I have been considering so far, are medical and health benefits, better therapies for disease and better methods to prevent disease. The social value of health research thus is its ability to collect information that might be useful to identifying improved methods to treat conditions and thus improve human health and well-being. Since the aim of health research is to establish whether a particular method is effective and safe for treating, even if a study is not successful, it still provides useful information for future studies.

One can argue that much of the research that has been carried out is in the private sector, in which a maximum return of the investment is expected. In industry funded research there is a potential for different types of benefits additional to the expected social value; profit to the pharmaceutical companies. For instance, industry-funded research often focuses on the development of identical to approved and already-in-use drugs that increase stock price and market share without increasing overall health and wellbeing<sup>37</sup>. This may suggest that different moral concerns are raised by the conduct of industrial research.

A further question then that should be considered is whether it is appropriate to adopt the same ethical principles for cluster research (and health research in

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<sup>37</sup> Having argued that society is morally obligatory to support studies to alleviate the suffering of serious health conditions, it could be claimed that studies aiming at the development of 'me too drugs' are normatively optional, following Jonas' argument. However, it could also be argued that studies testing identical drugs have considerable social benefit, since by this way treatments would be less expensive and thus more accessible for many people. I will not discuss this issue further here as what seems to be more important is to consider what level of research risks should be allowed for this kind of social benefit (especially when participants are not able to consent) given that treatment already exists.

general) sponsored by industry or whether it is more appropriate to argue for stricter rules in this case. For instance, it could be argued that individuals participating in a research by which industry gains a huge profit are exploited if they do not receive a fair level of benefits from the activity to which their participation is vital. On a standard definition “what constitutes a fair level of benefits depends on the risks and burdens that a party experiences as a result of a transaction and the extent to which others benefit from the participation of the party in the transaction” (Wendler 2012). Other ethicists disagree that for these types of research it is acceptable to pay research subjects for their participation (Grady 2005). Defining a fair level of benefit for participants seems a complex issue and will not be addressed here. This question also brings us back to the discussion on how research participant interests should be defined.

### **4.3 | The Libertarian approach**

The principle of respect for individual autonomy in this approach has a central role. According to the libertarian approach, informed consent is a necessary and sufficient condition for the ethical justification of health research. Following Mill’s words<sup>38</sup>, in order to justify exposing some individuals to risks for research purposes, investigators should obtain “free, voluntary, and undeceived consent and participation” (On Liberty, p. 67).

Advocates of this view hold that competent and informed individuals are free to act as they wish, provided that those whom they interact with are also competent, informed and in agreement. Thus, ethical challenges raised by the conduct of health research are resolved by satisfying the requirement of obtaining informed consent. Libertarianism seems to imply that health research is not a unique human activity and that when potential research subjects are fully informed, competent and not coerced, they have a perfect right to participate in any type of research they wish. The libertarian approach then would justify even very risky studies, provided that potential research subjects are willing to participate, on the grounds that the liberty of competent adults should always be respected (Stewart et al.

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<sup>38</sup> Mill is not referring to health research.



2008; Sullivan and Richard 2008). Advocates of the libertarian view often compare research activity with other risky activities in which individuals are allowed to take considerable risks, for instance dangerous sport activities: “So we happily allow professional football players to put their bodies on the line not because we think that the risks they take are necessary in any sense, but because we think that they are adequately compensated by the enormous salaries they receive” (Sachs 2009, p. 70).<sup>39</sup> In its strict form the libertarian approach considers research participation as an entirely personal matter (it is up to the potential subject to decide for themselves whether they should participate in a given study) irrespectively of the features of the study, i.e. the risks involved, the aims of the study or the motives of the participants. Financial inducements are also considered acceptable as long as individuals are free to decline their offer.

These positions are not endorsed in research ethics guidelines. The general presumption in the Declaration of Helsinki and national guidelines, as already mentioned, is that research participation is potentially harmful, or at least burdensome. Although there is significant weight on informed consent, in none of the research ethics regulations and guidelines it is argued that consent is a sufficient condition for ethical research and that it is acceptable for investigators who obtain free informed consent of the participants to conduct any research they wish. In contrast, researchers are allowed to enroll human subjects only when an independent ethics committees groups, charged with ensuring that the study is ethically acceptable, has approved the study (World Medical Association 1996). Moreover, most regulations place further limitations on the types of research that should be acceptable by ethics committees, even for competent adults, by stating that research must have important social value and risks involved should be minimised (Hope et al. 2008). Provision on the management of the exposure to risk of harm for the potential research subjects implies that a (hard) paternalistic

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<sup>39</sup> Although most advocates of the libertarian approach endorse the view that research is not a unique human activity, proponents of ‘research exceptionalism’, a view I also discuss in this chapter, do not necessarily believe that informed consent is a sufficient and necessary condition for a study to be morally permissible, as libertarians do.

position<sup>40</sup> is embedded in most regulations in research ethics. In non therapeutic research, for instance, most regulations demand that research, which involves more than minimal harm should not normally be carried out even if the potential subject gives fully informed consent, and even if the subject (perhaps out of altruistic motives) wishes to take part in such study.

It is argued that paternalistic limitations in research context have evolved from clinical medicine (Wendler 2012). In the context of clinical care physicians are morally charged with protecting and promoting the interests of their patients. A libertarian advocate then could argue that to justify these paternalistic limitations we need to explain first why clinical care and health care norms are relevant in the context of research, despite the fact that health research and health care are considered as normatively distinct activities. Failing to provide a sufficient justification for restricting the options that competent adults have in health research we risk prohibiting (at least sometimes) otherwise important (in particular, commercially valuable) research.

Another important feature of the libertarian approach is that it gives great weight to a potential participant's right of confidentiality and right to withhold consent to take part even when a study is expected to have great social benefit and involves no risk to subjects. Therefore, epidemiological studies, which involve the collection of anonymised data from individual patient records without the consent from the individual patients, are considered very problematic (Dorney 1990). The main issue for the advocates of the libertarian view is not that individuals do not get harmed, but that they have the right to control access to personal information and decide for issues that affect their lives.

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<sup>40</sup> The advocates of the libertarian approach cannot accept hard paternalism because it involves interfering with the liberty of an individual for their own benefit, despite the fact that the action being interfered with is made by non-coerced and informed competent individuals. Restrictions justified on hard paternalism are considered as restrictions on autonomous actions of the individual.

### 4.3.1 | The implications of adopting a libertarian approach in CRTs

The fact that for the libertarian approach informed consent is a necessary and sufficient condition to justify exposing a group of individuals to risks of harm for the benefit of others has several implications not only for certain conventional studies (RCTs), such as epidemiological research, but also for many cluster studies (CRTs) in which informed consent from individual participants is not feasible. The majority of cluster-cluster trials and individual-cluster trials which involve large size clusters that exclude the possibility of obtaining individual informed consent, irrespectively of their particular features (e.g. intervention involved, the aim of the study, the risks involved, etc.) are all considered inappropriate infringements on the free action of competent individuals and thus cannot be justified.

The almost exclusive weight to respecting individual autonomy that the libertarian approach gives, seems to be consistent with the first principle of the Nuremberg Code: “The voluntary consent of the human subject is absolutely essential”. This position however, has some far reaching implications. First of all a strict libertarian approach would consider as unethical any research with incompetent individuals, any paediatric research, research in many emergency situations, and research with the demented elderly (even research that involves only minimal risk). The result of adopting this approach, would be to reduce the number of studies that are conducted, as morally impermissible with great social costs. For instance, paediatricians would have no other option than to provide off-label treatment that could significantly harm children, a situation that can be avoided by identifying appropriate treatment through research.

However, this conclusion does not necessarily follow from the libertarian approach. The libertarians might well argue that incompetent adults and children are not right holders and that their theory provides an analysis of the conditions under which health research in competent adults can be justified and not the conditions of conducting health research in general. It does not therefore suggest that research, which involves subjects incompetent to consent, is morally unjustified, but that when competent adults participate in research, informed

consent is a necessary and sufficient condition (Wendler 2012). However, even in that case advocates of the libertarian view need to explain why research on non-competent individuals might be morally acceptable, despite their inability to exercise their right to consent.

Another difficulty with the libertarian approach is that it presupposes sufficient understanding as a necessary condition for valid consent, and valid consent as a necessary condition for the ethical conduct of research. In health research (and clinical research in particular) subjects are rarely sufficiently informed or have fully understood to make their own informed decisions about their participation. According to empirical studies most individuals (competent adults) that participate in research are not able to understand randomisation<sup>41</sup> within the time limits feasible for clinical research (Snowden 1997; Featherstone and Donovan 2002; Appelbaum 2004). It seems to follow that health research, especially randomised trials which provide the gold standard of evidence regarding the efficacy of health interventions, may generally be impermissible.

Since the opportunity cost in banning all these types of research would be great, libertarians are willing to accept certain limitations on health research, such as minimising risks and the requirement for independent review from IRBs and RECs, on the grounds of soft paternalism (Wendler 2012). Soft paternalism is defined as involving interference with the liberty of an individual “in order to promote their interests on the grounds that the action being interfered with is the result of impaired decision-making” (Feinberg 1986). Therefore restrictions justified as interference with the liberty of competent research subjects for their own benefit and not with their autonomy are considered consistent with a libertarian account. One then could defend the libertarian approach by arguing that the fact that competent adults fail to understand research and provide valid consent does not suggest that the libertarian approach is false. The libertarian approach could be considered as the ideal, which is not realised because competent participants often fail to attain it (Wendler 2012). In order then to be

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<sup>41</sup> i.e. the fact that the people being studied are randomly allocated to one of the different treatments under study.

implemented in practice, certain restrictions should be applied to enable valid consent.

Although this argument seems to suggest that moral restrictions and regulations in health research can be consistent with the libertarian approach, it fails to recognise a very important fact: the conditions on what one individual may do to another are not exhausted by what the second individual consents to (as discussed earlier a strong point of the precautionary approach is that it takes into account this factor). Even if a competent individual chooses to be treated with lack of respect, for instance if they consent to be tortured, it does not follow that it is acceptable to be treated that way. Moral agents need to know that they treat each other appropriately and that suggests that they need an evaluation beyond the fact that the affected by their actions individuals have consented to them. Irrespective of whether informed consent can be obtained or not, research subjects should be protected from harm and not be exploited by the researchers (Jonas 1969). Therefore, considering the protection of research subjects, informed consent does not exhaust the ethics of health research, rather an independent consideration of what is an appropriate behaviour on the part of investigators and society in general should also be included. This leads us to consider that certain limitations should apply to what researchers are allowed to do to their subjects. To determine the limitations of what sort of research investigators may conduct, we should consider the obligations that researchers have towards their subjects (an issue that will be discussed in Chapters 5 and 7).

We can therefore conclude that the fact that a study involves competent adults, who voluntarily consent to participate after being adequately informed, does not provide a sufficient reason to deem a health study morally permissible. The ethics of health research includes standards that are not limited to the respect of individual autonomy, as the libertarian account contends. What we need in order to decide whether a research study – and in our case a cluster study in which obtaining individual informed consent is not possible - should be permitted or not, is a moral approach that not only takes into account the protection of personal autonomy but which can also ensure that society does not encourage processes or

is not benefited by actions that exploit its members, even if those members are willing to be treated in that way.

#### **4.4 | The Communitarian approach**

At the other end of the spectrum is the communitarian view. Communitarianism, as an ideology focuses more on the common good and the public interest than on individual autonomy. For the communitarians, individuals are not considered as atomistic selves; as Charles Taylor argues “man is a social animal, indeed a political animal, because he is not self-sufficient alone, and in an important sense is not self-sufficient outside a polis” (Taylor 1985, p. 190).

According to the communitarian view, lives and identities of individuals are indelibly tied to the well-being of their community; for this reason, individuals have a vital interest in leading decent communal lives. Society matters because it is a collective of individuals and exists in order to promote their well-being. This could optimally be accomplished by assuring that some societal requirements are met; social responsibility, collaboration and solidarity are fundamentals for a meaningful life, both of the individual and the society (Etzioni 2003, Raz 1986).

In contrast to the libertarian view, in the communitarian approach, every decision individuals make has to be understood, and its implication assessed, in the context of the wider society and the public good. (Lederman 2014). Opponents of the communitarian view argue that the tight connection between individuals and their communities, that the communitarian view contends, often leads communitarians to consider interventions and practices that benefit the community as a whole, good for the individuals as well. They argue that this view permits direct trade-offs between the good of the community and the good of its members; “what is good for the whole is necessarily good for its parts” (Beauchamp and Steinbock 1999, p. 57) and thus, that when an individual’s interest in community conflicts with their other vital interests in leading freely chosen lives, communitarians would automatically give priority to the first.

In contrast to the libertarian view, for the acceptability of a health study communitarians would seriously consider the effect that the study would have on

the community. This view will favour interventions that promote the welfare of the citizens that would be likely to lead to considerable tensions in the libertarian framework. The libertarian approach, as already discussed, generally considers competent adults as autonomous individuals, able to weigh the benefits and risks of participating in research and make a decision based on their (own) understanding, their own values and interests and their own circumstances. Although these decisions in some cases may affect family and friends, they primarily affect the person making the decision and are thus considered personal. Communitarians on the other hand, often speak of the common dimension of morality in terms of a “shared common understanding,” “shared hierarchy of goods,” or “shared vision of the good life”(Callahan 2003). To assess whether a cluster study should be permitted or not, a communitarian approach will require that the very first questions be asked from a communitarian perspective, i.e. What will the study mean for all of us together? Is it sufficiently compatible with the common good to permit its use, and in case it is not wholly compatible, should it nonetheless be permitted on the grounds that a good society may on occasion permit potential harms to itself in the name of accommodating the special needs of some of its citizens (Callahan 2003)?

In studies where individual consent is not feasible, the communitarian view would argue that we should consider more the potential benefit and risks for the community rather than individual autonomy. A cluster research intervention considered as socially beneficial cannot be reduced to questions of individualism and choice. For the communitarians the fact that something is chosen by an individual after deliberation process does not necessarily make it more valuable than something, which is not, as this would imply that there is something fundamentally wrong with non-chosen projects or activities (e.g. we ordinarily consider ourselves as members of a family or community or nation which are often involuntary social attachments in which rational choice has played no role).

One could respond to the above argument by arguing that what is morally important is not whether a choice is desirable or not, but rather that individuals have the possibility to decide. Although non-chosen attachments are not critically endorsed and excessive deliberation could be counter-productive, all individuals

have a fundamental interest in being able to question and revise their ends (as people's ends may sometimes be problematic). In particular, liberals relying on the value of self-determination, which requires only that we are able to critically evaluate our ends if need be, hence that 'no end or goal is exempt from possible re-examination' (Kymlicka 1989, p. 52; Dworkin 1989, p. 489; Macedo 1990, p. 247) point out that no particular end or commitment should be beyond critical reflection.

The liberal argument for the value of self-determination is challenged by the communitarians. As they state, although we are able to re-examine some attachments, there are others so fundamental to our identity, that they cannot be revised and rejected. The mother-child relationship, for instance, could be considered a constitutive feature of one's identity and thus any attempt to deny it would ignore or violate women's special needs and experiences (Frazer and Lacey 1993). For this reason, communitarians argue that politics should not only be focused on securing the conditions that enable individuals to exercise their autonomous choice but also support and promote the social attachments fundamental to people's sense of wellbeing (Taylor 1985).

The communitarian approach encourages a cooperative way of thinking about research interventions, when they target a whole community, that other approaches ignore, particularly in some contexts where there is a strong sense of community solidarity. By providing a non-individualistic way to consider the benefits of participating in a research project the communitarian approach generally encourages individuals to participate in social life. In contrast with the libertarian view, potentially socially valuable studies that involve no risks for the participants would not be prohibited only on grounds that there could slightly restrict individual freedom. Moreover, this approach has an advantage of taking into consideration the social implications related to the conduct of a health study and does not simply assume that they should be left to autonomous choices of individuals.

The existing system of human subjects protections has recently been criticised by researchers for its sole focus on individual protections and lack of explicit



protection or consideration for communities. This is evident in the terminology used in the Belmont Report: e.g. ‘researcher’, ‘subject’. For this reason, Weijer et al. suggested a communitarian approach to inform and expand on the ethics articulated in the Belmont Report. Weijer argues: “I believe a fourth ethical principle must be added to those found in the Belmont Report: the principle of respect for communities” (Childress et al. 2005, p. xiii). To move the focus from solely the individual to include the community within which the individual lives or is a member, in 2001 the National Bioethics Advisory Commission proposed that regulatory oversight for research with human subjects be extended beyond the protection of individual research participants to include the protection of social groups. According to Weijer and colleagues, in their proposed approach the rights of the individual are still protected, but ethical considerations to the community level are expanded and inform new ethical questions.

However, despite these benefits, more ethical issues than those identified by Weijer and colleagues are raised with this approach. To identify and assess research risks and benefits for communities requires conceptualizing communities as entities that may be harmed or helped by research. Since risks and benefits for communities may be different from the risks and benefits for individuals, issues such as how ethical decision making should be made, when would communities need protection, how should ethical decisions be made when individual concerns and community concerns are in conflict, what is the extent to which the interests of the community might justify state interventions that impose limits upon the freedom of individuals and what is the extent to which individuals have moral obligations to contribute to or protect the community (Hunter 1994) need to be addressed.

Let us consider for instance the following example: An individual decides to enroll in a study that measures blood lead levels of residents who live in different city neighborhoods. The study is expected to offer individual benefit; in case a resident’s blood lead level is high it will provide treatments to reduce it. However, when results are released, there is a risk of neighborhoods with high blood lead levels being stigmatized as unhealthy, which would affect the community interest.

Should this study be forbidden even if it offers considerable benefit for the participants to whom they would not have access otherwise?

Possible tensions between individual interest and community interest may be even more problematic. A cluster study that is expected to be very beneficial for a community may involve more than minimal risk for the participants who happen to be the most vulnerable members of the community (for instance pregnant women). To avoid the danger of leading to the exploitation of some individuals for the communal benefit, we need to consider how much we can ask of individuals for the sake of their community, what kind of sacrifices it is permissible to ask them to do and why.

#### **4.5 | Contract Theory: Participation in research as moral obligation**

The exposure of individuals to research risks for the general benefit has also been justified on the grounds of a moral obligation to participate in scientific research. Caplan (1984) Harris (2005) Heyd (1996), Rhodes (2008) and other commentators, attempted to refute the dominant view that research participation is beyond the call of duty. They state that health research is so important that there is a positive moral obligation to pursue it and to participate in it: “we should not, however, forget the powerful obligation there is to undertake, support, and participate in scientific research, particularly biomedical research, and the powerful moral imperative that underpins these obligations” (Harris 2005). According to the advocates of this view, people who refuse to participate in research when an opportunity arises are not acting ethically. Although having a moral obligation to participate in health research does not necessarily suggest that informed consent should not be obtained from research participants, it could be argued that when this duty is strong enough then a study may be justifiable even if consent is not possible (Harris 2005; Rhodes 2008). In the following paragraphs I explore whether an argument for a strong moral duty to participate in research can be defended and thus whether such a duty could be sufficient to justify the conduct of cluster research where consent is not possible. In other words, aim of the following paragraphs will be to examine whether a universal moral duty to

participate in research could outweigh the right of a research subject to decide whether to be involved in a health study, and in particular when such study is employed by the cluster design.

The argument for a moral obligation to participate in research is often presented as follows: health research has offered important benefits to all of us, e.g. access to medical care, vaccination, and better health treatment. Since people currently living have received all these benefits, due to the fact that some individuals participated in research in the past, appeal to basic fairness suggests that those currently living have a general moral obligation to support health research so that future generations can be benefited as well.

The defense however of such a putative moral duty to participate in research has raised controversy. It is argued that the above argument falls to a logical error. Our obligation to the research participants in the past, due to whom we enjoy medical benefits today, cannot discharge by a participation in current studies (Schafer 2009). Likewise, by our participation in health research today we cannot pay back those who first served as research subjects.

An alternative approach to defend an obligation to research participation can be grounded on the overall social system of which health research is a part and not on the sacrifices of previous participants. An obligation therefore to participate in research can be based on the fact that we have received many benefits in the society in which we were born.

Rhodes (2008) follows the latter interpretation and states that there are three inter-related arguments for our duty to participate in research: the argument of *justice*, the argument of *beneficence* and the argument of *self-development*. According to the first argument, we all, as human beings, are vulnerable to disease, disability and pain. Most likely at some point in our lives we, or our loved ones, will have a medical problem or condition that needs treatment. In order then to have access to remedies and to improved standards of care, the conduct of health research is necessary (so that the causes and natural development of diseases can be identified as well as the effectiveness of treatments for different conditions). Since

health research can only be carried out by sacrificing some of the basic goods that we all hold as precious (privacy, comfort, safety, time), it is only fair that to share in the benefits of health advances, we all should do our fair share by participating in research.

Rhodes second argument, the argument of beneficence, leads us to the same conclusion. Because we all want to have access to effective medical treatment when we need to and because others' contribution is a precondition to achieve those medical advances, non-instrumental principles of universalization require that we should all offer ourselves to serve as research subjects to help others in need: "our emotional and genetic interrelatedness, the lack of an adequate alternative, and the commonality of the desire to benefit from medical knowledge create the participatory duty" (Rhodes 2008, p. 37)

Rhodes' final argument of self-development relies on Kantian grounds. She argues that the principle that we should all be good rulers over ourselves leads us to accept a duty to participate in research. Since health research is our only chance to protect ourselves from disease and disabilities in the future and, thus, retain our autonomy, we should take all the necessary steps to ensure that we achieve that (Rhodes 2008). By our contribution in health research then our own interests are also promoted.

#### **4.5.1 | A duty to participate in research addresses health disparities**

Rhodes argues that health research in general does not threaten the interests of the participants. With the exception of phase 1 trials, a good deal of research does not involve significant risks. In the case of riskier studies, Rhodes states that regulations and proper oversight could assure that risks have been minimised and that participants are exposed to only a reasonable degree of risk (Rhodes 2008). In contrast then to the common view that participation in research may jeopardise individuals' interests, Rhodes adds the 'prudential argument' to the principle-based argument for a duty to participate in research. Members from already disadvantaged groups that refuse to participate in research are less likely to benefit from medical advances in the future, since their condition/ disease will not be

studied and corrective measures that address health disparities will not be taken. As she notes: “The poor, those in the lower middle-class, part-time workers, those who have lost their jobs, those with chronic illness, undocumented immigrants and their children all lack good access to health care...however, I want to point out that existing injustices can only be exacerbated by members of those groups refusing to participate in research. If your group is not studied, it is less likely that advances to benefit people with your disease or with your genetic susceptibilities will be developed” (Rhodes 2008, p. 38). Furthermore, according to Rhodes, a duty to participate in research would ensure broad public participation (thus more studies) and that the results will not only affect and concern a small portion of the population. As she points out: “if you do not play, you have little say; in sum broad participation would best promote our goals and repair the existing problems” (Rhodes 2008, p. 38). A duty to participate in research will ensure everyone’s contribution and entitle everyone to share the benefits of research and set the research agenda.

Rhodes attempts to find a way to protect vulnerable groups, which participate in research and at the same time encourage scientific progress. Arguing for a moral duty to participate in research, according to Rhodes, will ensure that vulnerable groups will become better off by receiving the benefits of research in which they are entitled to. However, the history of health research has evidenced how easy it is to exploit vulnerable individuals by promoting scientific knowledge<sup>42</sup>. As De Melo-Martin (2008) points out, the lack of access to research products, the lack of compensation to research risks and the neglect of our most important needs in health research suggest that Rhodes’ approach does not take into account the current social context. As the group of people who bear the burdens of research is often not the same with the group that will get the benefits, it seems that a universal duty to participate in research will not result to fairer distribution of health benefits but to an additional burden to already disadvantaged groups and thus more unequal results (which could more easily be avoided by voluntary participation).

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<sup>42</sup> Rhodes’ argument seems also to imply that research participants from non-disadvantaged groups will not be found.

Rhodes acknowledges that the goal of research is to serve the common good and not the particular interests of the individual research subject (Rhodes 2005). As London (2006) points out, in cases in which research utilizes rigorous scientific and statistical methods to study questions of genuine social significance (i.e. in studies not designed to benefit participants) we need to consider the limits of what can be asked of vulnerable research participants in the name of the common good. As London commends, Rhodes argumentation does not address the underlying concerns of the utilitarian excesses of research abuse. Appeals to concepts such as ‘reasonable risk’ may not be sufficient to safeguard the basic interests of vulnerable groups. The balance between protection of the vulnerable individuals and social good that Rhodes assumes by her argumentation seems not achievable (in chapter 5 I argue for an alternative approach on how research can contribute to social good and at the same time protect vulnerable groups and individuals).

#### **4.5.2 | A duty to participate in research supports an adequate and accessible health care system**

Schafer (1983) makes a similar argument to Rhodes. He argues that a moral obligation on behalf of our society to provide medical care for everyone entails a moral and social obligation of its members to participate in health research: “One of the basic assumptions of Jonas's argument is that society has no right to exact from its members significant personal sacrifice for the public good. This assumption is questionable. It is now widely, though not universally, accepted that we have an obligation as a society to provide adequate medical care for everyone. This obligation would seem to entail that society promote the development of effective treatments. To forego medical experimentation would be to deprive ourselves of the benefits of new remedies; and not only ourselves, but future generations as well” (Schafer 1983, p. 77). Many people would accept that we all have a moral obligation to support a health care system, which is affordable and accessible for everyone in need. Does this obligation, however, entail a social and moral obligation to participate in research, as Schafer argues? Taxation is considered a standard procedure by which an adequate and fair medical care system can be supported. In particular, it is accepted that we all have a moral and social duty to support the health care system financially by paying our fair share.

Tax policy, despite the fact that it cannot rely on individual preferences and on the informed consent of everyone affected, is considered morally obligatory. Should the same apply for research participation?

Schafer seems to imply that research participation is a necessary condition to have an affordable and adequate health care system. As already discussed, the acceptance of a moral duty to improve the status quo requires an acceptance of a moral duty to support health research. Thus, Schafer's argument that our society has a moral duty to promote the development of effective drugs through health research seems plausible. However, this duty does not need to be as strong as Schafer and other advocates of this view argue. Considering the number and types of conditions left untreated and the standards of treatment that are currently available for each of them, it is difficult to conceive a society in which all of these problems will have been addressed (there always will be new untreated conditions affecting people's wellbeing). This of course does not suggest that a moral obligation to promote and support health research is unreasonable, only that a putative moral duty on behalf of individuals to participate and of society to provide therapies for every possible health condition is not realistic<sup>43</sup>.

A health care system is considered adequate when quality improvement methods have been reported to be feasible, effective and acceptable by practicing physicians; "The successful implementation of these methods is considered to be related to their being noninvasive, nonthreatening, and based on agreed upon standards of care" (Benbassat and Taragin 1998). A health care system provides adequate care when the infrastructure (e.g. hospitals, community health facilities), goods (e.g. drugs, equipment), and services (e.g. primary care) are available in all geographical areas and to all communities and when all health care is medically appropriate and of good quality, guided by quality standards and control mechanisms, and provided in a timely, safe, and patient-centred manner. A health care system that fulfils all these conditions is viewed as adequate and equitable irrespectively of the number of scientific studies that take place to promote its

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<sup>43</sup> This argument could only be successful if Schafer was referring to specific health conditions for which research has not been possible due to low recruitment rates.

efficiency. When there is not a universal health care system, adequate medical care could better be achieved by financial contribution in order treatments and care to be accessible to everyone in need.

### 4.5.3 | The argument of beneficence

John Harris (2005) observes that the vast majority of those writing about the ethics of research and regulation of research treat health research with suspicion, even hostility. He notes that the most popular view remains that participation in research is not an obligation but a supererogatory and, often, reckless act and that individuals who decide to be exposed to risks for the social benefit are considered as people who deserve praise. He then offers two complimentary arguments that, according to his view, justify our moral duty to pursue, support and participate in serious research based on our two basic moral obligations that we have as persons: the duty *not to harm others* and the duty *to be fair* (Harris 2005).

Similarly to Rhodes' argument of *beneficence*, Harris offers an argument to defend an obligation to participate in research based on our negative duty *not to harm* others. His argument, however, is more precise; he claims for an obligation to participate in *serious* research (i.e. research that is well-designed and has a reasonable prospect of resulting in important knowledge that will benefit future patients) (Harris 2005). He suggests that this duty entails that when our actions can prevent serious harm to others, and given that it is reasonable to do so (i.e. given the balance of burden to ourselves and benefit to others), we have a moral duty to act in this way. Failing to do so means that we should take responsibility for others' harm. He bases this argument on 'the rule of rescue'<sup>44</sup>. He explains that as people in need should be considered not only current patients but also potential patients and as those who are affected by others' needs, i.e. relatives, carers, society in general. Since health research is a necessary component in helping

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<sup>44</sup> Peter Singer first made a similar argument through the pond case. He claimed that to think about the ethics of what we owe to people in need, we should consider the importance of saving a child who has fallen in a shallow pond and appears to be drowning. To wade in and pull the child out would be easy but it will mean that we get our clothes wet and muddy. Weighting the cost it seems that there is no kind of excuse for not saving the child and that we still ought to do so irrespectively of whether there are other people who would equally be able to rescue the child but are not doing so (Singer 1972).



addressing these needs, supporting and participating in health research becomes a moral obligation. Harris's moral obligation except from participation also involves supporting research financially and politically <sup>45</sup>(Harris 2005).

There is however a moral difference between an obligation to *beneficence* (taking positive actions to do good) in which Rhodes arguments rely and an obligation to *non-maleficence* (avoiding or refraining from actions that cause harm) in Harris argumentation, that Harris seems not to take into account. While the duty not to do harm is a perfect moral duty that cannot be overridden by self-determination, the duty to do good is imperfect, it mainly depends on the duty holder's discretion how to execute it.

According to Harris when it is reasonable to prevent harm and we fail to do so, we should take responsibility for it. Many ethicists in contrast argue that there is moral distinction between actively causing harm and merely allowing harm to occur. In health research, investigators actively expose subjects to risks of harm. When those harms occurred, investigators actively harm the subjects for the social benefit. As research is conducted for and in the name of social benefit, society becomes complicit for these harms. On the other hand, if health research is not conducted, society allows individuals to suffer from diseases that might otherwise be avoided or treated. Although this is a bad situation, for many ethicists is not equally morally wrong. Brassington, for instance, states that failing to prevent harm is not as blameworthy as causing harm directly: "Naturally, from time to time there might be something morally problematic about leaving the world unaltered. But it is not qualitatively the same as positively making a deleterious alteration to the world. One person does not make another worse off simply by not making him better off" (Brassington 2011). For Harris, however, the distinction between actively and passively causing harm is not morally significant. In contrast to Jonas' view, he believes that future patients are actually harmed by society if its members refuse to participate and health research is not supported.

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<sup>45</sup> However, he notes that the duty to participate in research is not a duty to enable industry to profit from moral commitment and that benefits sharing are an essential part of the moral force of the arguments for the obligation to pursue research.

To understand his position is useful to remember that for Harris the interests of the subject should not automatically take precedence over other interests of future patients/ society, as they are both of comparable moral significance. Prioritising the interests of research subjects would imply that some people have a claim to overriding consideration. By relying on the widely accepted view that all people are equally important with respect to each other, Harris states; “being or becoming a research subject is not the sort of thing that could conceivably augment either someone’s moral claims or, for that matter, her rights” (Harris 2005, p. 243).

However Harris’ view (which is also endorsed by advocates of the consequentialist approach) does not take into account the context in which research is carried out. Researchers may only have special moral duties towards the specific individuals, those who participate in research. A special moral obligation towards all people who may be benefiting from a study seems implausible.

Moreover, a claim that human rights of research participants should not have primacy over researchers, that advocates of a duty to participate in research defend, could lead us to dangerous conclusions: the human rights of a research subject could easily be overridden by the interests of society, every time the latter interests can be demonstrated to be greater. Harris (2005) however claims that he does not suggest that the interests of vulnerable individuals who serve as research subjects be contrasted with the interests of an abstract ‘society’, but that comparable rights and interests between two groups of vulnerable individuals should be balanced: both of research participants and of patients who will benefit from research. This argument is also consistent with his attempt to rely a universal duty to participate in research on ‘the rule of rescue’. After all, he notes, “the rights and interests of research subjects are surely not served by privileging them at the expense of the rights and interests of those who will benefit from research”. He finally adds: “both these groups are potentially vulnerable, neither is obviously *prima facie* more vulnerable or deserving of special protection” (Harris 2005, p. 242).

However, even if we consider this statement as correct and accept that we should aim to balance the rights and interests of two potentially vulnerable groups, there are cases in which we still may believe that it is acceptable to give priority to the rights/interests of a particular vulnerable group to ensure that they have equal protection; in this case those who are already burdened because of their health condition and will first be exposed to the risks of an experimental treatment.

Let us now return to the argument of an obligation to participate in research based on our moral duty of beneficence. A moral duty to participate in research based on *beneficence* (or *non-maleficence* according to Harris) is not clear. There are different ways by which this argument can be understood. It could be interpreted as a duty to prevent *all* serious harms or a duty to *always* help others in need, whenever is reasonably to do so. However, since there are many different forms of serious harms not related to disease (for instance political prosecution) that we could reasonably prevent, a duty to help others in need can be fulfilled without necessarily taking part in research. A strong argument of *beneficence* then fails to show that we all have a specific moral duty to participate in research. Moreover, this argument fails to show why there is a specific duty to encourage and support research by our participation and not by other beneficent acts, for instance by financial support.

Yet, the main problem with a strong argument for a duty of beneficence is that it is over demanding. It demands that one should devote most of their time and resources to preventing any number of serious harms than engaging in any other less important projects (one's personal commitments or projects in life), as there are numerous occasions in which one can minimise harm or bad states of affairs. This principle destroys one's personal integrity and it turns a person to "a channel between the input of everyone's projects, including his own, and an output of optimific decision" (Smart and Williams 1990, p. 116). Trying to justify an obligation to participate in research based on the duty to beneficence conceived in its strong form, not only implies that individuals are morally obliged to serve as research subjects but also that they should perform many actions that are normally considered supererogatory.

However, a weaker formulation of the principle of beneficence is also possible. As Shapshay and Pimple (2007) note, Harris by adding in his argument the sentence “If we can reasonably do so” may support a less demanding moral duty: i.e. “to prevent some subset of serious harm of our own choice when we reasonably can” (Shapshay and Pimple 2007, p. 416). Yet, a weaker argument of a duty to participate in research also faces the same problem; it fails to establish a duty to participate in research *per se*, since there are different possible harms we can try to prevent and needs we can aim to address.

Finally, if we are to accept a duty to help others in need, as the ‘rule of rescue’ commands, participation in research should not be our priority. Minimising the most serious harm would suggest trying to address other harms that people face today not due to disease but due to preventable poverty: “Poverty is far and away the most important factor in explaining health deficits. Because they are poor, 815 million persons are malnourished, 1.1 billion lack access to safe water, 2.4 billion lack access to basic sanitation, more than 880 million lack access to health services, and approximately 1 billion have no adequate shelter” (United Nations Development Report of 2002) As Thomas Pogge (2002) argues, citizens of industrialised nations are materially implicated in the poverty related harms due to lending and trade practices that exploit for poorer nations. It seems then more reasonable and morally superior to argue for a duty to change unjust institutions than participating in research (Shapshay and Pimple 2007)<sup>46</sup>.

On top of these problems, I consider an attempt to support a duty to participate in research based on the ‘rule of rescue’ unsuccessful. The ‘rule of rescue’ describes the imperative people feel to rescue identifiable individuals facing avoidable death (McKie and Richardson 2003). In health research however, individuals are asked to bear the risks to benefit unidentified others (future patients). Harris by embedding the duty of beneficence to the ‘rule of rescue’ argues that, in contrast

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<sup>46</sup> Although the duty of beneficence is independent of how the harms are caused, the aim of this argument is to point out that because poverty is the most important determinant of ill health, the most significant harms facing people in the world today are not those that must be addressed through biomedical research. A duty to address harms due to preventable poverty is morally superior to a duty to address harms due to disease.

to the common attitude, research should not be considered as beneficial for unidentified others; Research gives us all hope for the future and security, not only for ourselves but also for those whom we care about and our decedents. For this reason, he argues, it is perverse to believe that research should be of benefit to the research participant to be morally justified (Harris 2005). He concludes that we all have a strong general interest that there will be research irrespectively of whether such research is related to our health condition and this interest obliges us to offer ourselves as research subjects. Therefore, by adopting a wide interpretation on what is in the interests of a research participant (in contrast to Jonas' narrow interpretation) Harris attempts to offer a stronger motive to convince people to participate in research<sup>47</sup>.

A broad interpretation of what is in the interests of a research subject, as already discussed, suggests that a study is compatible with the interests of participants if they can adopt the research aims as their own. The same may be true for other domains in life as well. One's decision to combat poverty, for instance, suggests that they adopt the aims of the organisation in which they are involved, as their own. By applying the 'rule of rescue' in such cases, we could argue that people may decide to help those in need (e.g. people struggling with poverty) even if themselves or their relatives are not in the same situation or do not believe that it is likely that they will ever be<sup>48</sup>. In contrast, in the case of health research, a broad interpretation of what is in one's interest cannot be compatible with the 'rule of rescue'. By applying the 'rule of rescue' in medical research, we are obliged to 'rescue' only those who suffer with the same disease or condition with us, as (with the exception of Phase 1 trials) an individual is eligible to take part in a medical study if they have the illness or condition that will be studied. It follows then that Harris' argument would have been more consistent with the 'rule of

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<sup>47</sup> As I discussed earlier Rhodes also makes a similar argument to encourage recruiting even among vulnerable groups.

<sup>48</sup> There are of course many other factors that could make the 'rule of rescue' even more complicated and more difficult to be used as a moral basis for a duty to participate in research; for instance there is no consensus on whether we have a moral obligation to help those near to us or all people irrespectively of national borders, whether we should aim to prevent likely harms and others.

rescue' had he based a positive duty to participate in research on a narrow interpretation of what is in a research subject's interest (or had he restricted the argument to Phase 1 trials). However, although a narrow interpretation would have been more consistent with the 'rule of rescue', it would also have led to the same problem with Jonas' position; such argument would not justify a great amount of valuable research and thus would make a universal moral duty to participate in research much weaker. Moreover, there are additional reasons for which a duty to participate in research could not be justified by the rule of rescue. Given the length of time that will typically be needed from participation in a research project to accessing the benefits from the knowledge generated from the study, as well as the significant degree of uncertainty involved, it seems difficult to argue that participation in health research could plausibly be considered as a case of rescue.

It should be noted however, that Harris' view offers a more collective approach to research ethics. Harris notes that we all have a strong general interest that well-founded research is conducted. A society that supports and actively accepts the outcomes of health related research benefits both patients and research subjects. Everyone who lives in a society where research is given a high priority also benefits from the knowledge acquired by research. As we are all vulnerable to diseases and conditions that could harm our health, it is in everyone's interest to support the conduct of research even if we are currently healthy. Although this view may not be appealing for most medical research studies to which Harris' arguments refer, especially when participants are asked to bear significant risks for the benefit of potential patients, in low risk health studies where whole communities (e.g. villages) are targeted and in which notions of solidarity are considered important, a broad interpretation of what is in a participant's interests could be more compatible with a duty to benefit others, based on Harris' argumentation.<sup>49</sup>

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<sup>49</sup> I discuss this in more detail in Chapter 8.

#### 4.5.4 | The argument of justice

It has been argued so far that the argument of beneficence (or non-maleficence) fails to provide a satisfactory justification for an obligation to participate in research *per se*. Let us now explore the argument of justice in defence of a duty to participate in research.

Advocates of a duty to participate in health research argue that this duty derives from an appeal to be *fair*. As they state we all benefit from health research. In particular the fact that most of us are alive today is due to the invention of antibiotics, the defeat or control of infant mortality, and vaccination (Caplan 1984). Moreover, many of us will continue to benefit from findings of medical and health advances such as genetic research or public health research i.e. clean water, sanitation and the knowledge of connections between exercise, diet and certain diseases and conditions that help us to prevent and calculate personal risk (Harris 2005). People gain the benefits of health research not only passively but also actively. Actively by (voluntary) having access to better and safer treatments, and passively by living in herd immunity due to vaccination. A person who accepts all the benefits enabled by health research and at the same time refuses to participate in a health study free rides on the people who pay their equal share (those who bear the burdens of research) by participating. From the moment we accept these benefits it is only fair that we contribute to the practice that enables them.

Harris claims that his argument of fairness relies on the ‘principle of fairness’ developed by Herbert Hart and John Rawls, which can be interpreted as follows: “those who have submitted to restrictions have a right to similar acquiescence on the part of those who have benefited from their submission” (Harris 2005, p. 243). Harris argues that our duty not to be a free rider could justify an enforceable obligation to participate in research, at least in certain cases. However, he states that compulsion should not be our first option to improve recruitment (Harris 2005), probably because this would discourage public support or altruistic behaviour.

A parallel, however, between the classic free rider case and an individual who does not contribute to research while accepting its benefits is not successful. In the free-rider case one is free to accept or decline the benefit, while the same cannot be true for research benefits. In modern industrialised societies, the benefits of biomedical research are ubiquitous and thus the only way to abstain their enjoyment would be

to move to other societies, which have never benefited by health research (and the question remains whether it is possible for an individual to move there). This suggests that it is not reasonable to claim that an individual that hasn't freely chosen to receive research benefits should support the institutions that enable those benefits. Advocates of a duty to participate in research then need to explain why individuals are obliged to help others only by the mere fact that they enjoy the benefits of the social system under which they live, without their knowledge or willingness or some prospective agreement. The justification of research on contractualist grounds is even more difficult if we consider pediatric research. Children are unknowingly, and often against their will, the beneficiaries of previous research and this means that they have not accepted the benefits of the social system under which they live (Gauthier 1990).

Harris believes that the fact that people cannot opt out of health benefits when they were not able for autonomous decision-making does not entail that they are not obliged to contribute. Few people would be willing to refuse the benefits of future advances (despite the fact that others have to bear the burdens so these benefits can be available) especially when they are in need (Harris 2005).

Yet, there is another reason the application of the free-riding argument seems problematic in the case of health research. As Jonas argues, this argument implicitly claims that by doing our fair share we alleviate others from the burdens of their contribution. Thus, individuals by participating in a research study, relieve current research participants from research burdens (Heyd 2003). However, an individual's participation in health research not only does not pay back any actual research participants for their contribution but also benefits someone who will not participate. More participation benefits future patients and society at large but does not pay back current participants. To support a moral duty to participate in



research based on fairness, we need an argument that would indicate that an individual's participation contributes to the aims of research: the production of generalised knowledge, not the alleviation of others' burden or risks from participation (Schaefer et al. 2009).

It is difficult to defend the view that those who benefit from research and refuse to participate in health studies act as free riders. Since people pay for the benefits they receive from scientific research through taxes and insurance it seems that even if they were free riders, free riding is not morally worrisome. As Brassington argues "people who do not support research, irrespective of whether or not they are free-riders, do not make the world a worse place" (Brassington 2011, p. 24). Based on M.B.E. Smith's words: "the obligation of fair play governs a man's actions only when some benefit or harm turns on whether he obeys" (Edmundson 1999, p. 81), we could argue that the principle of fair play would generate a universal obligation to participate in research, only if the research enterprise were small enough that any individual's failure to support it would reasonably be expected to damage the enterprise. However, health studies are not small enterprises and we can certainly consider cases in which one's refusal to serve as a research subject neither deprives anyone of any benefits, nor harms society in any noticeable way. It follows, then, that the principle of fairness cannot ground a positive moral duty to participate in research and that in the absence of a pre-existing agreement one cannot claim that another person's lack of action has made them worse off (Forsberg J, et al 2013).<sup>50</sup>

#### **4.5.5 | Participation in research as imperfect moral obligation**

Advocates of a positive duty to participate in research argue that research participation is a *prima facie* duty. Similarly to other moral obligations (e.g. our duties to our friends or ourselves), it can be overridden by other moral considerations in a given situation; for instance, if my participation in a particular study would be excessively burdensome for me but not for other potential

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<sup>50</sup> Although an individual, who refuses to participate in a study, cannot be considered as blameworthy for making the world a worse place, if not enough people sign up, a study cannot go ahead and thus further improvements in health (such as new treatments) will not be possible. I discuss this problem in the following paragraphs.

participants or if I have fulfilled my duty by participating in other burdensome studies and there are other individuals who haven't participated and could participate. In all these cases, although the duty to participate in research exists, it can be overridden by other moral considerations (Harris 2005; Rhodes 2008). Although this argument is plausible (no one would argue that a duty to participate in research is an absolute duty), the advocates of this view have not succeeded in showing that there is a moral duty *per se* to participate in research (except perhaps from emergency situations). From the above arguments it only follows that health research is a moral good among other moral goods.

Shapshay and Pimple (2007) argue that advocates of a duty to participate in research set up a false dilemma: either participation in research is supererogatory or it is a perfect moral obligation. They argue that there is a third possibility: participation in research is an imperfect moral obligation "we must make other's happiness our end and act in good faith to help some others some of the time, but we may justifiably use our own discretion as to whom, how and how much to help. Thus participation in research is not morally obligatory, neither supererogatory; it is one way in which people may choose to discharge their imperfect obligation to help others". Principles of beneficence and fairness can only rely on an imperfect duty to participate in research and thus an imperfect obligation to help those in need and reciprocate for other people's sacrifices.

Although an imperfect duty to participate in research is more convincing than a perfect duty, it does not provide any answers on how we should proceed when people decide to discharge their duties by helping others in ways that neglect research. As discussed earlier, the existence of fatal and painful conditions suggests that certain types of research are essential. In order for health research to take part other contributions in addition to funding are also necessary, such as being a participant or donating samples (Chan and Harris 2009).<sup>51</sup> Moreover, it has been argued that the idea that individuals have a right to decide how they want to contribute to research may be problematic for methodological reasons. When

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<sup>51</sup> More reasons for which the conduct of (certain) health research should not rely only on the preference of individuals are discussed in Chapter 6.

research participation relies only on the preference of each individual it imposes a risk of bias that threatens the validity of the results (because individuals who agree to participate may differ from those who do not) (Forsberg et al. 2011)<sup>52</sup>. There are therefore pragmatic reasons (i.e. low recruitment rates) as well as moral reasons (to relieve people from fatal and painful diseases or conditions that significantly affect their wellbeing) for which an alternative approach to the one existed in current research ethics regulations should be put forward for the moral justification of valuable health research in which individual consent is not possible.

#### **4.6 | The argument against ‘research exceptionalism’**

In contrast to the approaches discussed so far, opponents of the traditional view of research ethics (Sachs 2010, Stewart et al. 2008, and Sullivan 2008) argue that we do not need a special moral justification for the conduct of health research. According to this view, health research is not a unique human activity that imposes risks to some individuals for the benefit of others. Most activities in our daily life expose others to harm. For instance, when we use our cars to commute to work we expose our neighbours to risk of pollution for our own benefit. Factories expose their workers to harm to benefit their customers. Ambulances expose pedestrians to risks for the benefit of the patients they carry. Charities expose volunteers to risks for the benefit of their recipients. In all these cases, some people are harmed for the benefit of others, however, for none of them we consider the activities involved as inherently wrong. For this reason, advocates of ‘research exceptionalism’ argue that health research should be considered and treated similarly to other activities in our daily life.

Following this view, a further argument for the justification of cluster research, in which consent is not feasible, can be made; in all examples mentioned above individuals are not able to consent, despite the fact that their lives are affected. Moreover, in most cases individuals are unaware of the dangers involved that may

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<sup>52</sup> In this case however it can be argued that different recruitment methods could be used to increase recruitment that do not necessarily rely on a moral duty to participate in research (Lignou and Edwards 2012).

significantly affect their lives<sup>53</sup>. Yet, in none of these activities we argue that people are used as ‘guinea pigs’ or that there should be a requirement for written informed consent of all those affected based on adequate description of the risks involved, the purpose of the activity, potential benefits, duration of the activity and others.

Advocates of the traditional view of research ethics would strongly object to this claim. In their view, there are significant differences between research activity and other activities in our daily life that justify the extensive regulations and guidelines standardly applied to medical research. First of all, the fact that many of the risks people face in daily life are involuntary or unconscious (for instance when pedestrians cross the street while an ambulance is coming) suggests that they cannot provide a moral justification of intentionally exposing individuals to the same level of risks for others’ benefit. Moreover, even activities, which are consciously and voluntarily accepted by most people (e.g. sport activities) cannot provide a moral justification to exposing other people to same risks or same level of risks for a research activity. People usually decide to be engaged in sports or actions in which there is high probability of risk involved because of the potential personal benefit they anticipate from them; for instance many people choose to spend their vacations on road trips because they assume that the benefits justify the risks. In contrast, health research is designed to primarily benefit others and often involves processes that are not as pleasant as sport activities or travelling.

Furthermore there are other important differences between research activity and activities in daily life, which suggest that distinctive moral principles should apply for research. We often decide to ignore risks of daily life based on the assumption that they are so low that it cost us more to being aware of them, for instance when we drive to work (Wendler 2012). In other cases, when we ignore risks of daily life, we are not relying on a (fully) rational process. We often neglect risks that are familiar or based on our perceived level of control (Tversky, Kahneman 1974; Tversky, Kahneman 1981; Slovic 1987; Weinstein 1989). Finally, another reason

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<sup>53</sup> The fact however that cluster members are not able to consent does not necessarily mean that they are uninformed about the risks involved.

that we tend to ignore the risks involved in our daily activities is that they are often more than we can consider or process readily in the time we are engaged in them; for instance, we do not consider all the risks involved when we cross a street unless there is a reason for special concern (when we hear a siren) (Wendler 2012) Thus, although many of our activities in daily life appear to be voluntary choices, they are actually an expression of rather unreflective habitual behavior (Slovic 1987).

It seems then that the main reason that we do not calculate the risks or ask for specific consent from the individuals affected by our actions, even when serious risks are involved, is that it gives us the ability to achieve our daily tasks. This is the main reason why research activity normatively differs from daily life activities. Besides, there has been little philosophical analysis of the conditions under which it is acceptable to impose risks on people in the way we do (Hayenhjelm and Wolff 2012) and thus types or levels of risk in which people are exposed to in daily life cannot serve as moral guidance to assess health research.

Advocates of ‘research exceptionalism’ however have also used examples of intentional and controlled activities in daily life, which involve exposing some individuals to risks for the benefits of others. A typical example is the one of factory workers. It is generally acceptable to expose factory workers to risks for the benefit of others if they agree to work in the factory and if they are paid a fair wage for their work. Likewise, one could argue that it is acceptable to expose subjects to risks of research for the benefit of others provided that they consent and are paid a fair wage for their contribution (or receive health benefits depending on the type of study) (Wertheimer 2011).

Although research activity normatively differs from daily life activities, comparing health research with activities in daily life, which involve intentionally exposing some to risks for the benefit of others, gives us a solution that is less restrictive from current regulations and which encourages scientists’ efforts to improve the lives of future patients even when consent is not possible. Moreover, in contrast to current regulations and guidelines, according to this approach the liberty of potential research subjects who are willing to participate in risky

research activities should be respected<sup>54</sup>. Moreover, this approach is less permissive than the Libertarian analysis in that it presupposes as a necessary condition that research subjects are treated fairly and are by no means exploited by their participation, even if they consent to be treated in a different way.

Yet, there is another important challenge that this approach to research ethics needs to address. Proponents of the traditional view of research ethics believe that many of the existing regulations are too restrictive and unjustified yet they haven't been able to provide a set of positive recommendations or regulations for medical research that follows from their perspective. Let's consider again the example of factory workers; how can we find good comparisons which provide a useful lens for considering the ethics of cluster research, since, there is not general consensus on the regulations that should apply to industry (there is no consensus on whether a minimum wage laws should be endorsed, whether governments should set safety standards, whether workers should be able to unionize or whether there should be rules protecting workers against discrimination) (Wendler 2012).

Considering health research as similar to other activities in daily life does not provide us with a satisfactory account of the conditions under which it is morally acceptable to expose some individuals to risk of harm for the potential benefit of others and as a result cannot provide any answers concerning the conduct of cluster trials when it is not feasible to seek consent from cluster members.

## 4.7 | Conclusion

In conclusion, the aim of this chapter was to present and discuss different approaches to the moral justification of health research in order to examine which of them could be used as a default justification for the conduct of cluster research particularly in cases where informed consent is not feasible. From the different approaches presented, two main directions can be identified. First, the attempt to stress the importance of scientific progress by claiming that society can be

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<sup>54</sup>In contrast, current guidelines demand that risks should be minimised and an independent ethics committee should approve the study.

justified in recruiting individuals without their consent in health research: a) because all people have a moral duty to participate in research to pay the debt they owe to previous research subjects or the society they live in (Harris, Caplan, Rhodes) b) because all individuals have a social obligation to advance the community interest (assuming that the proposed research has community value) (communitarian approach), c) because by research participation suffering from diseases or painful conditions is reduced and general health benefit is maximised (utilitarian approach). On the other hand, other approaches attempt to justify the use of individuals as research subjects by giving main priority to the protection of their autonomy either by a) stressing the importance of individual rights and informed consent (libertarian approach) or b) by prioritising their interests and minimising the risks in which they are exposed to (precautionary approach).

The main problem we face in formulating an ethical approach for cluster research (in which individual consent is not feasible) is the difficulties associated with the ethics of health research generally: i.e. finding a way to protect research subjects from exploitation without restricting the progress of scientific research. A society, which follows the libertarian or precautionary approach, would have no or few cluster studies, while a society, which uses appeal to social or moral duty or encourages its members to act to maximise the general benefit must ensure that by supporting a great deal of cluster research does not exploit its members or misplace public trust.

In Chapter 6, I argue that although none of these approaches found in research ethics debates can be used as a default theory for the moral justification of health research in general, and cluster research in particular, an alternative approach could offer a better understanding on how this balance could be achieved in the case of cluster research where consent is not possible.

# Chapter 5

## **The Ethics of health research in developing countries: Arguing for an alternative approach in research ethics based on the human right to health**

In the previous chapter, I discussed different approaches to the justification of health research and, argued that none of these views could provide an adequate justification for the conduct of cluster randomised trials in developing countries when consent from participants is not possible. I concluded that some of these approaches rely on overprotecting rules<sup>55</sup> that exclude valuable health research (e.g. precautionary approach) and thus fail to offer a satisfactory response on what kind of research should be pursued, while others do not provide clear guidance on how to ensure that participants are not exploited for the general benefit (e.g. utilitarian approach). In this chapter, I argue that a more successful approach for the moral justification of health research must conceive health studies, and in particular collaborative studies in developing countries, not as isolated activities but within the broader social context in which they take place. I discuss the human right to health, a principle of the widely respected law and conventions, and claim that this principle can be adopted as a pragmatic tool, which captures many of the strengths of the philosophical theories critiqued in the previous chapter, while

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<sup>55</sup> In RCTs lack of informed consent when participants are competent adults is only acceptable in emergency situations and when comparing the efficiency of two widely used therapies.



avoiding some of their most important weaknesses. I go on to argue that the human right to health can provide the moral basis for a more robust interpretation of the principles in research ethics. I then discuss the application of this framework in relation to three important moral issues in collaborative health research in developing settings (the selection of potential participants, the social value of research and post trial access). I conclude that a moral framework based on the human right to health can provide better safeguards for the protection of participants in health research and at the same time support and encourage socially valuable research by taking into account a variety of health related studies that have not been given much attention in existing guidelines. The suggested framework will guide the discussion in Chapter 8 on how difficulties related to the inability to obtain consent from the participants in cluster trials in collaborative health research should be addressed and thus will constitute the moral basis for identifying and addressing ethical issues in cluster randomised trials in low-income settings.

## **5.1 | Social value of research and the duty of justice**

In chapter 4, I argued that certain health studies, because of their great social value (those that have the potential to significantly improve the wellbeing of people by alleviating pain and suffering or by discovering therapies for fatal and serious conditions), should not be considered as morally and socially indifferent matters<sup>56</sup>. I then discussed the view of a universal moral duty to participate in research and concluded that the advocates of this view do not successfully prove that such a perfect moral duty exists. In this chapter, I focus on the conduct of health research in developing countries. In the following paragraphs I discuss the reasons for which health research in developing settings is important and argue that there are even stronger reasons to claim that health advances, and thus health research in developing settings, should not be neglected. However, I note that a moral duty to support and encourage collaborative health research based on a universal moral duty to participate in research remains problematic especially if we considered the context in which collaborative health research takes place. I

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<sup>56</sup> See my arguments against Jonas's view.

conclude that these difficulties lead us to accept an alternative way of arguing for a moral obligation to support and promote valuable health research in this context.

As previously discussed, advocates of a universal moral duty to participate in research derive their arguments from a more basic (and generally accepted) obligation to prevent harm to others; as they note, medical research treatments (e.g. antibiotics) have prevented or treated serious harms and many people today would have been much sicker, or dead, if health-related research involving human subjects had not taken place in the past. People who discourage the conduct of research by refusing to participate, without having a legitimate excuse for non-participation, fail to prevent others from future harms, and thus are morally blameworthy. This argument is complemented by the free rider argument, according to which because all of us have accepted benefits from health-related research in one way or another, to which others have contributed through their participation, we all have a moral obligation to act in the same way (take part in health research). Individuals who enjoy the benefits of research without bearing the burdens of participation (if they do not have a legitimate excuse) are blameworthy. In the previous chapter, I discussed several conceptual reasons for which the above arguments are not convincing. In this chapter I consider further moral reasons for rejecting this view based on the broader context in which health research takes place.

The main difficulty with accepting a universal moral obligation to participate in research is that it rests on the assumption that health research is a reasonably just, mutually beneficial, cooperative practice. Harris in particular states that his arguments rely on Hart's 'principle of fairness', according to which "when a number of persons conduct any joint enterprise according to rules and thus restrict their liberty, those who have submitted to these restrictions when required have a right to a similar submission from those who have benefited by their submission" (1955, p. 185). This view assumes a situation where each of us can reasonably regard the health research enterprise as a cooperative enterprise, which we have an obligation to maintain by serving as research subjects (for cooperation is what makes it possible for any individual to enjoy the benefits of the practice). Yet, as de Melo-Martin (2008) observes, in real life health research is far from a just

mutually beneficial cooperative enterprise. In practice, those who often bear the greatest burden of research are not the same class of individuals who will benefit from such research. In contrast to what is assumed in the above arguments, de Melo-Martin points out that the current research enterprise often disadvantages certain groups, who are ‘drafted’ to carry the disproportionate research burden<sup>57</sup>.

Members of less privileged groups have also expressed concerns that there is disproportionate allocation of burden and benefit in health research. According to the Institute of Medicine (2003) many in low socioeconomic backgrounds, particularly those in marginalized ethnic groups, believe that marginalized groups are pursued to participate in research that privileged populations would and could avoid and suspect that researchers are using them as “guinea pigs” for their own agendas and others’ benefits (Ho 2008). These problems, which are clearly relevant in the context of a duty to participate in research, are even more significant when considerable costs or risks are involved<sup>58</sup>.

Harris has relied a universal moral duty to participate in research on the rule of rescue. However, as I previously discussed, a moral duty to participate in medical research based on the rule of rescue cannot apply to all<sup>59</sup>, as Harris claims, but only to individuals who are in a similar situation as those in need of rescue<sup>60</sup>. In the previous chapter I argued that Harris’ argument could only account to a limited duty to participate in health research and that it is not compatible with a general duty he wants to defend. Taking into account the empirical facts about the way in which health research is conducted in practice, it follows that a universal moral obligation to participate in research cannot justify the conduct of research studies, which outcomes are unrelated to the health needs of research participants

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<sup>57</sup> De Melo Martin’s distinction is based on the social/ economical differences between the people who participate in research and those who do not participate in research and not between research subjects and future patients.

<sup>58</sup> Harris (2005) has claimed that although a moral duty to participate in high risk trials exists, it should not be enforced as this would result in some people disproportionately carrying out the burdens of research.

<sup>59</sup> Even in Phase I trials participants must fulfill certain entry/ eligibility criteria (e.g. age, general health status, medical conditions and others).

<sup>60</sup> Similarly to cases where mountain climbers commonly assist each other.

and where participants' ability to benefit from the research outcomes is not taken into account. Consequently, Harris' approach would also fail to protect and prevent vulnerable groups from being used for the benefit of the most privileged ones.

It is evident that restricted access to research benefits should impact on the moral status of participation generally. As Schaefer et al. (2009) argue there is no prima facie duty to participate in research if inequities prevent an individual from receiving the research outcomes. However, it could be argued that even when individuals have equal access to state-provided health care (for instance within a society such as the U.K.,) a universal obligation to serve as a research subject remains problematic. Prospective research participants remain largely outside of the scientific enterprise, the function and operation of which are relatively nontransparent and unchallenged (Ho 2008). Research participants have minimal knowledge of or impact on how research priorities are set, who determines the scientific agenda, how research protocols and data are assessed by various scientific and ethical regulatory frameworks, and where and how data will be disseminated or used. As De Melo-Martin points out, research priorities are often determined by funding sources and other considerations such as "minimization of economic risks and maximization of profits" (De Melo-Martin 2008). Moreover, researchers are often accused that scientific and ethical flaws of various research programs are not published and until horrendous events occur, such as the deaths of participants, they are left unnoticed.

In sum, considering the injustices in the broader social context within which research is conducted (unequal access to research outcomes) and the fact that health research often mainly serves the interests of the research industry and thus does not automatically take into account important health needs and priorities, it seems that to demand of individuals that they participate in research could be problematic and unfair. This leads us to the conclusion that in order for a moral duty to participate in research to be valid, other conditions than those in which health research is currently conducted must apply.

These problems are even more prevalent in collaborative health research. In developing countries (in which 80% of the world's population lives) the imbalance between the need for preventive and treatment measures of disease and the ability to meet these needs is widely acknowledged. Millions of people suffer and die from conditions for which effective treatments and preventive methods have existed for decades in developed countries because of their prohibitive cost (Varmus and Satcher 1997). Moreover, health related research aiming at the discovery of more affordable and efficient treatments is severely constrained by limited financial and human resources, and by the lack of appropriate infrastructure to deliver healthcare. An additional problem that developing countries have to face is the considerable gap between their particular health needs and the globally set research priorities. As the majority of research projects aim at addressing conditions and needs of the minority of the world's population (Benatar 2005) a universal obligation to research participation would lead to the disempowerment of most vulnerable populations. An argument for instance that a housewife in rural India has a moral obligation to participate in an externally funded study, which potential benefits cannot be enjoyed by her community<sup>61</sup> or which aims are not related with her population health needs, seems difficult to defend even if no considerable risks are involved<sup>62</sup>.

Considering that research takes place in contexts of huge inequalities between research institutions or pharmaceutical companies and host communities, and taking into account the urgent need of host communities for affordable and efficient treatments and the advantaged position of their sponsors (i.e. patents, drug development and profits), an argument for a universal moral obligation to support and encourage health research would be more persuasive if participants

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<sup>61</sup> For a more detailed discussion on the notion of community in health research see the Appendix.

<sup>62</sup> In contrast to the views of Harris, Rhodes, Heyd, Caplan and others, I argue that a universal moral duty to participate in research is problematic even in low risk studies if the research aims are irrelevant to the needs of participants and their communities; in such cases research subjects cannot adopt the aims of the study as their own. My view, however, differs from Jona's view, as it does not consider non-beneficial studies as morally problematic (I discuss this view in more detail in section 5.5: *The principle of beneficence and the social value of research*).

and their communities could get a direct benefit from such studies (Schaefer et al. 2009) or if there were a fair exchange of some valued benefits between researchers, participants and communities (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries). However, what should be considered as a fair benefit in collaborative health research is more an issue of dispute, mainly because of several difficulties that do not permit the wider community to get direct access to research outcomes. As it is more likely that those who would ultimately benefit from the conduct of a research in a developing setting are not those in need but the already better off, (i.e. researchers in terms of reputation, pharmaceutical companies in terms of financial profit) before arguing for a change to the status of research participation from optional to obligatory in order to encourage the conduct of valuable health studies, we should first consider in whose interest this change will be. Taking into account the factors discussed above, it seems that a society, in which everyone would be morally obliged to serve as research subject (irrespective of the conditions in which they live, their health status, their ability to access the results of the studies), would be an unfair society which not only fails to distinguish between valuable and less socially important research (the gap between needs and global research priorities shows that other factors than health needs (i.e. profits) are considered more important) but which would also be unable to provide better protection for participants, especially those that are more in need for protection.

## **5.2 | The human right to health and the duty of justice**

The need to reduce poor health and suffering by finding effective and affordable means, especially in disadvantaged populations, is too critical to be neglected. The importance of valuable health research being conducted leads us to accept that there is a moral obligation to support (certain) health studies in developing countries. However, following the discussion above, it is evident that this duty should not fall on individuals. In this section I argue that a moral obligation to support valuable health research should primarily fall on governments, based on the view that states have a duty to look after the important needs of their people individually and collectively (WHO 2000). I outline an alternative research ethics framework within which, in my view, the moral justification of health research

could be better explained (compared to the approaches discussed in Chapter 4) and issues raised in collaborative health research in developing countries could better be understood and addressed (Benatar et al. 2003). To discuss such issues, I will employ Farmer's thesis on human rights (Farmer and Campos 2004). In particular, I will advocate a human right to health based on the application of the principles of social justice and equity. This moral framework grounded in existing widely respected practice, would specify the aim of health research and its social value and would demonstrate the way by which inequalities in global health should be considered and addressed (Benatar et al. 2003).

Recent studies have shown that the health of populations depends on and is affected by a combination of different factors: political, social, and economic. Poor social conditions and poverty make people living in the developing world more susceptible to a wide range of illnesses and to other health problems in the form of a wide spread of endemic diseases, poor quality of life and high rates of premature death. This is the reason that global health inequalities are so significant; for instance, life expectancy at birth ranges from 34 years in Sierra Leone to 81 years in Japan (World Health Statistics 2011). In Chad, 1 in 5 children dies before they reach the age of 5, while in the European Region, the under-five mortality rate is 13 out of 1000 (World Health Statistics 2011). These alarming differences in health and life opportunity are not based on biological or genetic reasons (WHO 2015)<sup>63</sup>. Major health inequalities are not only evident between countries but also between the most and least advantaged populations in the same country (World Health Statistics 2011). Under these circumstances even the most basic universal human rights cannot be achieved for all.

Human rights are a well-entrenched set of internationally recognised standards. They mark the threshold at which each individual human beings' interests

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<sup>63</sup> There are different interpretations for the pattern of global inequality, and this discussion is beyond the aims of this thesis. My main focus here is not to discuss different interpretations concerning the existence of injustice on a global scale, but its implications for those who are in the position to improve those disparities, thus those within the developing countries, including governments, research councils and those outside of developing countries, foreign governments, private companies and researchers.

generate duties or obligations on the part of others to respect, protect and promote those interests in various ways. In Article 12 of the International Covenant on Economic, Social and Cultural Rights a fundamental right to health is codified: “The States parties to the present Covenant recognise the right of everyone to the enjoyment of the highest attainable standard of physical and mental health”. The immediate consequence of claiming a human right to health, is that all humans, irrespectively of the conditions under which they live and the location of their residence, deserve it and have an equal claim to it. The human right to health serves not only our interest in health, but also various other interests which being in a certain state of health enable us to realize, such as autonomy and accomplishment.

According to institutional law, the duty to meet such rights burdens the particular government (first order duty) (Wolff 2011). The duty of the government to meet its citizens’ human right to health ranges over obligations concerned with the provision of health care services and through public health measures and with the securing of certain social determinants of health. However, occasional failures to meet the human right to health in developing settings are apparent. Due to the dramatic shortage of resources and an accompanying lack of social, economic and political structures, the aim to protect the health of the populations is often not materialised (Benatar and Singer 2010). In these cases it is evident that governments fail to sustain the rights of their subjects (Wolff 2011) by failing to ensure the social conditions needed so that a sufficient level of health can be achieved. Since the human right to health is a basic human right, its claims are not restricted to national borders; inequalities in child survival, life expectancy, health and others between rich and poor communities are considered a profound injustice that global community has the duty to redress. Thus, when a state fails to secure the rights of its subjects, the international community has a second-order duty to help the national government to fulfil this duty. By inference, developed countries have a duty of justice to support the improvement of health in countries that require assistance towards meeting these ends.

A second-order duty may be attended by providing financial help or technical assistance to a developing country whenever it is necessary and desirable (Wolff



2011). Since the aim of health research is to sustain and improve health, collaborative health research can partially pursue this second-order duty tailored to address particular needs of the local population by taking into account their special living conditions and behavioural patterns and on discovering more effective ways of delivering new or existing interventions. Considering then the inherent limitations of endogenously generated investment and in autonomous conduct of research, and the fact that developed countries have the greatest capacity to effect change because of their privileged position, the role of transnational health research that would address context-specific health problems becomes evident.

### **5.2.1 | The social value of non-clinical health research**

Different types of health related research might take place in developing countries. These include basic research, which is often dependent on the use of samples from patients (usually laboratory-based and includes studies at the cellular level, and of immunity and pathogenesis); Clinical research, which is often conducted with patients in a medical setting, such as a hospital, and is designed to obtain better information on the natural history or pathogenesis of a condition that may lead to improved strategies for diagnosis, treatment or prevention of a disease; Epidemiological research (usually involves population-based investigations, which may be cross-sectional surveys of selected populations (case-control studies) or all members of a community, or longitudinal studies of a population over time (cohort studies)<sup>64</sup>; Social and behavioural research which is often a component of epidemiological research and focuses on the study of behavioural and social factors that may modify risk of disease in individuals or in populations<sup>65</sup>; Intervention studies, including clinical trials and community-based trials, which are conducted to evaluate the impact of specific

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<sup>64</sup> Often such investigations involve the study of large populations and they may be observational or interventional in nature. The aim is to identify strategies for the better prevention or treatment of disease, through an improved understanding of risk factors for disease or for progression of disease.

<sup>65</sup> Such research may involve the collection of sensitive information about a person and their lifestyle (e.g. sexual behaviour). While some forms of research may only involve observation others may involve studying or testing ways of changing behaviour or social circumstances.

interventions on the prevention of disease, often in the context of community-based intervention trials, or in modifying the clinical course of disease, often in the context of clinical trials<sup>66</sup>; and health services and operational research, which are concerned with the study of methods of delivery of healthcare, access to treatment and quality of care, with the aim of finding improved methods that lead to better care<sup>67</sup>(Nuffield Council on Bioethics 2005).

As mentioned earlier the health status of individuals and populations is dependent of many factors. Thus although the majority of people living in developing countries lack access to medical care, their health status is not only dependent on the quality of healthcare available but has many other determinants. There is a range of health studies that may benefit developing countries; from research into genetic determinants of disease at one end to practical methods of implementing effective treatments at the other. In such studies, different types of interventions may be involved (clinical trials, experimental medicine and population research), which may apply to patients, healthy individuals or a group population more widely (Nuffield Council on Bioethics 2005). Although studies in developing countries focusing on new or improved medicines and vaccines are given high priority, in many circumstances research on finding better ways of delivering existing products and services to those in need, or investigating the causes of diseases and possible treatments, are often equally or more important (Prince 2000). Non-clinical research, such as the provision of better nutrition, improved sanitation, clean water and personal preventive measures may have a significant impact on diseases (for instance, to control HIV infection not only research on treatments and potential vaccines is needed, but also studies of individual behaviour).

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<sup>66</sup> Such research may provide the basis for policy decisions and priority setting. Intervention studies usually involve the comparison of different treatment or prevention strategies in which the current intervention method is compared with another method, often new, that may be more efficacious than the existing intervention. If there is no existing effective intervention, a placebo or 'no intervention' may be used as the comparison against which to assess the impact of the new intervention. Ideally, individuals are randomly allocated to receive the different interventions being compared in the trial.

<sup>67</sup> Such studies often include an evaluation of the cost of providing the intervention and the benefit it provides (Nuffield Council on Bioethics 2005).

Population based research (epidemiological studies and surveillance, that I discuss in more detail in chapters 6 and 8), which affects not only individuals but also integrated groups of individuals, and often of significant size, has considerably improved health and decreased mortality and morbidity. It represents one of the great triumphs of science in the 20<sup>th</sup> century (Gostin 1999). The development of such research interventions may have the dual effect of directly promoting improved health and leading to further health benefits through the impact that such improvements will have on socio-economic development; for instance non-clinical population-based studies aiming at addressing the health needs of the most vulnerable populations may also reduce socioeconomic inequalities as the fundamental means of improving health (Nuffield Council on Bioethics 2005).

### **5.2.2 | The advantages of arguing for a moral framework based on the human right to health**

It is obvious from the above that there are critical general issues about economic disparities, injustice, deprivation, and exploitation that should be taken into account when considering the ethics of collaborative health research. The implication of adopting a moral framework based on the human right to health is that in contrast to the traditional research ethics framework (see Belmont Report principles discussed in Chapter 1), based on which various approaches for the justification of health research have relied, it is less individualistic and considers individuals as part of their wider social communities. Having argued that there is an intimate connection between health research interventions and the field of health and human rights, the human right to health approach secures certain minimum conditions of a decent life (Miller 2004; Buchanan 2011) and protects all people against certain standard threats to their basic interests (Beitz 2009; Wolff 2013) Moreover, within a context dictated by the duty of justice, the proposed framework emphasises the fact that sponsoring and host countries are equal partners. Therefore, there is no room for implicit acknowledgments of predefined status quos, but promotion of processes, terms and forms which suggest greater equity, and which may, under the right conditions, assist the host country in developing the capacity to autonomously meet the rights of its citizens.

At this point it is important to note that by arguing for a second order duty on behalf of developed countries to assist countries with restricted resources to meet for the people under their discretion their basic right to health, I do not suggest that the needs of their own communities should not have first claim on this duty and thus on the resources available. My main point is that by the conduct of collaborative health research, developed countries may aid developing countries to (partially) fulfill their first order duties towards their citizens. Therefore, it does not follow that a moral duty to support collaborative health research should not be overridden by other moral claims. In contrast, this view implies that there is a difficult task for governments in both developed and developing countries to strike an acceptable balance between competing ways by which this duty can be fulfilled. In addition, this understanding of the ethics of collaborative research does not contradict the view that it is in the moral interest of all (both in developing and developed world) that effective health research is conducted, but it sets certain limits on how this interest should be materialized and under what conditions it should be pursued, which I discuss further in the following paragraphs<sup>68</sup>.

Given the complex ethical issues raised by the practice of collaborative transnational research, a human right to health approach in research ethics provides a framework within which we can more clearly consider the ethical challenges researchers, research committees, sponsors and host communities face when a study in a developing setting takes place. In the next paragraphs, I will explain how these moral considerations affect the duties, obligations, claims and expectations of those involved in collaborative health studies by discussing an expansion of the principles in which current research ethics guidance rely and their interpretation according to the proposed framework. I then explore the application of these principles in three very challenging issues in collaborative health research: the moral criteria for the selection of potential participants, the social value of health research and post trial access to research benefits in

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<sup>68</sup> I acknowledge that there are important criticisms concerning the human right to health, however, my aim in this chapter is not to defend this theory but to consider how it can inform an alternative approach in addressing research ethics challenges in developing settings beyond the traditional model of clinical ethics.

developing settings.

### 5.3 | Revising the principles in research ethics

The Belmont Report principles<sup>69</sup> provide the foundation for contemporary regulations designed for the protection of human subjects in research. Yet, despite the wide acceptance of the moral principles that should guide research, there is much dispute on how these principles should be interpreted in different cultural, social and economic contexts. Guidance provided by international guidelines is considered difficult to apply in practice; for instance, there are residual, unaddressed questions such as: What does exploitation mean given the different levels of risks in which people in developing countries are exposed to everyday? What happens when cultural or community values conflict with those of developed countries? And how can we ensure that participants and their broader communities are both protected and respected?

Moreover, as I mentioned in chapter 1, the focus of the principles in Belmont Report is primarily on individual rights and duties and thus does not capture broader issues such as welfare and equality of populations. However, an individualised framework in research ethics is problematic for two reasons. First, because it does not recognize the moral significance of considering health research within the broader context in which it takes place. An individualized framework in research ethics fails to acknowledge that the conditions in which individuals in developing countries live and which affect their health status should not be acceptable and that these individuals and populations are entitled to more than they currently enjoy (because their governments have failed to meet their basic human rights).<sup>70</sup> Second, because the principles that the current framework supports mainly focus on clinical research and they do not take into account the variety of health studies that may be significantly valuable in developing settings and in which whole communities rather than individual participants may be

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<sup>69</sup> See previous discussion in Chapter 1 on a standard view of research ethics.

<sup>70</sup> As I explain later this is significantly important to ensure that the interests of participants and their communities are protected in research.

involved<sup>71</sup>. It seems then that a different interpretation of Belmont principles than that found in current guidelines is necessary, which could address both of these problems.

### **5.3.1 | The principle of respect for persons**

How should the principle of respect for persons be interpreted considering the moral framework discussed above?<sup>72</sup>

The principle of respect for persons is usually interpreted as a moral duty to respect the autonomy of individual participants and the protection of those with impaired or diminished autonomy. This principle is viewed as suggesting that we should not use others as mere means for research purposes, because everyone is worthy of respect, and thus that researchers should secure participant interests, protect their participants from exploitation by minimizing the risks to which they are exposed and abstain from practices such as deception and misinformation. Moreover, those who participate in research should be involved in the decisions that affect them, since a person should be free to determine what is good for them. The principle of respect for persons is thought to include a duty to protect human dignity, a duty of confidentiality, and a duty not to exploit the vulnerable.

Considering the human right to health, this principle would demand not only that participants should be protected in research, i.e. that they should not be made worse off because of their enrolment, but also that research should aim to help improve the conditions in which these people live so that their health status can be improved and that they will be able to develop and express their capacities and lead meaningful lives. Therefore, respect of the moral worth of the individual, according to a new interpretation, is not limited to the avoidance of harm (the avoidance of exploitative practices) but also commands that researchers and their

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<sup>71</sup> This is particularly important to ensure that valuable health research is supported.

<sup>72</sup> As mentioned earlier in this chapter, the human right to health is adopted in the thesis as a pragmatic tool grounded in existing widely respected practice and conventions. The suggested framework captures many of the strengths of the moral theories discussed in the previous chapter (such as protection of research participants from exploitation), whilst avoiding some of their most important weaknesses (such as restriction of valuable research)

sponsors have positive obligations towards their participants to meet their basic rights and capacities.

Moreover, the proposed moral framework recognises that the communities of the participants may be indirectly affected by the conduct of research (e.g. by stigmatization) and suggests that the principle of respect for persons should not be restricted to a duty of respect for individual participants but that it should extend to the community in which these individuals belong. Moreover, taking into account that in certain communities individuals' sense of self-respect is often closely associated with their community values and principles (individuals often tend to think of themselves in the light of the concepts and understandings they have acquired in their society (Nuffield Council on Bioethics 2005)), the principle of respect for persons should also be related to the respect for the host community's cultural values. In addition, the integrity of participants' intimate relations, their values and customs should not be disregarded. As the cultural practices in the communities in which individuals live, shape their understanding of family, status and matters of authority, illness and health,<sup>73</sup> respecting the cultural values of a host community is another implication of the fundamental principle of respect for persons<sup>74</sup>.

Communities may also be directly affected by health research. Many research interventions may involve the use of demographic, social or behavioural data or may actively intervene in the social and family interactions or behaviours and lifestyles of communities (Gostin 1991). For this reason Gostin (1991) has proposed extending to groups the protections now reserved for individuals. Likewise Weijer (1999) claimed that a fourth ethical principle, 'respect for communities', is needed to address the increasing vulnerability of groups. Weijer and Emanuel (2000) also argued that community has a right to respect and protection, and thus its involvement in the research should be considered as a

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<sup>73</sup> As I explain later this is particularly relevant when a decision about participation in an externally sponsored healthy study needs to be made.

<sup>74</sup> However, as I later explain in chapter 8, if local cultures transgress values inherent in this principle, researchers will need to follow different procedures from those prescribed in the local culture.

partnership with the researcher (Crouz et al. 2004). Along these lines King et al (1999) contended that federal regulations should expand beyond the synchronic (slice-of-time) ‘principalist paradigm’ of Belmont evident and include a ‘relationships paradigm’. As they explain, following the ‘principalist paradigm’, researchers often conduct studies that focus on “balancing principles of autonomy, beneficence, justice, informed consent and confidentiality” assuming “ethical universalism (not moral relativism) - truth (not stories); and maintain an atomistic focus-small frame, centred on individuals” (p.15). In this way the moral principles held to govern research with human subjects remain current and meaningful but make sense only in context. “Thus the ethics of human subjects research may be universal but is at the same time deeply particularised, so that what autonomy or informed consent or confidentiality or even benefit and harm mean depends on the circumstances” (p. 213). They claimed that a shift from the ‘principalist paradigm’ to the ‘relationships paradigm’ in research ethics approach would account for both the interactions between subjects and their communities and subject–communities with researchers. By recognizing the breadth and depth of relevant relationships between individuals and groups in a community, the ‘relationships paradigm’ incorporates the relevant contexts including culture, gender, race/ethnicity, history, community, place, and other factors affected by research. Others (Ahmed et al. 2004) have claimed for the use of CBPR as a way to bridge cultural gaps between researchers and communities and increase trust between researchers and communities, especially marginalised communities. The main idea in all these suggestions is that the individualised approach in the Belmont Report should extend to include a duty to respect populations’ wellbeing and integrity. Interpreting the principle of respect in this way suggests that there is another level of harm (harm to the community) that the traditional research ethics framework does not take into account, which should constrain the ways by which a research intervention aims to improve the health status of developing populations.

Extending the principle of respect for persons to groups is considered particularly important when a study affects minority communities and where cultural and historical context are particularly relevant. The expanded principle of respect for



persons and communities would suggest that some form of consultation in the process of informed consent is essential as it can help researchers understand the social context in which community members understand and assess the aims of research (Sharp and Foster 2000). Creating meaningful partnerships between researchers and sponsors and researched communities, means that different mechanisms of community involvement in research should be encouraged, as they contribute to the protection of communities and their members and the development of meaningful research. Those involved in research should as far as possible take account of the local culture and find ways that respect local practices even in cases they complicate their research (Nuffield Council on Bioethics 2005).

Finally, it is important to note that considering research as a partnership between the sponsored and the host country requires stronger duties on behalf of researchers than those that are usually considered as necessary; the principle of respect is not fulfilled by simply obtaining informed consent. A frequent issue in externally sponsored research is that researchers fail to disseminate and share with the studied community their results, even though the duty of respect for communities is considered to entail transparency with the local community and its members and other stakeholders in the research enterprise (Federman et al.2003).

### **5.3.2 | The principle of beneficence**

The second principle, the requirement of beneficence, is taken to include maximising benefits and minimising harms. In the case of collaborative research, it requires that a proposed research study must offer some benefit to the host community in order to be justified. However, according to the suggested research ethics framework, this interpretation is not satisfactory. A more appropriate way to consider this principle would be to require that any proposed study serves the interests of the participants in the host country so that they are better off than they were before their participation. A research initiative should aim to the improvement of the conditions in which participants live, the reduction of their suffering and ill health. These are the aims that should guide the discussions between the stakeholders when making decisions about a research project: i.e. the scientific questions that should be explored, the identification of research initiatives that should be funded, the selection of the country and community

where research would be conducted, and the way it could benefit the populations that are most in need for help.

When a study should be considered beneficial for a host community is often a controversial issue, which I discuss in more detail later in this chapter. Although a host community may benefit in different ways and to different degrees from a research initiative (details about the level and type of benefit require value judgments that should be assessed case by case) some practical implications of this principle are easy to consider. When a study is conducted in a developing country where there is high unemployment or when participants are only able to take part in research programmes with support (such as reasonable financial compensation for travel expenses or for time away from life sustaining work) (D'Alessandro et al. 1995), payment of expenses incurred by the participant, or remuneration for loss of earnings suffered should not only be considered acceptable but also necessary (Nuffield Council on Bioethics 2005).

It is important to note that the duty of beneficence should be constrained by the duty of justice and the duty of respect for persons. Aiming to improve the health status of developing populations and to alleviate their suffering differs from the utilitarian view (discussed in Chapter 4) that the less suffering there is, the better the research initiative. As I have already argued, the duty to meet a human right to health is closely related to fairness. The aim of an externally sponsored research to alleviate suffering is thus significantly constrained by the principle of protecting the most vulnerable and the principle of respect for persons; a research intervention that offers the most straightforward way of reducing suffering but at the same time fails to protect and promote the interests of the participants or their communities should not be considered morally legitimate. Researchers need to ensure that their research will improve the capacity of the hosting country to rely on basic social structures that would meet the basic health needs of its citizens without permitting unfair practices or the exploitation of its participants for purely scientific purposes or based on a more loose sense of the social good. These elements are closely related and should not be considered separately.

### 5.3.3 | The principle of non-maleficence

The principle of beneficence is considered as complementary to the principle of non-maleficence, which requires that health research should not add to the burdens those in the developing world already face. This principle rules out any research proposal that would make either participants or their broader host community worse off. Although aim of collaborative health research is to address the critical health-related needs of the developing world at the same time it is also capable of imposing additional burdens on participants and their communities. The challenge, then, underlined by this principle, is to ensure that research actually benefits people in the host country without further exacerbating their already profound deprivation.

A critical question related to the harm principle raised in collaborative health research in developing countries is to define the degree of acceptable risk when aiming to improve the health status of developing populations. The Declaration of Helsinki states that “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects” (2013, paragraph 16). But how should the risk to benefit ratio be interpreted when we consider the issue of health inequity? Given the prevailing living conditions and the limited access to medical care, it is evident that the social benefit of a tested intervention may potentially be much higher in a poor country. Should a wider scope for the social benefit suggest that higher risks could be considered acceptable?

As I discussed in chapter 4, by arguing for a universal moral duty to participate in research advocates of this view aimed to restore public trust in health research (clinical research in particular) so that research can more effectively serve its proper social aim. Yet, their views fail to provide a clear account of the social purpose of research and a more precise view on how to consider acceptable/reasonable research risk. As London (2006) points out, in order for research ethics to gain social support as a means of serving the common good, it is essential to clarify the nature of the common good. By relying on a human right to health, I addressed this concern and explained how research ethics may provide a conception of the social purpose of research that “overcomes the dichotomy

between the good of the many and the interests of the few” (London 2003). I also argued for a vision of social justice in the research context, which provides more precise operational content to the concept of reasonable risk.

In the revised moral framework the potential risk of harm to research subjects and their communities should be established irrespective of the geographic and economic setting in which research is undertaken (Nuffield Council on Bioethics 2005). The fact that participants of health research happen to live in a poor or disadvantaged country should not, in any way, imply acceptance of different rules in relation to their protection. A research ethics approach relying on the human right-based context, should not ask what conditions the subjects sustain, but rather what conditions they should enjoy according to their right to health (another example that shows that the principle of beneficence should be constrained by the principle of justice). An argument of relative exposure to risk appears extremely unfair, especially if applied to people of different social class in the same country or community; would for instance be acceptable to argue that those who experience better living conditions, and therefore lower exposure to risks, should enjoy higher protection standards? Arguably, following different risk standards in a developing setting would be contradictory to the objective of establishing global health equity. The duty of a researcher to protect their subjects’ interests should not be compromised, since that would constitute violation of their human right to health.

According to the suggested research ethics framework, the researchers duty to maximize any benefits and minimize any risks in research (considering as a threshold the moral entitlements of participants and not the status quo) should extend beyond the principle of respect for persons narrowly conceived. A study that involves risks that would have been unnecessary or could have been avoided should not be allowed, even if people in the developing country were willing to

participate<sup>75</sup> (thus even if potential participants and their communities did not view those risks as unacceptable)<sup>76</sup>.

Finally, as with the requirement of beneficence, the requirement of non-maleficence should not be restricted to considerations regarding individual harm but also consider harm for communities. Research interventions may involve risks for communities such as spread of infection to persons outside the trial, premature dissemination of findings that may result in harmful changes for communities or false hopes for cures or social stigmatization (Levine et al. 2004) which suggests that it is not only the health of the individual research subject that should be considered but also the harms to their community affected by the study.

### **5.3.4 | The principle of justice**

The principle of justice is conceived as requiring that all individuals be treated equally and thus that the distribution of burdens and benefits in research be equitable. However, there is no further explanation in current guidelines on the moral criteria based on which potential participants should be selected or not selected nor on what should be considered as fair or appropriate distribution of

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<sup>75</sup> I view this issue in more detail where negotiations between sponsored and host countries are discussed.

<sup>76</sup> A prominent issue in relation to the conduct of transnational research has recently been the ‘standard of care debate’; i.e. the level of treatment that should be provided to the control group in externally sponsored research. Advocates of a ‘universal standard treatment’ (Lurie and Wolfe 2006) claim that allowing research methods that would have deemed unacceptable in a sponsoring country, implies acceptance of double standards for poor and wealthy populations. This thesis has been contested by African researchers and national and international committees (Lie et al 2004; Macklin 1999) for failing to take into account resource limitations and local specifics that may not allow the application of a worldwide optimal standard. Taking into account both positions, I argue that when a universal standard of care cannot be realised (because of resource limitations, different needs, etc.), research designed to correspond to local health needs should be considered acceptable, since it acts against neglecting the needs of the most disadvantaged. However, in order such research to be justified it should also ensure that participants are not exposed to unnecessary and avoidable harms despite the fact that researched populations may live under extremely disadvantaged and unhealthy conditions (Lignou 2011). Researchers carry research in an appropriate manner when they do not accept different rules in relation to the protection of their research subjects and when they do not reproduce conditions that impose risks that could and should have been avoided in a controlled environment of a trial. Adopting a relativistic approach on the protection of participants is contradictory to the objective of establishing global health equity (Lignou 2011).

benefits and risks. These ambiguities pose important difficulties when considering the duties of sponsors and health investigators towards participants and their wider communities during the trial and after its completion, which I discuss later in this chapter (e.g. should they provide ancillary benefits such as prevention and health care services?).

A moral framework based on a human right to health has certain implications for the issue of justice in international health research for both the needs and susceptibilities of the host population and the capacity of health research to benefit and to burden. As the majority of people living in poor countries do not meet their potential best health because of a "toxic combination of bad policies, economics, and politics" (World Health Organization 2008) these problems represent a failure on behalf of a state to control over the basic social structures and to protect the interests of the community members. Those who suffer in these cases can legitimately claim, as a strict obligation of justice, an entitlement to relief from such sufferings as they are denied effective opportunities to develop their basic capacities (London 2005) As populations in host countries are already worse off, it is important to first consider why they were chosen to participate in research.

Although developing populations may initially be chosen based on financial and administrative criteria, mere convenience should not be viewed as sufficient justification for imposing burdens or risks to developing populations. The principle of justice traditionally conceived requires that vulnerable subjects be selected only if research is relevant to the condition of person or group it belongs. As people in developing settings live in already disadvantaged environments, they constitute vulnerable participants that should only be considered as eligible candidates when the aims of the study are related with their needs or health condition. A human right to health would command that researchers have a moral duty to aim to make the disadvantaged members of society both better and more equal when applying their interventions in the studied communities. It would command that local political and economic elites should not seek to pursue their own goals at the expense of populations participating in research and that researchers should not select economically or politically weak populations to

pursue their scientific aims unrelated with the needs of those populations or for the benefit of wealthier communities.

A moral framework relying on the human right to health, would suggest that there are two aspects of justice that should be taken into account in collaborative health research in developing countries: first, the improvement of the health status of individuals and populations who have been denied fair opportunities to meet their basic rights and second, the fair treatment of those who are more disadvantaged. The duty of justice thus will define the wider roles and obligations of all those involved in research: including governments, researchers<sup>77</sup>, and pharmaceutical companies. Because of the large inherent inequalities between sponsored and host countries in economic and political power, individuals and communities in developing countries are inherently likely to be exploited; community members or community leaders may be more susceptible to different kind of inducements because of their restricted autonomy (because of their poor health they may not be able to refuse excessive research risks in order they or their families to have access to treatments). The principle of justice would require that governments, sponsors and researchers should not allow or support, in other countries research which does not confirm to ethics review standards at least equivalent to those within the nation (Miller 1988). Considering the principle of justice in the light of the human right to health, not only equivalent standards for the distribution of benefits and risks must apply but also additional safeguards should be taken to

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<sup>77</sup> It is worth noting at this point that the ethical principles found in current guidelines are only enforceable through sanctions imposed on members of the profession, which was responsible for the particular guidance. The Declaration of Helsinki, produced by the WMA, only binds physicians. Similarly, the CIOMS guidelines only bind members of the signatory organisations. As health research is not merely conducted by medical practitioners but other disciplines may also be necessary (psychologists, sociologists, geneticists, and others), many researchers involved in collaborative health research are not accountable under these guidelines (Nuffield Council on Bioethics 2005). It seems then that guidance on the ethical responsibilities of researchers are not sufficient to cover all the responsibilities that researchers have towards their participants. For this reason Nuffield Council of Bioethics has suggested that national and international research sponsors provide for the education and training in the ethics of research of all of those professionals involved in research and ensure that the requirements of relevant guidance on ethics are met (Nuffield Council on Bioethics 2005).

ensure that any form of exploitation is avoided.<sup>78</sup>

Let us consider now the implications that these moral considerations have on the obligations and rights of those involved in health research. In the following I will discuss three main issues in collaborative health research in developing countries: What should be the moral criteria of choosing potential participants? What should be considered as beneficial study? Should post trial limitations restrict the conduct of a study in a developing setting? Although extensive and more detailed discussion would be more appropriate for addressing these complex issues, for the current purposes I aim to discuss the main points in each case to clarify the implications of the suggested research ethics framework and to clarify the conditions under which collaborative health research in developing countries should be considered acceptable. Taking these conditions into account I will later discuss (chapter 8) practical solutions to the problem of consent when cluster design is used in collaborative health studies.

#### **5.4 | Justice and Fairness in health research: moral criteria for the selection of potential participants**

A fundamental problem in research ethics (and collaborative health research in developing countries in particular) is how to conduct a health study so that both risks and benefits are fairly distributed; thus a fundamental problem in research ethics is an issue of social justice. The issue of fair distribution is associated with considerations concerning risk – benefit balance but is also closely related with the moral criteria based on which potential participants are selected. Although the selection of research participants is often random and not related to any morally rational choice, as it would be unfair if certain members of the population or groups of individuals were to receive important benefits and others were excluded (given that criteria of eligibility are met and research risks are minimized as provided by the regulations), the alternative research ethics framework discussed earlier would in certain cases not only justify but also suggest that moral criteria

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<sup>78</sup> By additional safeguards I do not suggest that overprotecting rules should apply, as I later explain those rules may eventually harm communities and individuals with restricted access to health treatment. I rather argue that additional benefits –not directly related with the research project –may be necessary to meet participants' basic needs.



are used for the selection of potential participants.

Rawls's work on *A Theory of Justice* has been very influential in discussions of these problems in biomedical ethics, although he never pursued these health issues. He argued that a social arrangement forming a political state is a communal effort to advance the good of all in the society. Rawls argued for a positive societal obligation to reduce barriers that prevent fair opportunity and to correct or to compensate for various disadvantages. His view that we should aim to make the disadvantaged members of society both better and more equal to those currently with greater advantages can have certain implications when considering the conditions in which health research should be conducted.

An essential part of improving the health status of populations in developing countries is to identify and improve patterns of systematic disadvantage that undermine the well-being of people who have limited prospects for good health and the capacity to change these conditions (for instance people that live in slum areas). To meet the human right to health by reducing ill health (discovering therapies or preventive measures for the specific needs of the host populations) and improving the conditions in which people live (e.g. sanitation, clean environment) research projects often need to focus on the needs of the most disadvantaged<sup>79</sup>. Studies that aim at addressing the needs of the most disadvantaged groups of the population within the larger host community may significantly improve the conditions in which these populations live and also contribute to social equity.

There are of course numerous dimensions of disadvantage. Many causal agents, such as poverty, substandard housing, poor education, unhygienic and polluted environments, and social disintegration, can lead to systematic disadvantage not only in health, but also in nearly every aspect of social, economic, and political life. Inequalities cause other inequalities, and existing inequalities reproduce and produce a multitude of deprivations (Powers and Faden 2006). To determine who

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<sup>79</sup> Considering that the principle of beneficence should always be constrained by the principle of justice, this view avoids the problems that Rhodes approach presents as it sets certain limits on the degree of risk that should be permitted when vulnerable populations are involved in health research.

are most vulnerable and at greatest need, who should have priority in participating in health research, how best to ameliorate their condition and how to fairly distribute benefits and burdens to participants and their wider communities, are questions that will depend on the type of intervention, the aims of the research project, the design used, the needs of populations involved, the available resources and thus will need to be informed by empirical data and assessed by case.

## **5.5 | The principle of beneficence and the social value of health research**

I have argued so far that an alternative research ethics framework based on the human right to health could help us better define the conditions under which health research in developing countries should be considered as morally acceptable. Based on the suggested approach aim of collaborative health research should be to address health needs that cannot be feasibly or more efficiently met with existing knowledge and the resources of the host country. It suggests that researchers and sponsored agencies could significantly contribute to narrow the research gap by investigating ways of bridging the space between a community's health needs and the capability of its social institutions to meet those needs. It follows then that based on the suggested framework a necessary condition for a collaborative health study to be morally acceptable is to directly relate to the health needs and priorities of the hosting country. There are however several difficulties for this condition to be satisfied.

In order for a health study to be related to the specific needs of the host country it is important that the host country defines its own health priorities and research concerns so that useful partnerships can be developed between them and their sponsors and researchers<sup>80</sup>. However, the capacity of developing countries to set their own health priorities for research may vary considerably. The setting of national priorities for research is a complex process involving national and international research objectives, institutions and individuals that some developing countries lack (Nuffield Council on Bioethics 2005). As a result, many

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<sup>80</sup> See for instance the arguments for community involvement and the principle of respect for communities, discussed above.

developing countries lack the resources to make a comprehensive assessment of the prevalence and effects of disease and ill health within their borders (Nuffield Council on Bioethics 2005). To address this problem, several sponsoring agencies today have advisory panels involving members from both developed and developing countries to help them identify areas of priority for support in consultation with the relevant communities (UCL Institute of Child Health 2015). Moreover, some companies have several R&D projects to develop treatments for diseases and conditions prevalent in developing countries (for instance GlaxoSmithKline company).

Nevertheless, most funding agencies in collaborative health research (national governments, research councils, private sponsors, non-governmental institutions or agencies and pharmaceutical companies) have their own approaches for the identification of areas, which they wish to support, despite the health priorities of the populations they target. Although there are cases where a health condition is also relevant to developed country markets (and thus there is potential for mutual benefit) and also others where the research sponsorship may be altruistic (Nuffield Council on Bioethics 2005), in most cases collaborative research in developing countries is undertaken by pharmaceutical companies and the criteria for selecting a particular country are based on convenience. Although factors such as the availability of suitable participants, the availability of high quality collaborators, and appropriate infrastructure for delivery of clinical care to the participants are important for the completion of a study, they are not sufficient to argue that a study is morally justified.

As already discussed, because of the inherent inequalities of power and advantage between sponsoring and host countries, it is essential that any tendency on the part of the sponsor to pursue their interests to the disadvantage of those of the host country be restrained. Nuffield Council on Bioethics suggests that when a research funded by external sponsors falls outside the national priorities for research by a host country, the study should be justified and approved by appropriate research ethics committees in both the host and sponsoring countries (Nuffield Council on Bioethics 2005). The main issues that research committees need to consider in such cases, to ensure that participants and their communities

are protected against exploitation, are the relevance of study to the host country's needs (discussed below), the prospect of maintenance and implementation of the research intervention, if proved to be successful as part of the host country's health policy system (discussed in 5.6), as well as other relevant matters concerning the way in which the study is conducted, for instance respect for cultural differences (discussed in more detail chapter 8). Let us consider these factors separately.

### **5.5.1 | The relevance of study to the host country's needs: Direct and indirect benefits for participants and their communities**

The kind of improvement that is needed to argue that a given study is beneficial for a host country is a matter of dispute. It is generally assumed that if the research agendas do not match, often the financial influence of the sponsor becomes the driving force and the host country is exploited (for instance, research teams merely collecting samples or data to be studied elsewhere has been repeated several times in the past (Nuffield Council on Bioethics 2005). These cases however should be distinguished from the cases where a researcher pursues a study of legitimate interest that does not address a health priority in the host country but may provide considerable long term or indirect benefits to the participants and/ or their broader communities.

Some of the studies carried out in developing settings are designed to offer direct benefits to the participants (e.g. treatment of a particular disease) while others indirect benefits (e.g. identify the causes of a disease). Much discussion on the research ethics literature has focused on clinical studies (which usually provide direct benefits) and thus the importance of different types of health research, which have the potential of great value for the populations of developing countries (for instance basic research into causes and mechanisms of disease and their diagnosis) has been neglected. As poverty and lack of scientific and administrative infrastructures limit the ability of many developing countries to conduct research that may provide useful knowledge for the understanding of their specific health problems, externally sponsored research aiming to fulfill this gap should be given appropriate attention and support.

### 5.5.2 | Ancillary benefits

When the main objective of a study is to advance scientific and medical knowledge without involving any direct benefit to the participants or their communities (for instance immunological studies), other types of benefits may be considered appropriate and be provided as part of the study (Nuffield Council on Bioethics 2005). Some of these benefits may not be directly associated with the project and may be offered both to individuals and communities (for instance clean water or food). In other cases benefits offered to individuals and communities may be integral to the research process, such as treatment services, diagnostic tests, enhancement of the local expertise of researchers and the provision of community facilities.

As stated in Principle 17 CIOMS (International Guidelines for Ethical Review of Epidemiological Studies, 1991) “While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates”. Health research then could be of significant social value by providing long term benefits; for instance, the development of local expertise and improved infrastructures during the research may be a valuable contribution as it can add the potential for continued improvement in healthcare once the research is complete. In this way health research may contribute to the strengthening of the limited social structures of developing countries to meet the health needs of their populations given the unique social and environmental circumstances in which they live (Flory and Kitcher 2004).

There is however much debate on research ethics literature regarding the provision of benefits not directly associated with a research project. The main concern is whether and when providing ancillary benefits to developing populations constitute ‘undue inducements’ especially to vulnerable people to participate in research. A research ethics framework based on the human right to health would suggest that to decide whether such benefits should be offered, we should consider whether by providing such benefits researchers meet the basic

needs of those taking part in research (Lignou 2011). Thus although it is often argued that sponsors or researchers have no moral duties to provide ancillary benefits as part of their project, the suggested research ethics framework would maintain that the provision of such benefits could be consistent with researchers' specific moral obligations to the host community which members have stronger claim of assistance. A duty to offer ancillary benefits becomes stronger when researched communities lack the capacity to treat the ancillary health problems that researchers are likely to face. In such cases providing research participants with benefits might be a means to reduce the level of risk in which participants are exposed to and thus such ancillary benefits may be considered as part of researchers' special moral obligations to prevent harm (i.e. access to certain health care services or other minimal services may be considered significantly important to meet participants' basic health needs). Yet, there are cases where providing benefits not directly associated with a project could constitute undue inducements, for instance when payment is involved, and careful considerations need to be taken before they are offered to potential participants<sup>81</sup>.

According to current research ethics regulations, health research is morally acceptable when it has the potential of being socially beneficial and when the interests of the individuals are sufficiently protected. Satisfaction of these conditions suggests that the interests of research subjects are not undermined in the pursuit of obtaining scientific information and therefore the main ethical concern raised by health research (the potential of them being exploited) is being addressed. The precautionary approach (the approach that is adopted by current guidelines) is often criticised for imposing strong restrictions on international health research that prevent host communities from participating in otherwise beneficial studies. By taking into account different types of benefits (direct, indirect, long term ancillary benefits) that could be offered to both individuals and their communities, we can conclude that a variety of health studies may address the needs of a developing population and contribute to the improvement of the

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<sup>81</sup> Offering participants a considerable amount of money may help them meet their basic needs but it would not facilitate the realisation of the purpose of health research to improve the health status of developing populations. It would thus be inconsistent with the moral approach discussed earlier in this chapter.

health status of its members even if it does not fit with the research priorities of the host country or even when a host country lacks the ability to clearly define its own research agendas. Yet, in every case it should be clear that the level and type of benefits that a health study is expected to bring are related with the needs of the host country, in order a study to be both approved as morally justified by responsible research ethics committees and accepted by the host communities.

## **5.6 | Post trial access in collaborative health research in poor settings**

When considering whether it is appropriate to conduct a specific health study within a developing country, an important ethical challenge arises: What happens once research is over? Would the intervention be affordable in that country if it were shown to be effective?

Aspects related to post-trial access to the tested intervention raise concerns about transnational collaborations and global justice. However, legislation and guidelines are ambiguous about many aspects of Post Trial Access. For instance in the Commentary on Guideline 8 CIOMS (International Ethical Guidelines for Biomedical Research Involving Human Subjects, 1993) it is indicated that “As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product<sup>82</sup> developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified ...” A similar statement is also found in the NBAC recommendation. It is required that research proposals for externally sponsored research submitted to ethics committees should include an explanation on how new proven interventions could be made available to some or all of the host country population. If post trial access is not possible, researchers should justify, to the relevant research ethics committee, the reasons their research should be conducted.

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<sup>82</sup> However, as I have already explained, not all health studies concern the testing of a product.

In none of these guidelines researchers' obligations regarding participant access after the completion of the trial are clear (especially when a study is not conducted by physicians) and the standards that research ethics committees should follow and the requirements that should be asked to researchers regarding this issue are not specified. As a result, participants who reasonably expect post trial access are denied the intervention and public trust in research is often undermined (Sofaer et al. 2014; Grady 2005; Emanuel et al. 2008; Hawkins 2008) In general it is argued that these general recommendations do not meet the needs of highly diverse situations (Lavery 2008)<sup>83</sup>.

The discussion on post trial access arises worldwide (CIOMS 2002; Sofaer and Strech 2011) whenever participants want continued access to a study intervention that is unaffordable or otherwise unavailable and are most pressing when participants are seriously ill and the study intervention is more effective than the standard treatment or is the only (remaining) option (Sofaer et al. 2014). There is much controversy over whether and when research participants should have access to the study intervention after the completion of a study and about when post trial access to the intervention should be considered beneficial (some argue that the intervention should be regarded as beneficial only after the intervention has received regulatory approval, while others argue for a lower standard of evidence (Sofaer et al. 2014)). Nevertheless, this issue becomes even more serious in collaborative research in developing countries, because of the major health needs of the poor populations and their inability to respond to those needs. The main question that should be answered in this case is: Could the conduct of a trial in a poor setting with restrictive post trial access be morally legitimate and thus compatible with a moral framework based on the human right to health, discussed earlier?

There are differing views to the question of whether it is morally acceptable to allow research in a community that could not afford the intervention being tested. Some argue strongly that it is not acceptable under any circumstances. Others

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<sup>83</sup> These difficulties are also acknowledged by the US National Bioethics Advisory Committee (NBAC 2001)'s report on clinical trials in developing countries.



consider this problem as an essentially separate political and economic issue. Others have argued that this is a decision that developing countries should be entitled to decide for themselves, so that they are not excluded merely on the grounds that the intervention could not be afforded after the completion of the study. Let us consider how this issue could be addressed within the suggested research ethics framework.

There are two groups of people that should be considered regarding the provision of the outcomes after the completion of a study: the participants in the research project and the wider community in which the research took place.

### **5.6.1 | Post trial access for participants**

In the revised Declaration of Helsinki (2013) it is stated that study participants should receive the outcomes of the study, if proven to be successful<sup>84</sup>. This claim seems to be compatible with the moral framework I outlined earlier. However, providing the control group the intervention once a trial is completed is not always the right solution. There are cases in which there is likelihood of long-term adverse effects, which cannot be assessed with certainty, as the opportunities for longer-term observation and for the detection of later deleterious effects are lost when the trial is completed and there is no longer a control group for comparison with the participants who received the intervention (Nuffield Council on Bioethics 2005). In such cases it is important that short-term benefits be weighed against possible long-term adverse effects, in order to decide whether people in the control group (or the wider community) should have access to the intervention after the completion of the trial. In order then to argue that an obligation to provide post trial access exists, the provision of the treatment should be relevant and appropriate. This decision should be made on a case-by-case basis, as particular circumstances have to be taken into account (the likelihood and magnitude of the benefits and risks)

Access to the research intervention, if proven to be successful, may be crucial in other cases; for instance, when participants have conditions that require on-going

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<sup>84</sup> The Declaration identifies the sponsors, researchers and host country governments as the main agents responsible for complying with the post-trial obligations.

treatment. However, the fulfilment of this requirement may not be possible, especially in relation to ongoing treatment for chronic diseases. For those cases the US National Bioethics Advisory Commission (NBAC 2001) recommends that researchers should endeavour before the start of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee. This solution however does not seem helpful to assess whether a given study should be permitted.

A human right to health approach would suggest that in such cases participants may be made worse off and thus the study should not be permitted<sup>85</sup>. It could thus be claimed that researchers' responsibilities extend beyond the completion of their study (because of their special moral obligations towards the control group) and that when such problems arise it is more appropriate for a study to be conducted in communities that have the capacity to translate the research results into benefits for their populations or which have appropriate health infrastructures. However, in most cases the communities that are not capable of implementing the results of the study into sustainable benefits for their populations (because of the restricted capacities of their social structures) are the most vulnerable and thus those in most need of health improvement. People living in rural areas have little or no access to health care facilities and health counselling, which are necessary for an effective intervention to be efficacious. On the other hand, an absolute decision to prohibit health research in such cases may be ultimately harmful especially for the most vulnerable individuals, as it would restrict investigations that are relevant to their health needs and which may provide significant improvement to their health status.

A possible solution to this problem could be for the host country to collaborate with partners that are willing to contribute and help the community to implement

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<sup>85</sup> Although the maintenance of continuation of a treatment is not a requirement in developed countries (Nuffield Council on Bioethics 2005), taking into account the social context in which research is conducted, it seems reasonable to argue that this requirement should be fulfilled in externally sponsored research conducted in poor settings.

the study outcomes in their health policy (and by this way fulfil their second order duty discussed earlier). The pharmaceutical industry has been involved in various donation programmes and partnerships (Nuffield Council on Bioethics 2005). An example of this case was a recent study in Uganda. Oral nevirapine was administered to pregnant women infected with HIV at the onset of labour, and the newborn babies received nevirapine syrup within 48-72 hours after delivery. Results showed that a 50% reduction in transmission of HIV-infection from the mother to the baby at 14–16 weeks in the group receiving nevirapine, compared to the control group, which received AZT alone. Because of the results of the study the Ugandan government introduced a policy of providing the treatment involving nevirapine to all pregnant women who were HIV positive. Despite the low cost of the treatment, the country couldn't afford it, and the pharmaceutical company offered the medicine free of charge for use in the prevention of transmission of HIV from mother to child.

Considering international health research as collaboration between host and sponsor countries, it is essential that decisions concerning the access of research participants to the research intervention if shown to be successful be made in advance. This means that information concerning the cost of the intervention and other related matters should be known to the host country before a decision of its acceptance is made, as well as the reasons for which a particular community has been chosen to participate. In cases where a solution for post trial access cannot be found and lack of access would have important consequences for participants' health, involving the most disadvantaged communities in research should not be considered acceptable, despite the magnitude of short- term benefits or the willingness of participants/ communities to accept the study.

### **5.6.2 | Post trial access for the wider community**

Problems regarding the implementation of the study outcomes in the wider community are more complicated. As I have already discussed, not all health studies would have outcomes that can have any immediate practical application; for instance research into the progression of an illness may not be translated directly into practice. Yet, I have argued that such studies should be considered as beneficial and morally legitimate because they play an important role in efforts to

address the profound health needs of developing world populations by contributing to the understanding and prevention of disease (typical examples are research on diseases such as malaria, yellow fever and sleeping sickness). In other cases, research results may show that a given intervention is not safe or suitable and thus should not be applied in the wider population (for the reasons I already discussed). Finally, there may be practical implications that do not permit health related benefits to be directly integrated into local health systems of the host country. The size of the population for instance is a determinant factor for an intervention to be widely available. When health research is conducted in large countries the implementation of study outcomes might have to be limited to a region, or part of a region of the host country. An important question that needs to be answered in such cases is whether an unequal distribution of study benefits should be accepted and thus whether such studies should be permitted in developing settings. Following the discussion in 5.4. it could be argued that unequal distribution of research benefits could be justified when a study aims at addressing the specific needs of the most disadvantaged groups of the population within the larger host community. By improving the conditions in which particular groups or communities live unequal distribution of research benefits may contribute to social equity. The acceptance of a study in such cases would depend on the aims of the study, the local needs and the acknowledgment by the host country that offering research benefits to those that need them the most consists a fair and morally acceptable distribution.

When the cost of an intervention is high, its applicability in the wider population and continued availability may be very difficult; For instance when there is need for expensive equipment that the hosting country cannot afford or when medical procedures, such as vaccines, need to be implemented for which the cost of manufacture and purchase is very high. Non-clinical interventions may also be very costly, as the implementation of appropriate infrastructures, personnel training and counselling may not be afforded by a developing country.

Although cost is the main factor that prohibits the implication of a successful research intervention into the wider community, it should not necessarily exclude the possibility of its being tested in a developing country. First of all expensive

interventions may become affordable within a short period of time. There are several examples where solutions have been found of substantially reducing the costs of providing a medicine or a vaccine that has been shown to be effective, in developing countries after a trial was completed (Nuffield Council on Bioethics 2005). In certain cases drug manufacturers or sponsors of research have agreed to provide substantial quantities of a vaccine with no or at subsidised cost after the completion of the trial. One such example is a large-scale trial of a hepatitis B vaccine conducted in Gambia. At the time the market price of vaccine was about US \$60 per course. Within a few years the market price for developing countries had dropped to approximately US \$1–2 per course, which made the vaccine affordable and implemented in the national health policy programme of Gambia and Taiwan. Moreover, because of this development more incentives were given to find cheaper ways of producing the vaccine and to introducing it into the childhood immunisation programmes of many developing countries (Nuffield Council on Bioethics 2005).

There are cases however, where the costs of some interventions may not drop and it may take a considerable time after the conclusion of the research to be available. Should these studies be rejected as unethical?

The responsibility for implementation and continuation of a successful research intervention falls to the government of the country (the local health authorities and government should determine the level of healthcare and the range of treatments and medicines that are provided to populations). Although, global inequalities restrict successful research outcomes being integrated into local health systems even decades after a study's completion (Marmot 2005), there are certain methods that could realistically apply such as external aid, subsidy or negotiations between the various stakeholders (Schaefer et al. 2009) to facilitate the implementation of successful research outcomes into the health system of a host country. I have already discussed examples where research interventions became available because of sponsors' altruistic motives, let us now consider negotiation strategies between sponsors and researched populations.

As I have already mentioned some commentators argue that the host country

should take the decision regarding the conduct of a trial when post trial access is not possible. Restrictions concerning the permissibility of international health research when post trial access is not possible have been condemned as unjustifiably paternalistic especially by people in developing countries, because they limit the autonomy of their countries to decide for themselves in which research activities are worth participating. Moreover, Gostin (1991) has argued that the important question that should be answered in collaborative research is not whether a study is needed in a host country but whether it is wanted and claimed that legitimate representatives of developing populations should decide whether the study is desired and how its outcomes should be distributed.

Although, it is reasonable to argue that the host communities should decide for themselves whether a study is compatible with their specific needs, and thus whether their enrolment is justified, research benefits should not be considered fair as a result of a bargain mechanism (London 2005). While in the first instance this mechanism seems compatible with the principle of respect for autonomy through democratic consultation (principle of respect for populations), to define a package of benefits as fair we should not merely rely on the fact that the members of the host population agree that those benefits constitute a sufficient return for the burdens associated with the research. Since people living in poor settings have more urgent health needs and fewer treatment alternatives (McManus and Saywell 2002), they are placed in a weaker bargain position than those living in developed countries because they may have more at stake if they are restricted from participating in research. This means that it is more likely that the proposed study will serve the interests of the sponsors rather than the needs of the host communities.

As already discussed an important implication of relying on a research ethics framework based on human right to health is that collaborative research partnerships are not considered in isolation from the existing social, political, and economic relationships in which the different parties exist. Taking into account that the conduct of health research is a collaborative activity, and that the status quo should not serve as a normative baseline, in order a research initiative to be considered as fair it should offer mutually beneficial terms of cooperation that

each party can freely accept (London 2005) As Barry notes, while principles of reciprocity or fair play specify terms that cooperative endeavors must meet in order to be fair, they do not “say that it is unfair for a practice that would, if it existed, be mutually beneficial, not to exist.” (Barry 1982, p. 22). This factor is not considered by the traditional research ethics approach. Current research ethics guidelines do not take into account how the relative advantage of each party may influence the bargaining process. Moreover they fail to acknowledge that people in the developing world are entitled to a higher threshold than their current status quo and thus that this entitlement imposes specific requirements on stakeholders.

Decisions regarding post trial access, i.e. to what extent health improvements should be continued after the research is completed, are complex and difficult to be made. As there are many social, political and economic factors, which may influence the likely availability and implementation of a research intervention, a straightforward answer to this problem would not be appropriate. To assess whether a costly intervention should be permitted in a poor setting, many factors should be taken into account: the prevalence and seriousness of the condition being studied or of the health need that it aims to address, the need to carry out the study in the particular country or community, the impact of interests of the participants once the treatment is stopped, the complexity of and feasibility of delivering the treatment. On one hand health research should not be restricted based on the fact that research interventions could not currently be afforded; the cost of a treatment might change, or special prices could be negotiated or alternative routes for support and supply of an intervention may be possible. On the other hand it is important to consider international health research as a partnership between sponsoring and host countries. This suggests that resources and capacity to function as equal partners should be given to the host communities, so that any form of exploitation is avoided while their local health needs are addressed, stability for meeting their population needs is gained as well as the potential for future research studies (Gostin 1999). Considering international health research as a partnership also suggests that the possibility of the application of a successful intervention in the wider community as well as alternative ways to make the outcomes available should be decided before a

decision of whether a study should be accepted is made.

Before completing the discussion on post trial access, it is worth considering the moral responsibilities of the investigators according to the suggested moral framework. Researchers are mainly responsible for the conduct of research and thus are not expected to have a prime role in making successful research interventions publicly available (as already stated this is the role that the governments of the host countries should fulfill). Nonetheless it is commonly argued that health investigators have some responsibility regarding post trial access, although there are different views on how far that responsibility extends. Despite these differences, it is agreed that research findings are used for advocacy purposes with respect to the future provision of the intervention (Nuffield Council on Bioethics 2005). This means that research investigators are responsible for helping policy-makers to understand the implications of the study and to use their results for advocacy purposes with regard to the future provision of the successful intervention. Their advocacy role also involves drawing attention to problems that have been neglected, or conditions whose impact has been underestimated, and demonstrate that there are possible solutions. Researchers have played that role in the past. For instance they improved care for children by advocating for the iodination of salt to combat goitre in Nigeria. Additionally, another way by which researchers (and sponsors) may facilitate the research is by the strengthening of local healthcare facilities (Nuffield Council on Bioethics 2005).

The most important responsibility of researchers, however, after the completion of the study is to make the results available to the hosting country and community. Arguments for making the outcomes of a study publicly available are based on the principle of justice. Since sponsors, investigators and industry gain benefits from these studies and profits, there are strong reasons to argue that those involved in the study, and who bear the burden of experimentation, are entitled to at least have access to the results of the study irrespectively of their ability to implement those results in their policy.

## **5.7 | Conclusion**

To decide how problems related with the inability to obtain informed consent in



cluster trials in developing countries could be resolved, we should first consider the moral framework within which ethical challenges in health research in general are addressed. The aim of this chapter was to present an alternative research ethics framework to that found in current guidelines. The human right to health principle was selected as an existing element grounded in widely accepted practice and conventions and was adopted as a pragmatic tool for engaging with problems of cluster randomised trials. Despite its limitations (which are not the aim of discussion in this chapter) I argued that the human right to health could better inform our moral reasoning on research ethics and determine the scope and limits of collaborative health research in developing settings. I argued that within this moral framework broader issues of social justice could be better addressed as well as other practical and moral dilemmas that researchers, research committees and sponsors face when conducting research in a developing setting.

To facilitate the development of the discussion in the following chapters, let us summarise here the key points of the human right to health framework. A moral framework based on the human right to health:

- Specifies the aim of health research and its social value and demonstrates the way inequalities in global health should be considered and addressed.
- Argues that collaborative health research in developing settings should aim to assist the host country to meet for its citizens their human right to health by improving the conditions in which developing populations live (e.g. environmental studies), by reducing ill health (e.g. research on new treatments or prevention strategies) and by helping them develop the capacity to autonomously meet their basic health needs (e.g. personnel training, appropriate infrastructures, counselling).
- Is less individualistic and considers individuals as part of their wider communities by arguing that it is not only the health of the individual/participant that should be considered but also the harms and benefits to their communities.
- Secures certain minimum conditions of a decent life and protects all people against certain standard threats to their basic interests considering as a threshold the moral entitlements of participants and not the status quo.

- Commands that researchers have a moral duty to aim to make the disadvantaged members of society both better and more equal when applying their interventions in the studied communities.
- Suggests that those involved in research should as far as possible take account of the local culture and find ways that respect local practices even in cases they complicate their research.
- Emphasises the fact that sponsoring and host communities are equal partners and commands that equivalent standards for the distribution of benefits and risks must apply.
- Acknowledges the inherent inequalities between sponsored and host countries and supports processes and terms, which suggest greater equity (e.g. it does not consider bargain mechanism as sufficient to define fair distribution of research benefits, it argues that study approval by appropriate ethics committees in both host and sponsored countries is needed and that decisions regarding post-trial access are made in advance).
- Constitutes a robust moral basis for identifying and addressing ethical issues in cluster randomised trials in low-income settings

# Chapter 6

## **The ethics of Population-based research**

In the previous chapter, I presented a range of health research initiatives which could significantly contribute to the reduction of the major health related problems afflicting people in developing countries; (e.g. research into genetic determinants of disease, clinical studies on new or improved medicines and vaccines, non-clinical research on finding better ways of delivering existing products and services, and others). However, I noted that despite their value, such health studies are not adequately considered by the current research ethics regulations and guidelines (which focus mainly on medical research). I argued that a broader research ethics framework should be introduced which could take into account the wide variety of health studies that may be significantly valuable in developing settings.

As the ethics of medical research involving individual participants is well regulated and extensively discussed in the existing bioethics literature, aim of this chapter is to explore and discuss the ethics of research interventions that involve populations or groups/ communities instead of individuals, and which often constitute the most effective ways of improving health in developing settings. By relying on Taylor and Johnson's definition of population-based research, I present the ways in which such interventions differ from conventional clinical studies (Taylor and Johnson 2007) and discuss the distinctive moral issues they present. I conclude that population based research is a distinct type of health research

involving human subjects, because of its focus on populations rather than individuals, and that for this reason it should not be considered within the current research ethics framework. I then discuss the advantages of adopting a moral framework based on human right to health when the practical and moral challenges in the conduct of population-based research are presented. I finally argue that the distinctions that Taylor and Johnson (2007) make between population-based research and disease-based research can help us better understand and address the ethical challenges raised in the cluster design and in particular the problem of informed consent (which I discuss in more detail in Chapter 8).

## **6.1 | Definition and distinct features of population-based research**

Several approaches to distinguishing public health practice from public health research and traditional clinical research have been supported. Yet, my aim in this chapter is not to discuss or assess these different approaches, but to focus on those features that are morally significant for an ethical approach to population-based research. The discussion below is based on Taylor and Johnson's account (2007). I believe that their approach could help us identify the morally relevant distinct features of population-based activities and in this way distinguish between those ethical issues that are common in health research in general (and which have been already addressed in the current research ethics literature and regulations on medical research ethics) and those that mainly concern population based activities, (which have not be given much attention by the existing bioethical framework). Moreover, the aim of the following discussion is to help us consider the moral obligations of health investigators who are not involved in clinical studies and determine whether ethical challenges presented in their work demand solutions beyond those provided by the current (clinically focused) guidelines.

Taylor and Johnson (2007) define as 'population-based research' research conducted on human subjects, with the objective of improving the health of populations and to discover interventions that raise the baseline health status of

entire communities<sup>86</sup>. A significant difference between medical research and population-based research, based on this definition, is that medical research is disease-based, meaning that it aims to find treatment for particular diseases that affect individuals regardless of where they live or under what conditions they live (Taylor and Johnson 2007), while population based research aims to identify population-based methods that protect the health of populations and to investigate population-based risk factors and interventions that prevent and reduce population based diseases or conditions (such as malaria or HIV). According to Taylor and Johnson (2007), a condition or disease is considered a population-based concern when the community in which individuals live or belong to is at risk of this condition or disease and not because of the individual risk or the vulnerabilities of the individual members of these communities.

Taylor and Johnson (2007) also distinguish population-based research from public health practice (which also involves population-based interventions) by delineating a more normative than technical definition of population-based research. Although a number of authors have argued that there are several technical criteria that distinguish these activities (such as performance authority, intention to publish, funding source, data collection methods, study design, and/or the investigator-participant relationship), Taylor and Johnson (2007) believe that the most significant feature that differentiates population-based research from public health practice is that the latter involves implementing standard or proven methods for the protection of community health, whereas the aim of the first is the discovery of new interventions for the protection of community health.

According to Taylor and Johnson there are five distinctive features that uniquely arise in the design and conduct of certain kinds of population-based research due to its focus on populations rather than individuals: these concern the aim of the study, involuntary participation, the type of risks and benefits involved and its commitment to social justice<sup>87</sup>.

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<sup>86</sup> Population-based research includes epidemiologic research and surveillance, and intervention epidemiology (e.g. field trials for drugs or vaccines) (Gostin 1991).

<sup>87</sup> As I explain later this is not a universally accepted moral claim.

### **6.1.1 | Aim of population-based research**

The principal aim of population-based research is the discovery of new information for the protection and improvement of community health. It usually targets healthy individuals or those at risk of contracting a disease (instead of patients as in disease-based studies). Although individuals in the community may gain personal benefit by their involvement in the intervention, the objective of population-based research is to raise the baseline health status of their entire community. For instance, let us consider the example of a study testing the effects of fluoride water in a community. Although many of those living in the community may be personally benefited by the intervention, the aim of such study is to improve the dental health of an entire community and not to benefit particular individuals in that community.

This feature is also present in public health practice. For instance a common community-wide policy in public health practice used to prevent the onset or progression of transmitted disease is the requirement for all medical facilities and laboratories to report the name of any citizen diagnosed with a transmitted condition to a local public health authority for contact tracing and treatment. Although the contact with the public health clinic may be beneficial for the infected person and their relatives, the principal aim of the public health practice is to control and limit the spread of the disease to the community (Taylor and Johnson 2007).

### **6.1.2 | Population-based research may affect all members of a group/community regardless of their individual preferences**

Another important difference between population-based research and conventional medical studies is that in the population-based studies individuals may be involved in or affected by a research intervention regardless of their personal preferences. The reason for that is that population-based measures in general (in research and practice) need to affect all or most members of a particular community in an effort to protect the health of their community. As Taylor and Johnson (2007) point out, compulsory compliance with public health measures and non-voluntary participation in population based research are both

features of the broad and general way in which population-based measures need to be implemented. Typical examples are the mandatory check-ups for HIV <sup>88, 89</sup> in public health policy and the involuntary participation of individuals when a new insecticide is tested in their community in population-based research.

### **6.1.3 | Population-based research involves community risks and benefits**

An additional distinct feature of population-based research is that it may adversely affect the interests of the community members involved in the study as well as the interests of the community in which the study takes place. As population-based interventions involve groups (communities) rather than individuals (as in RCTs which may not contact with each other or have nothing in common), they may lead to a stigma that affects a whole community targeted by the study. Investigators involved in population-based research must thus have an additional responsibility to the investigators involved in disease-based studies to protect the social interests of the population in which their research is conducted additionally to the individual interests of their members (Mastroianni and Kahn 2002). Social interests or group interests however, haven't been well understood and addressed in the ethics codes and literature (Weijer and Anderson 2002) and thus guidelines regarding their protection have not been developed. Yet, increased involvement by community leaders and community members has been encouraged and supported in public health interventions, as well as the need to discuss and reveal concerns for causing social harms with the researched communities (Popay and G. Williams 1996).

Taylor and Johnson (2007) claim that because population based research involves a different level of commitment for communities, it is at least morally appropriate, if not mandatory, to offer some kind of community-wide benefit when the study is

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<sup>88</sup> Although a medical intervention is involved in this case, vaccination is considered a population-based measure because it aims at the protection of population health.

<sup>89</sup> Mandatory vaccination is a controversial public health measure, which I discuss in more detail in the next chapter. The reason I use the example of vaccination here is to illustrate that population-based interventions may also involve medical procedures and yet not be classified as disease-based because the reasons for which they are used is the improvement of community health.

over. This view is missing in current research ethics guidelines for disease-based studies.

#### **6.1.4 | Commitment to social justice**

An aim of population-based research is to identify population-based risk factors and interventions to prevent the onset of, interrupt the progression of, or ameliorate a population-based disease (e.g. interrupt the progression of malaria to communities that are at risk) (Taylor and Johnson 2007). For that reason in population-based research it is assumed that in general, what makes an individual more or less susceptible to infection is its membership to a particular community. Susceptibility is considered in relation to where and under what conditions individuals live. Apart then from the distinction between diseases and populations, according to Taylor and Johnson, there is a normative difference between population-based and disease-based research (clinical research); they claim that population based research “must be concerned with the larger systemic effects that research in that population will have” (Taylor and Johnson 2007, p. 296).

Taylor and Johnson (2007) view population-based research as concerned both morally and practically with the political, social, and health condition of populations. Following Madison Powers and Ruth Faden view that social justice should be the “foundational moral justification for the institution of public health” (Powers and Faden 2006), they note: “Population-based research seeks to promote social justice through testing unproven interventions that hopefully provide knowledge on how to improve the health status of populations with health disparities or other social, political, or economic disadvantages that result in poor health” (Taylor and Johnson 2007, p. 296). This commitment to social justice “is a hallmark of public health,” which means that population-based research has both a strong moral authority to learn more about how to better ameliorate health problems, but also a similarly strong obligation to protect and consider the interests of the populations they study (Taylor and Johnson 2007). According to



Taylor and Johnson, this fundamental mission<sup>90</sup>, combined with the ways in which population-based interventions must function, creates ethical considerations that are unique to population-based research.

## **6.2 | Considering population based research within a broader research ethics framework**

Having discussed the distinct features of population based interventions it is now clear that population-based research differs in important respects from disease-based studies. Verweij and Dawson (2009) observe that many of the classical cases of morally problematic studies in health research are those that target communities, populations or groups of individuals rather than individuals. Taking into account that the focus of most discussions and regulations on research ethics is on medical studies (disease-based research), it becomes obvious that the reason that population-based studies are viewed as ‘particularly problematic’ and challenging in on going research ethics debates is that they are considered within the narrow principles of clinical ethics, despite their significant differences to disease-based studies.

Let us consider for instance non-voluntary participation, one of the distinct features of population-based interventions (common in both population research and public health practice), which is the main focus of the thesis. Although, in disease-based studies competent adults may never be subjected to an experimental intervention without their voluntary consent, in most experimental public health or community-based interventions informed consent is not an option. Although both disease-based and population based studies involve human subjects, population-based research has a fundamentally distinct goal that disease-based research does not necessarily share: it aims to improve population health and to discover interventions that raise the baseline health status of entire communities. In order to achieve this aim many population-based interventions have to be administered at group level. Moreover, although some population-based studies

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<sup>90</sup> However, we should note that this is a controversial normative claim; while justice is a common orientation in public health, it is not universal, for instance, it has been argued that Geoffrey Rose’s population strategies of prevention may inadvertently worsen social inequalities in health (Frohlich and Potvin 2008)

may involve medical interventions that can be applied directly to individuals, for instance when testing a new vaccination, many others, such as the provision of health-conducive environments, are not related to medical activities (and they do not directly apply to individuals). In addition, many population-based studies, similarly to many public health measures, do not involve bodily intrusion but merely interference with people's choices or liberties. Finally, In contrast to conventional disease-based studies, population-based research (for instance epidemiological research) may not involve interventions at all, but consist of the collection and analysis of medical and non-medical information of different populations. The borderline between such population-based research and 'regular' public health work (for instance surveillance of infectious diseases) is often unclear (Verweij and Dawson 2009), which suggests that research is not that different from everyday practice.

It is obvious that population-based research constitutes a type of research that is not compatible with the standard narrow approaches dealing with ethical questions in conventional clinical studies. Since individual level principles grounded on the current research ethics framework aim to protect personal autonomy, requirements such as informed consent, privacy and confidentiality may not be sufficient or appropriate to provide guidance on more complex issues raised by population-based studies, where the interests of a whole community or population need to be taken into account. New ethical challenges raised in population-based studies need to be considered within a non-individualistic moral framework, which in return should inform current regulations and ethics guidelines.

Most research ethics regulations and debates about revisions of regulations fail to acknowledge that health research is a complex and morally challenging activity, which may substantially differ between various types of studies. The aim for instance of the recently issued revised CIOMS International Ethical Guidelines for Epidemiological Research (1991, 2008) is to provide guidance on the area of public health research. However, as Verweij and Dawson (2009) point out these guidelines fail to provide any guidance on the most important issues in the area of public health. They note that an explicit aim of CIOMS (2008) is to unify the

epidemiology guidelines with the clinical trials guidelines (CIOMS 2002), through the use of the same set of ‘General Ethical Principles’ which have their origin in the Belmont report. As a consequence, these proposed ethical principles for epidemiological research fail to capture what is important about population-based research, since the focus is on individuals, and there are no collective concepts such as ‘population’, ‘public’ or ‘community’ that capture the distinct context of these studies. Moreover, Verweij and Dawson note that CIOMS regulations imply that informed consent is so important that there ought to be a presumption in its favour despite the fact that in public health interventions (in particular) there are situations where on balance it might be considered important not to seek individual informed consent (for instance to avoid bias). Finally, the conceptualization of harms and benefits in CIOMS (2008) does not take into account any non-individual benefits and thus that public health studies may involve population or community benefits which the individual may also benefit from (Verweij and Dawson 2009). Considering that the main aim of population-based studies is often not to benefit particular individuals but the communities in which these individuals belong, the principles on which CIOMS guidelines rely provide no guidance on how health investigators should behave towards the tested communities. In order for research guidelines and regulations of health research ethics to be helpful for research committees and investigators, it is important that they differentiate between the distinctive aims of studies, the nature of the intervention involved and the proposed methodology.

The inadequacy of the current research ethics framework to address different types of health research demonstrates the need to establish a more practical and philosophically rigorous approach to identify norms for health research that could guide action without marginalizing population-based research. In the previous chapter, I discussed an alternative research ethics framework based on the human right to health; does this framework capture the distinct moral features of population-based studies?

As previously discussed a moral framework based on human right to health suggests that we should focus on the broader socio-political context in which research initiatives take place. In this framework it is generally assumed that

research on people involves them not merely as individuals but as parts of a larger social unit. Thus, the suggested framework departs from the individualized model of current research ethics guidelines, and as a result may apply to a variety of health studies. Moreover, the suggested framework emphasises the importance of research interventions that directly promote improved health and at the same time lead to further health benefits, through the impact that such improvements would have on socio-economic development, especially for developing settings acknowledging that many factors may impact on the health status of populations and individuals. Thus, within the suggested framework, although new medical discoveries are considered important, non-clinical research (e.g. studies on preventive measures, investigation of causes of diseases), which may affect not only individuals but also whole communities, is viewed as equally or more valuable. Moreover, as discussed in the previous chapter, the human right to health approach would suggest that it is not enough to claim that a study is clinically beneficial or not harmful for an individual to be morally justified. Health research should also have value for the community where the individual/participant belongs (see revised principle of beneficence in Chapter 5). It follows then that in this respect a research ethics framework based on the human right to health, captures and justifies research that is directed towards meeting the ends of population health such as promoting and protecting the health of the public, improving well-being in communities, and contributing to social justice.

In Chapter 5, I argued that considerations of social justice have not received adequate attention in the research ethics literature. I also argued that an ethical framework based on human right to health demands that the main aims of collaborative health research are the reduction of health inequalities and the improvement of the conditions that would enable individuals to meet their basic rights. Based on the discussion above, it could now be clear that although both disease-based and population-based studies in developing countries may be designed to address health disparities and improve the health status of those in need, they may do so in very different ways. Disease-based studies similarly to population-based studies may aim at the treatment of diseases that burden the

most vulnerable populations, for instance children, but support this aim primarily as a way of promoting individual welfare. Failing to identify the significant differences between disease-based and population-based studies will lead us to wrong conclusions when issues such as the need to obtain informed consent from research participants (which is discussed in the next chapters) are raised. A research ethics framework based on the human right to health offers a more comprehensive set of moral principles that should guide any health research initiative on humans but at the same time permits the development of different regulations that will be suitable for different types of studies. Population-based research, according to this framework, is subject to the same general moral principles as disease-based research (justice, beneficence, non maleficence and respect for persons and their communities), but is not considered as morally problematic because of its differences with medical research. In Chapter 8, I will discuss this argument in more detail by presenting different population-based research interventions, such as surveillance, vaccination, environmental studies and others, where informed consent is not feasible. I will explain under what conditions such interventions can be morally justified based on the human right to health approach.

### **6.3 | New ethical challenges in the cluster design**

As discussed in chapter 1 cluster randomised design is an important methodological tool in health research used to test different interventions on human subjects (community based intervention studies, public health research, epidemiological studies, knowledge translation research, quality improvement research). In all these cases intact social units or groups of individuals, rather than individuals themselves, are randomly allocated to differing intervention arms. Since the choice of the trial design depends on the question and hypothesis addressed by the trial (the ways in which a research intervention must be implemented will depend on the aim and the nature of the intervention), ethical challenges raised in cluster trials are related with the type of the study tested (its aims and the nature of the intervention involved). Following the discussion above, it is now clear that new ethical issues presented in cluster randomised trials are due to the distinct features of population-based interventions, which are not

present in conventional medical studies where individual patients are tested for eligibility and then offered entry to the trial<sup>91</sup> In order to address these new moral challenges, we should depart from the paradigm of clinical research and consider the context in which population-based interventions could be justified.

On the other hand, there are problems raised by the cluster design, which are also present in clinical research, when a conventional research design is used (for instance when the use of deception should be morally justified) and for which solutions already exist in the research ethics literature. Distinguishing therefore between different types of health research we could identify a most appropriate way of dealing with ethical issues in cluster trials. Regarding the problem of obtain informed consent in cluster trials (solutions to which are discussed in chapter 8), it seems that a different approach to that suggested in the current literature on cluster ethics should be followed. What is most important to consider is the reasons for which researchers decide to test an intervention by using a cluster design (and whether such reasons are morally justified) before examining the technical features of the study (whether it concerns an individual-cluster or cluster-cluster intervention and thus whether individual consent is feasible or not; see Chapter 2.4).

## 6.4 | Conclusion

As most work in research ethics in recent years has centred on the ethics of clinical medicine, the ethics of population health research has been neglected. Population-based studies, which are often the most effective ways of improving health in developing countries, can differ in important respects from clinical research. The aim of this chapter was to describe the distinct morally relevant features of population based research and explain why they cannot be adequately addressed by the current research ethics framework. Moreover, in this chapter I aimed to demonstrate that in order to effectively resolve issues raised by the use of cluster design we should first consider whether they constitute features of

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<sup>91</sup> For instance, public health interventions often do not focus on individuals but on groups of individuals since they aim to study group level effects. Epidemiological studies are often not easily distinct from other public health activities, since their aim is to collect and analyse data on populations or groups (Verweij and Dawson 2009).

population-based interventions and thus whether they should be addressed beyond the current clinical research ethics framework.

# Chapter 7

## **The role of informed consent in clinical ethics and public health ethics**

In the previous chapter, I argued that new ethical challenges presented in cluster research derive from the distinct features of population-based interventions. I also discussed the reasons for which population-based research and practice significantly differ in moral and practical respects from clinical research and practice, and argued that the traditional clinical research ethics paradigm is not appropriate to provide moral guidance for the conduct of population-based studies and thus for the new<sup>92</sup> challenges presented in cluster randomised trials. In this chapter, I argue that to decide how problems related to the involvement of populations or communities in health research should be addressed, such as whether and how to justify involuntary participation, we should consider how similar health interventions are justified in public health practice and whether the same justifications may be valid for research purposes. However, cluster trials, because of their experimental nature<sup>93</sup> also inherit most of the ‘generic’ issues of

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<sup>92</sup> I consider as new moral challenges those that cannot be adequately addressed by the traditional clinical ethics paradigm.

<sup>93</sup> Definition of research in the Common Rule: “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge”.



health research<sup>94</sup>, as well as similar moral problems with clinical research when clinical procedures are involved. In order then to achieve a comprehensive approach on the issue, we should also examine the reasons for which informed consent is considered an essential requirement in the clinical context, as well as the justifications for allowing exceptions to the consent requirement. Comparing the requirement for informed consent in these two different domains, clinical research and practice and public health, would help us estimate when the informed consent is relevant in cluster research, and thus when it could be waived or considered necessary for the protection of participant interests while taking into account the broader context in which a population-based research activity takes place.

In the following paragraphs, I first explore the justifications for the informed consent requirement when humans subjects are exposed to experimental conditions, and, in particular, when it is feasible, when and why it is important and when it is not feasible and not important to obtain informed consent in the clinical context (7.1). Then I explore the role of informed consent in public health practice to consider the conditions under which it is considered morally legitimate to limit individual freedom or personal autonomy in a population-based context (7.2). In the last session of this chapter (7.3) I discuss the common points between these two different settings and identify three broad categories of cluster studies regarding the issue of informed consent: a) studies where informed consent is necessary, b) studies where the informed consent requirement can be overridden by other moral values and c) studies where informed consent is not relevant. I also explore the justifications and norms concerning the consent requirement that apply in these different domains (public health policy and clinical research and practice) in order to explore which of them may apply in the case of cluster research (issue which I discuss in Chapter 8).

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<sup>94</sup> The investigation of effective means to improve population health suggests that those means might not proved effective while people will be subjected to uncertain risks of harm.

## 7.1 | The role of informed consent in the clinical context

The notion of consent is established in health care law and policy and much of the bioethics literature as a powerful and necessary condition for the moral acceptability of a medical activity. According to the World Medical Association (2013), and other ethical codes and laws, no intervention that may expose someone to significant risk is morally permissible unless the person concerned agrees to being exposed to the risks by waiving her corresponding rights. The core notion of consent has its origins in the 1947 Nuremberg Trials of German physicians (The Nuremberg Code 1947) and was later incorporated into the Declaration of Helsinki and other ethical codes and guidelines. Despite its central role in medical practice and research, there is much dispute on the conditions under which consent is ethically acceptable: the degree to which it is or should be considered informed, explicit, specific, the degree to which it is genuine and informed.

The main disagreements, though, regarding informed consent are about the reasons for which it is ethically important; for instance whether consent is needed to respect a person or to respect the autonomy of a person and if the latter is true, which conception of autonomy is relevant (O'Neill 2002), or whether informed consent procedures are required as a degree of assurance that patients have not been coerced in the course of clinical practice (Faden and Beauchamp 1986; Wolpe 1998; O'Neill 2002) and others. Some of the main arguments put forward for the moral justification of informed consent are presented below:

### 7.1.1 | Justifications for the informed consent requirement in clinical research and practice

#### *Respect for personal autonomy and free choice*

The predominant justification of informed consent requirement is grounded in personal autonomy (Appelbaum et al. 1987). Some argue for a Kantian interpretation “Recognition of every human being as having a unique dignity as human, and as therefore being an end in every relation in which others may morally stand to him, entails that no human being may legitimately be interfered with in pursuing his conception of his happiness in whatever way seems best to

him” (Donagan 1977, p. 31), while others (O'Neill 2003) argue that this rationale illustrates a Millian notion of individuality associated closely enough with well-being: “Over himself, over his own body and mind, the individual is sovereign” (Mill 1869, p. 134). There is also disagreement between the advocates of this view on the extent to which autonomy is good for us. Generally, the concept of autonomy has been used to bear connotations of freedom, independence and self-determination (Schermer 2002). The requirement of informed consent based on personal autonomy in medical research and practice, however, has mainly relied on the influential work of Ruth Faden, Tom Beauchamp and James Childress (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research 1979) and is understood as governance over one’s own agency: “Personal autonomy encompasses, at a minimum, self-rule that is free from both controlling interference by others and from certain limitations such as an inadequate understanding that prevents meaningful choice” (Beauchamp and Childress 2008, p. 100-101). Given the dependency of patients and research subjects on investigators and physicians and the knowledge gap between them, informed consent is considered to secure individuals’ self-control and freedom (Levinde 1998). The importance of personal autonomy is strongly supported in medical experimentation on human subjects as it allows patients the knowledge over what is happening to their bodies and the power to agree or object to it. This interpretation also explains why the requirement of informed consent is especially important in research, in which the knowledge gap is greater, and is accompanied by the right to withdraw from research at any point. According to this argument, lack of consent can never be justified despite any benefits in the end (Kattow 2003).

To justify informed consent on personal autonomy, however, further questions need to be answered. First of all, the role to patients’ autonomy in medical and research decisions seems to be obscured (Varelious 2006). Although there are good reasons to consider that personal autonomy has an instrumental value, as it is plausible to argue that autonomous persons are often in the best position to determine what would be good or bad for them (Sumner 1996), some bioethicists argue that patients should be allowed to make their own choices about their

treatment even if it is clear that others would be in a better position to decide what would serve the patients' wellbeing (Glover 1997; Buchanan and Brock 1990). The latter position is often based on the view that although in certain cases protecting a person's wellbeing and promoting autonomy may conflict, the main reason that we value respect for personal autonomy is that as a general rule people make choices that advance their wellbeing (Gillon 2003). However, the strength of this argument will depend on how we should understand what it is to respect one's autonomy and the weight that should be given to that principle.

Those who follow a non-instrumental account of autonomy argue that it is important to respect people's free choices because people have a right to freely choose what to do with their lives even if such decisions are detrimental to their overall wellbeing'; in other words, when such choices are autonomous they morally ought never to be overridden (Faden and Beauchamp 1986). There are however more serious problems when grounding informed consent in autonomy, based on a non-instrumental account. As O' Neill (2002) notes, a justification of informed consent based on personal autonomy does not clarify whether informed consent is needed to respect a person or to respect the autonomy of a person, and if the latter is true, which conception of autonomy is relevant (O'Neill 2002). Moreover, as Savulescu (1994) argues, not all acts that violate informed consent preclude autonomous decision-making; for instance it has been argued that forced care is legitimate when a capacitated adult refuses an urgent and beneficial operation because of misunderstanding (Savulescu 1994) and that "the state has the right to prevent self-regarding harmful conduct...when... that conduct is substantially non-voluntary..." (Feinberg 1986, p. 12).

Equally, some acts are considered less acceptable than others, despite their similar impact on autonomous action. For instance performing a testicular cancer exam without the patient's informed consent is very problematic and much harder to justify than a non-consensual facial scrutiny on the mole of a patient's cheek to detect cancer (Eyal 2011). The main difference between those cases is not that the patient's exercise of agency has been blocked (the nature and number of their actions and plans haven't been changed) rather that a sensitive area of the patient's body has been touched without the patient's permission, which can

constitute extreme battery (although extreme battery may involve greater interference with a person's autonomy, it may imply extreme contempt towards the patient as a sovereign agent, which is not the case in this example).

Although many bioethicists argue that the main justification for requiring informed consent is our duty to treat each other as autonomous and rational persons, opponents of 'research exceptionalism' note that this does not necessarily explain why the informed consent requirement should be enforceable in research and not in other cases. For instance, we are not legitimately forced not to lie to other persons, although their autonomous decision-making may be breached. But even if we believe that research differs from other daily activities (as I discussed in Chapter 4), we still have to take into account that it is significantly difficult to protect personal autonomy in the clinical context given problems of comprehension, recall, and other circumstantial barriers to patients' understanding (Sugarman et al. 1999; Dawson 2009). It follows then that to establish an enforceable informed consent requirement, we need a more satisfactory account, which does not simply rely on respect for personal autonomy (Eyal 2011).

### ***Protection from abuse or possible harm***

The informed consent requirement is often considered necessary to protect the health and welfare of potential research participants and patients from investigators' overzealous attempts to promote science (Gillet 1989). Advocates of this instrumental rationale for informed consent argue that despite doctors' assurance that their actions are in their patients' or subjects' best interests, research participants are typically the best judges of their own good. This argument reflects a utilitarian rationale against paternalism (Kattow 2003).

The problem, however, with this justification is that it fails to explain why an individual's consent should be respected when an individual makes a decision that is clearly against their medical interests (for instance to fulfil a religious commitment). Although it could be argued that one's best interest in that case is being consistent with their religious beliefs and not with their medical interests, this rationale does not provide a satisfactory account of why informed consent is necessary in the medical context. Its main weakness is that in reality (especially in

the clinical setting) patients and research subjects are usually not capable of fully (or even adequately) understanding medical information and thus not capable of efficiently protecting themselves as their ignorance usually exceeds that of doctors or clinical investigators (as noted in chapter 4, this is the main criticism against the libertarian view which maintains that informed consent is a necessary and sufficient condition for the moral justification of an action between two competent adults). Moreover, following a utilitarian rationale it could be also argued (also discussed in chapter 4) that the requirement to obtain informed consent can be easily overridden when collective health is set back, for instance when a new therapy has to be developed and there are no volunteers to serve as study participants (this will be discussed in more detail later in this chapter).

Informed consent is also considered as having instrumental value in preventing abusive acts such as coercion, deceit or exploitation (Manson and O'Neill 2007). However, by considering the role of informed consent as instrumentally valuable to impede abusive acts, other duties that researchers or physicians have towards their patients and research subjects are disregarded; for instance, a physician's duty to enhance their patient understanding regarding their care despite the fact that their explanations were clear and no deceit or exploitation were involved (Lignou and Edwards 2012)<sup>95</sup>.

Moreover, even if we agree that aim of informed consent is to prevent abusive conduct, fulfilling this requirement is not sufficient to argue for a restricted liability for any possible harmful consequences of research. Informed consent procedures cannot be required as a degree of assurance that patients have not been coerced in the course of clinical practice (Faden and Beauchamp 1986; Wolpe 1998; O'Neill 2002). Since the purpose of a consent form is to record what has been agreed between the researcher and participant, research subjects are not protected from possible harm, except to the extent that the consent form reveals information, which may lead a potential participant to choose to take part in the research and run a certain risk. Finally, what is not explained by this account is

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<sup>95</sup> I consider the instrumental justification being the only form of justification and not part of a more complex account.

why investigators are required to give research participants the opportunity to decide on their participation in conventional clinical research, in cases where investigators are closely monitored and research subjects are not likely to be abused.

### ***Respect for bodily integrity***

Another rationale for the requirement of informed consent is based on bodily integrity. Based on John Locke's idea that "every Man has a Property in his own Person" (Locke 1988, p. 305), under this justification, informed consent is needed even when an intervention is safe, beneficial, low impact and requires no agency on our part. When the owner's permission is not given, intervening into the private sphere of one's body cannot be accepted even when it involves only touching and the owner is foolish or selfish to reject it (Archard 2008; Thomson 1990; Nozick 1986). This rationale emphasises our special relation to our bodies and thus on this interpretation, bodily integrity underlies self-ownership norms. One's body is irreplaceable and inescapable; "If my architect doesn't listen to me and this results in a house I do not like, I can always move. I cannot move from my body." (Dworkin 1988, p. 113). "A prophylactic line that comes close to making the body inviolate" (Dworkin 1983, p. 39). The main argument for obtaining consent from research subjects in medical research according to this approach is that research is liable to be intrusive, and intrusion is only legitimate if consent is obtained. A main problem, however, with this justification is that it fails to explain why intruding in sensitive areas of the body without the owner's consent is worse than intruding less sensitive parts of the body without consent, since violation of someone's property is not a matter of degree. Judith Thomson, for instance, has pointed out that there are different degrees of violation of bodily integrity and she explained that the typical degree of injury to personal integrity also depends on how and why a person's areas are touched (Thomson 1990). Cecile Fabre has argued that a requirement of informed consent based on bodily integrity derives much of its force from the view that by violating an individual's bodily integrity one is interfering with their life to an unacceptable extent. Yet considering the previous example, we could argue that not all violations of bodily

integrity interfere with a person's ability to lead a flourishing life. Moreover, this rationale leaves unclear the relation between bodily integrity and the offense of battery. Let us for instance consider the following example: would it be permissible to treat a patient against their will without touching their skin (and thus without battery) (Brock 1999, p. 529)<sup>96</sup>? It follows then that a straightforward appeal to the importance of the body is not sufficient to argue that informed consent is necessary.

### ***Safeguarding trust in medical practice***

Another rationale for the requirement of informed consent surrounds trust. Onora O'Neill (2002), Torbjorn Tannsjo (1999), Jennifer Jackson (1994) and other bioethicists, attempted to ground the importance of informed consent in its role in safeguarding trust in medical practice: "Autonomy has been a leading idea in philosophical writing on bioethics; trust has been marginal. This strikes me as a surprising... Trust surely is more important, and particularly so for any ethically adequate practice of medicine, science and biotechnology... Informed consent... is generally important [in part] because it can make a distinctive contribution to the restoration of trust" (O'Neill 2002, p. 145). This is a future-looking rationale that underlies the importance of ongoing trust of the society in medical institutions, so the public will continue to accept medical advice, volunteer in medical research, and fill in organ donor cards. Lack of trust in medical research and practice can have worrying consequences. Moreover, as Brock (1999) argued, violating informed consent requirements is wrong not merely because it reduces effective use of medicine, but because it diminishes the 'fragile social source' of trust.

However, an argument that trust in medical practice is necessary for ensuring effective use of medicine is too strong; many patients may provide consent

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<sup>96</sup> For instance, to improve adherence and the care of patients, clinicians and patients' relatives sometimes resort to hiding medication in food or drink. This practice is referred to as covert/surreptitious medication and is well known in the treatment of psychiatrically ill. Medicating patients without their knowledge is not justifiable solely as a means for doctors or families wishing to calm a troublesome patient and thus alleviate some of the burdens of care giving. The paramount principle is ensuring the well-being of a patient who lacks the competence to give informed consent (Latha 2010). Performing this practice to competent adults would be morally unacceptable.



despite the fact that they are, to some extent, distrustful (Bock 1999). In addition, Eyal (2012) has argued that the ‘trust promotion’ argument is consequentialist because it takes the value of informed consent to rely on its role in ensuring trust in medical practice, whereas trust is instrumentally valuable because it promotes health through use of the medical system, compliance with treatment, and participation in research. Moreover, he notes that this rationale does not explain why informed consent should be respected in any case in which the public could never discover that there was a violation of this requirement. For instance, based on this requirement a physician who considers administering a medicine to his patient without consent, should take into account how chemically traceable is the medication, since that would affect future trust of the public to physicians (Eyal 2012).

A different way of arguing for this rationale is by considering informed consent as intrinsically valuable, as a way to honour the fiduciary relationship between a physician and their patients, or a clinical investigator and their subjects (Joffe and Truog 2010). Yet, this justification fails to explain why informed consent is considered necessary for bodily intrusion even when it is outside a fiduciary relationship (for instance between two strangers) (Eyal 2011). It follows therefore that despite its initial appeal, the ‘trust-promotion’ argument fails because the importance of promoting trust in medical practice does not suffice to account for the importance of informed consent.

### ***Pragmatic reasons for obtaining informed consent***

Finally, it could be argued that there are pragmatic reasons for which the requirement to obtain informed consent is considered important. We can claim that, under normal circumstances, research subjects who have consented to their participation in a study are more likely to be willing to cooperate than those who haven’t agreed to take part. This means that obtaining informed consent from research subjects raises the chances of conducting a successful study (John 2005). Although this justification does not take into account any of the reasons for which it is important to respect and protect the interests of research participants and thus cannot be used as a solely moral ground for the consent requirement, it justifies the reasons for which obtaining consent is important even when a study is

beneficial, non intrusive and does not involve any risk of harm (physical, psychological, social etc.) against which participants would need protection.

### ***Informed consent as a person's right***

An alternative way, by which we can consider the relationship between research and consent, is in terms of an individual's rights. Medical research is viewed as taking place against a set of rights and obligations, for instance a right not to be harmed, not to be coerced, and others. The reason, then, that we must obtain informed consent to an individual's participation according to this view is because not to do so would constitute a violation of their rights. Informed consent is necessary for research to be morally justified because it serves to waive one (or various) of their rights, regardless of specific questions regarding personal autonomy (John 2009). This suggests that different kinds of rights and obligations might be relevant to understanding the moral weight we place on consent requirements in various research contexts; for instance, when a study involves surgical intervention the need to gain the subject's consent to their participation might be explained by appeal to their right to bodily integrity. In other cases, informed consent would suggest that a patient waives their special right and relieves their physician of the correspondent special obligation to minimise the risks of physical harm that their patient face by being enrolled in a study that would otherwise involve a breach of this special obligation (John 2009). I consider this comprehensive approach as more convincing from the ones previously presented and will discuss it further in section 7.1.6.

### **7.1.2 | Exceptions to the informed consent requirement: cases where informed consent is not necessary in clinical research**

Despite lack of a clear justification, the requirement of informed consent has a central role in clinical ethics. In clinical research and practice physicians are not permitted to perform any act on a patient's body against their will (although there are cases where a patient's or subject's agreement may be based on invalid consent because of false beliefs, deception, misunderstanding and so on). A possible explanation for this is that in most cases it is practically impossible to gain access to a person's body if some sort of agreement is not given, unless for

instance the person is unconscious or force has been employed (Wertheimer 1987). This however does not mean that the requirement of informed consent is absolute. Not only in clinical practice but also in clinical research there are cases where informed consent is neither necessary nor sufficient for a study to be morally legitimate.

Although in current research ethics guidelines the informed consent requirement is considered paramount, in certain cases medical studies may precede without participant consent. In cases where a research subject is not able to consent (cognitive incompetent adults, unconscious patients) proxy consent, a different kind of consent, is typically given on behalf of the patient by their relatives. Yet, there are cases where research may be conducted though no kind of consent is being given. These cases are discussed below.

### ***Emergency circumstances***

Obtaining consent from patients or research subjects or their families is impossible in emergency medical research. This is because actual consent is infeasible due to the patient's condition (for instance when they are unconscious) and also because in most cases the preferences of the relatives cannot be known in time. In emergency medical experimentation different medical interventions are compared which may not always be in the best interests of research subjects<sup>97</sup>. For the advocates of informed consent a different form of consent justifies these interventions: presumed consent. By presumed consent they mean that “presumably the patient has given actual (albeit tacit) consent” or “presumably, the patient would have consented to the intervention, if, under the current circumstances, they were decision-capacitated” (Eyal 2011). However, this view has been criticised as a contrived ‘myth’ or ‘fiction’ of actual consent (Harmon 1990; Brownsword 2004, p. 232–3; Beauchamp and Childress 2008, p. 107;

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<sup>97</sup> For instance, the CRASH Trial (Corticosteroid Randomisation After Significant Head injury) which started in April 1999, aimed to answer the question of whether or not there is any benefit to giving high dose of corticosteroids after significant head injuries. Patients were randomised to receive either the standard care for head injuries or a 48 hour infusion of corticosteroids in addition to the standard care. Since the trial had to start within 8 hours of injury and all eligible patients had reduced level of consciousness, informed consent was deemed unnecessary (Foex 2001).

Dworkin 1988, p. 117) by some authors who claim that it is fraudulent to presume consent when consent is not explicitly given and when there are no relevant conventions clarifying that silence expresses consent in such cases (Eyal 2011). An alternative and more convincing argument however may also be possible; because the field of emergency medicine cannot progress without experimentation, emergency research interventions are so important that exceptions to consent requirement are justified despite the high level of risk involved (Fost 1998; Largent et al. 2010).

### ***Beneficial and low risk medical care and research interventions***

In routine practices in clinical care, when the risk is very low, for instance when performing a blood test, informed consent requirements are not considered necessary. Following the process that is typically followed in more major medical interventions (i.e. mandatory disclosure and form filling) is considered excessive for routine low risk medical procedures. Even when a patient is ignorant about the procedure, it is generally not considered necessary that they are given detailed explanations about the process, for instance the minor and remote risks related with the use of a sanitized needle pick (Eyal 2011). Likewise, in the research context when research involves only minimal risk to the subjects or the impact of the study is low and the study is considered safe it is generally considered acceptable for review boards to omit some or all elements of the informed consent requirement (Truog et al. 1999). In certain research projects (for instance when two widely used drugs are tested to determine which is more efficient) obtaining consent from those involved is feasible but sometimes omitted, as a requirement for explicit informed consent is viewed as unnecessary<sup>98</sup>.

Low risk beneficial studies are used as an example by those who want to challenge the informed consent requirement and who argue that the way informed consent has been institutionalized in biomedicine is very much a process (Manson and O'Neill 2007, p. 81f), a 'fixation' of bioethicists (O'Neill 2002, p. 47–8;

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<sup>98</sup> In medical research, United States federal regulations authorize review boards to omit informed consent requirements on many occasions when "research involves no more than minimal risk to the subjects" (Eyal 2011).

Brownsword 2004, p. 224). They note that those who argue that informed consent is a necessary requirement in medical research to prevent potential subjects from coerciveness and exploitation need to explain why for studies that involve minimal risk, informed consent is not always required despite the fact that these studies may as well be exploitative.

In response, advocates of informed consent maintain that, in most of these cases, the core of informed consent remains fundamental. For instance, during a blood test, a patient usually gives verbal consent or tacit consent by stretching their arm forward (Beauchamp and Childress 2008, p. 107; Manson and O'Neill 2007, p. 11). Although, problems associated with tacit consent are discussed in the next chapter, this argument illustrates that there are some elements of informed consent that need to be respected even if no risk is involved and interventions are clearly beneficial; For instance no one would agree that if a patient refused to provide blood sample physical duress would be acceptable.

### **7.1.3 | Informed consent as a non sufficient moral requirement in clinical research**

As discussed in chapter 4, a soft form of paternalism is generally accepted in health research (even for libertarians) as it could generally be argued that it is more difficult to solely rely on individual independence (and thus personal autonomy) in medical research compared to other areas of daily life. In many cases this goes without question as patients and research participants have reduced capacity to give informed consent and as a result to express and protect their personal autonomy: children, individuals with cognitive limitations. The same could be argued for cases where ill health limits a person's competence to fully understand or process information. However, even when capacitated adult individuals (whose capacity is not constrained by their health condition) are involved in a medical study, they are not able to fully assess research risks by themselves or understand all the technical details involved. Medical study itself includes stages that are not based and cannot be based on individual consent: research development, testing and evaluation. Thus although competent adults are generally considered capable of deciding what is best for themselves, they actually are not (and cannot be) the main decision-makers regarding the conduct

of a health study, as any health study should be first approved by an ethics committee. If certain rules do not apply (e.g. if the risks involved are not reasonable in relation to anticipated benefits, if the study is not scientifically valid and others), consent from individuals is pointless, as the study cannot be permitted. When such safeguards are in place competent research participants could enjoy a minimum expression of personal autonomy; freedom to refuse or accept what clinical investigators offer them.

#### **7.1.4 | Cases where informed consent is a necessary requirement in clinical research**

Although there is no agreement on what is the right justification for the requirement of informed consent in clinical research, there is a common understanding: when a study involves exposing human subjects to risks of physical or psychological harm it can be ethically permissible only if research subjects have given their informed consent to their participation. Restrictions on what investigators are allowed to do to their human subjects (although those cannot be guaranteed by filling in consent forms) are ethically paramount. Despite these limitations, the principle of voluntary consent is difficult to disagree with when values such as bodily integrity, personal autonomy, integrity may be at risk. Unquestionably, failure to obtain consent, and failure to inform research participants of the consequences of their participation, has been at the root of serious violations of human rights in the past.

#### **7.1.5 | Adjusting the consent requirement on the level of risk in clinical research**

It is obvious from the discussion above that justifying the informed consent requirement is more complex than is usually assumed.

First of all, the overview of the justifications for requiring informed consent in clinical research and practice presented above, illustrates that there is not a straightforward appeal to a single moral principle for which informed consent is essential in medical research. Moreover, although standard exceptions to the consent requirement (research on incompetent to consent participants, emergency research), can be reconciled with its central justifications (Eyal 2011), for instance

in situations where it is clear that personal autonomy cannot be promoted by requiring individual consent<sup>99</sup>, there are other cases where there is no a straightforward justification for omitting consent (cases where informed consent is possible but it is argued that there is no need to obtain it; e.g. low risk beneficial studies). Those cases raise the question of how to assess when informed consent is necessary and based on what justification?

In the Council for International Organisations of Medical Sciences Guidelines it is stated that “by informing the potential subjects...and by ensuring that each individual understands each procedure, investigators elicit their informed consent...” (CIOMS 2002). This statement seems to suggest that investigators are responsible to ensure that information is disclosed in a comprehensible way, ensure that participants’ decisions are based on adequate understanding and that they are not the result of coercion and undue influence. In low-risk research where there is minimal risk of physical, psychological or other harm involved (e.g. in a single blood draw), there is usually no or little concern for possible exploitation and thus for the need to protect research participants' health and welfare through informed consent procedures. In such cases it is possible to replace the implied consent with explicit consent procedures, as in risky and complicated medical procedures. However, it would constitute a laborious process, which is not expected to offer much benefit to those involved. Since information disclosure, understanding and giving permission are main elements of the consent requirement this rationale would suggest that it is acceptable for participants to be enrolled into a health study without their autonomous authorization, when the study is unlikely to pose serious harm to them.

The same justification may also apply in cases where doing research involves performing actions that are indistinguishable from other actions that are performed in a non-research context, for instance when established effective treatments regularly prescribed are compared. In such research studies patients are often not aware that they are part of a study, as patients who are participants in the

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<sup>99</sup> The focus of this analysis is on adults.

research, would otherwise have received either of the tested treatments<sup>100</sup>. Moreover in such research studies potential clinical benefits for participants are considered to outweigh the risks (when a comparative effectiveness study of two established treatments and involve no other research procedures) (Bromwich and Rid 2014). Along these lines, Franklin Miller and Alan Wertheimer have argued that defective understanding does not make consent invalid in studies in which clinically indicated treatments are compared (Miller and Wertheimer 2011), others have question the necessity of seeking specific consent in studies of licensed interventions (Robert Truog et al. 1999) and other research ethicists extend this idea to comparative effectiveness research (Faden et al. 2014). These proposals seem to be supported by recent proposals for regulatory reform. For instance, the European Clinical Research Infrastructures Network suggests disclosing no more than “light information” in trials with marketed drugs that are used for a new indication (European Clinical Research Infrastructures Network 2010).

According to this rationale in low risk studies, individual consent is not necessary and thus lack of informed consent does not necessary make a research study unethical. In other words, we could argue that the requirement of consent even in the clinical context should not be considered as absolute (Emanuel et al. 2000). This justification seems to contradict the view that Jonas and others have expressed that all experimentation, even when it is not harmful, treats the research subject as a passive token and threatens the dignity of the person as a unique individual, which is an essential element in our moral code (Jonas 1969). A similar position has also been expressed by Levine (1988): “The use of a person as a research subject can be justified only if that person, or one authorized to speak on his or her behalf, consent to such use”. In general advocates of the consent requirement usually refer to the history of medical experimentation to claim that exploitation even in low risk studies is possible when individuals are enrolled involuntary. It seems then that though from a consequentialist point of

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<sup>100</sup> As Wilson and Hunter (2010) note even if the treatments involved risky procedures, this does not suggest that the research study was itself risky and thus that subjects consent would be necessary as these risks would have been present even if the research project had not been undertaken. In order research to be morally problematic it must introduce new risks that would not otherwise be present.



view refraining from obtaining consent in low risk and beneficial studies may be easily justified, for a deontologic perspective we still need to explain how the plausible intuition that consent standards should be adapted to the level of risk involved can be compatible with the impermissibility of enrolling competent individuals into studies without their autonomous authorisation (Bromwich and Rid 2014).

As I have already argued an alternative way to justify informed consent requirements is in terms of one's rights. We could consider that informed consent ties together several requirements with different levels of stringency, some of which are necessary in more contexts than others (Eyal 2011). In other words, we could argue that though all the values for which informed consent is important need to be respected (personal autonomy, bodily integrity, personal dignity, self-ownership and others), some of them may be necessary in some contexts and not relevant in others. Therefore although a rationale for informed consent requirement, such as self-ownership may not justify a waiver of informed consent in low risk and beneficial studies, the fact that subjects' welfare and interests are well protected may suggest that the value of self-ownership may not be relevant or equally important in cases where other moral values are met.

In research ethics guidelines it is clear that an individual's right not to be exposed to risks without their consent is much stronger than their right not to be used as research subjects in general without their consent. Moreover, as Bromwich and Rid (2014) note anecdotal evidence suggests that it is common practice for researchers to have short informed consent discussions in low risk studies and some research regulations allow adjustments of some or all elements of informed consent in low risk studies (U.S. Code of Federal Regulations 1991). This view is also supported by empirical research, which shows that potential research subjects in minimal risk research seek less information than what is indicated in informed consent documents (Desch et al. 2011; Antoniou et al. 2011). As Bromwich and Rid (2014) note proper understanding of the standard view of informed consent reveals that consent is more likely to be invalid as the risks of research increase.

Taking into account that a combination of several requirements may justify the need to obtain consent and that those are more likely to be satisfied in low risks studies, it seems reasonable to argue that the requirement to obtain informed consent from research participants should be adapted to the risk–benefit profile of a given study. Moreover it could also be argued that as the risks of research increase, so should concerns about the validity of consent given by the average potential participant and that consent standards should be more relaxed when there is a favourable risk-benefit profile for the individual research subject. However, since research refers to a diverse range of interventions, conclusions that are valid for some purposes and research activities are not necessarily applicable in others. In order to decide then on standards regarding the consent requirement, we should define broad categories of research intervention by the level of risk involved and identify broad types of cases that require robust or minimal consent.

As I discussed earlier in this chapter a better approach to argue for the informed consent requirement in research ethics literature would be to rely on a combination of moral justifications, some of which may be more or less relevant for different interventions. It would be then reasonable to argue that the informed consent process should not only be adapted to physical and psychological risk involved in the study but also to other factors that may threaten some of the values which informed consent is meant to protect; for instance controversy surrounding study aims may significantly affect personal autonomy, trust or the willingness of participants to cooperate (both instrumental and intrinsic justifications of the consent requirement may apply). Although research ethicists (Sreenivasan 2003; Miller and Wertheimer 2011; Truog et al. 1999) and stakeholders in research (European Clinical Research Infrastructures Network 2010) focus almost exclusively on relaxing consent standards in low-risk research, it seems that a more comprehensive risk-adapted perspective on informed consent would be more appropriate. Bromwich and Rid (2014) suggest that although we should shed consent requirements in low-risk and otherwise simple research, we should also add safeguards for consent to higher-risk and more controversial research (Bromwich and Rid 2014) and that it is in the investigators' moral duty to

consider whether a study is likely to be controversial in the target population (whether the research might violate religious or other deeply held beliefs). They also argue that in cases where a study is considered controversial, researchers should informally or formally test whether participants comprehend what they are signing up for. (Bromwich and Rid 2014). Taking these arguments into account we could argue that based on a more comprehensive notion of risk in medical research, the need for robust informed consent is obvious not only when a medical intervention is risky, controversial, physically invasive or when it affects a private area of the body (Archard 2008, Joffe and Truog 2010, p. 358; Miller 2010, p. 391; Beauchamp and Childress 2008, p. 101; Beauchamp 2010, p. 70–1) but also when there are reasons to believe that a competent individual may refuse the intervention (for instance for cultural reasons) .

Finally, as the previous examples have shown, arguing that consent is not an absolute requirement suggests that on occasions where the need for robust informed consent is lesser high costs may easily override that need (Miller 2010, p. 393). Thus the informed consent requirement could be outweighed by competing values, such as the advancement of scientific research<sup>101</sup> even in cases where research subjects may not know that they are in an experiment and thus even in cases where all the elements of the consent requirement are absent. In studies, where informed consent cannot be obtained, for instance when methodological reasons are not compatible with the requirement of consent, there are ways by which the values that consent is meant to protect can be secured for instance by confidentiality or close monitoring.

Based on the discussion above, we can conclude that the consent requirement in the clinical context should not be ‘unquestioned’. A common objection however to this view, by those who consider informed consent as an essential requirement for a research study to be justified, is the risk of repeating the practices of participant abuses in the past. It is important to note though that the main problem

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<sup>101</sup> Outside the clinical context it is clear that the notion of experiment is not necessarily compatible with individual consent. Observational studies, interventional studies in which use deceptive means to produce scientifically valid data are justified and explicitly allowed for waiver of the consent requirement when specific conditions apply.

with such experiments is not related with the fact that informed consent was not obtained by research subjects. There are several reasons for which these studies were unethical: the way research participants were treated, the fact that their interests were not protected, the controversial aims of the studies, the unethical criteria for selection of research subjects, the health condition in which research subjects were while participating and so on. One could argue that if research subjects were free to decide whether they wanted to participate or not they would certainly refused to be involved in such studies. However that objection takes us back to the main point addressed in the previous chapter: those experiments were unethical because they were based on unacceptable conditions (which would not have been approved by a research ethics committee). It follows then that the examples of abuses in human experimentation do not prove that health research without consent should by default be considered as unethical.

## **7.2 | The role of informed consent in public health practice**

In the previous chapter, I argued that new moral challenges in CRTs are related to the distinct features of population-based interventions. To decide then how problems related to our inability to obtain informed consent in CRTs should be understood and addressed, we need to review the role of informed consent in interventions, which aim to promote population health instead of individual health care.

The aim of this section is to discuss several types of public health interventions (environmental health interventions, standards in clinical practice, measures against infectious diseases such as isolation and vaccination, surveillance, the use of medical and personal data for public health purposes, and organ donation) and explore the role of individual freedom in each of them. I focus on particular interventions in public health practice which may be used for research purposes and be implemented by cluster design (these research interventions are discussed further in the next chapter). I then discuss whether the same reasons that justify restriction of individual choice in public health practice could also apply in public

health research<sup>102</sup> taking into account the difference between established and experimental conditions<sup>103</sup>.

## 7.2.1 | Public health interventions

### *Environmental public health interventions*

Let us first consider public health measures in environmental health interventions. In this category fall policies, such as sanitary measures, the protection of food or water supply and the regulation of air quality. In all these examples obtaining individual consent from those affected by the intervention is not considered as necessary.

The main reason for which environmental interventions are considered legitimate despite lack of informed consent is because informed consent procedures are inapplicable when certain types of goods, public goods<sup>104</sup> are to be provided. Public and common goods are goods that individuals cannot attain on their own and thus role of the government is to set constraints in individual decision-making to accommodate the interests of the entire community. In contrast to consumer goods, these goods must be provided (or not provided) for a whole population. Since it is practically impossible to suit variation of individual preferences for

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<sup>102</sup> Or population-based research based on Taylor and Johnson's account in Chapter 6.

<sup>103</sup> My aim thus in this chapter is not to suggest a way of resolving the complex arguments in public health surrounding autonomy at either an individual or population level.

<sup>104</sup> The term public good usually refers to goods or services that are non-rival; i.e. the consumption of the good by one individual does not reduce availability of the good for consumption by others, non-excludable; i.e. no one can be effectively excluded from using the good, and external; i.e. they impose both costs and benefits on individuals Samuelson (1954, 1967). The main moral concern in the provision of public goods is about free riding; if enough people decide not to pay their fair share, then the good will be not be supplies. However, some authors note that the notion of 'public good' is controversial and complicated because it contains large and vague connotations (Zhang 2010) and that the notion common good is more appropriate for goods such as clean water, clean air and sanitation. Common goods are goods, which are non-excludable; i.e. one individual cannot prevent other individuals from using them and rivalrous; i.e. the use by one individual may prevent the use by others. When an individual overuses a common good, it destroys its use for all others. Garret Hardin has called this 'tragedy of the commons' (Hardin 1968), so if everyone was allowed to act according their interests, then the common would not survive. The role of individual autonomy for common and public goods is less important than in the clinical context since individual choices would prevent these goods to be available.

standards of public or common goods (such as the quality of water and air waste disposal), public health measures cannot rely on personal preferences; in contrast, they need to be uniform and compulsory to be effective: “if a public good is provided for any, it has to be provided for many” (O'Neill 2002). It is obvious then that difficulties in obtaining individual consent in the public health setting are more difficult to be resolved compared to those raised in the clinical setting (where for instance obtaining proxy consent may be appropriate).

Another reason for which informed consent is not considered necessary in most environmental health interventions is that they usually involve low risk of harm for the affected individuals. In environmental health interventions, such as water fluoridation, the state interference only limits certain individual choices, which means that fewer concerns for the protection of individual autonomy and personal integrity are raised. In addition therefore to pragmatic reasons, there are moral reasons for not seeking informed consent in environmental health interventions.

In public health interventions personal freedom may be restricted when other more important moral values outweigh the need to obtain informed consent. As already stated decisions concerning public health measures cannot rely on individual preferences because that would make basic public health standards impossible; public health standards, such as environmental health standards, are preconditions to our ability to exercise autonomy or secure bodily integrity in the first place. It follows then that individual choice cannot have the same central role in a public health settings as in the personal life of the individuals or as in individual medical treatment. Moreover, since individuals lack relevant knowledge and expertise on the subject (it would be unreasonable to expect that each individual would be able to decide whether the standards of fluoridation are

appropriate for all those affected<sup>105</sup>), it is obvious that such issues need to be decided at higher level.<sup>106</sup>

In cases where individual choice is not possible (or when there is little room for the individual to act as they wish) community input is considered necessary, so that group interests in the decision-making process are taken into account, especially in cases where there is mistrust on a public health measure. Community consultation, which is not a substitute of individual consent, has been extensively discussed lately (CDC 1997; CDC 2011) and different mechanisms have been developed to incorporate community input for different decisions concerning environmental measures before their implementation. Despite the difficulties that different forms of community consultation present (see discussion in chapter 3) the importance of this strategy is that it takes into account group interests and provides community approval or gives the opportunities for concerns to be raised and addressed to government interventions where individual choice and consent is not possible. Berg (2012) argues that public health officials have corresponding obligations to inform and consult with affected communities in environmental interventions to those that physicians have in the clinical context to disclosure and consent to the surrogates of incompetent patients. Although proxy consent is not applicable in this case, and thus this parallel not successful according to the discussion on informed consent in chapter 2, the right of communities to be informed about these interventions is obvious. In public health measures information disclosure is not only important for the individuals to be aware of risks, benefits and achieve compliance but also for public accountability.

Moreover, although individual choice may be restricted in environmental public health interventions, the rights of the individuals to be informed by the benefits, risks and alternatives are maintained. As Berg (2012) states, while individual decision may not be possible, informational disclosure, another aspect of

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<sup>105</sup> Even for consumer goods some compulsion, in particular for safety standards, to protect the individuals that lack the relevant information is justified.

<sup>106</sup> There is however the risk of corruption and abuse in the public system and for this reason, as I later explain, public health service should be clearly defined and carefully controlled.

informed consent (which aims to protect personal autonomy and self-determination), in these cases should not be neglected: “there is nothing in the analysis of commons or public goods that would support limiting information disclosure. In fact, the information disclosure remains crucial to protect autonomy” (Berg 2012, p. 16). Considering that only personal freedom is constrained by environmental public health interventions, we can argue that by being informed, individuals maintain some aspects of their personal autonomy. This is more evident in certain environmental interventions where there is room for individual choice, for instance in water fluoridation. It seems then that another reason for which municipalities should inform local communities (about for instance the protective measures applied to their water supplies, such as the quality of water, potential benefits and risks of the intervention) is to offer to those that strongly oppose to the intervention the opportunity to opt out by taking alternative measures to the extent individual choice is allowed (e.g. bottled water in the case of water fluoridation).

### ***Regulations in clinical practice***

Another public health measure where individual consent is not considered relevant, and thus necessary, concerns the application of health care interventions at a practice level, such as the introduction of a change in a general treatment policy across a clinician’s practice. Although personal autonomy has a dominant role in the medical context, there are aspects of clinical practice where individual consent is not considered relevant. The number of providers, the kinds of services they deliver; prices and the types (and even quality) of services that can be provided, the introduction and diffusion of new products and technologies are all practices not tailored to individual choice (Rice 2001). Clinical practice is controlled by legislation and regulation (which are also enforced by coercion) and these controls (quality control, institutional certification, inspections), which are aimed at professionals rather than the patients, are considered as acceptable conditions of professional certification and employment and not as threats to doctors’ autonomy. As O’Neill notes: “A focus on clinical medicine has been extended into many discussions of health and justice, which often focus mainly on the just distribution of individual (access to) clinical care. If health provision



considered entirely of clinical provision, it could in practice be based on voluntary, consensual relationships between patient autonomy (however conceived). The good to be distributed could not then be health care itself (let alone health!), but rather access to health care or opportunity for health care. This way of thinking preserves the view that health measures are the province of clinical medicine, and the compulsion is unacceptable outside narrowly defined areas” (O’Neill 2002, p. 38). In sum, clinical care, professional training, institutional structures, public funding, physical facilities are all goods that have to be provided to uniform standards and formats and whose provision can reflect democratic processes, and thereby not individual preferences or expressions of personal autonomy but certain forms of collective choice.

Unlike the public health interventions discussed above, other public health measures may apply at the individual level.

### ***Emergency situations***

In emergency situations public health authorities may quarantine or isolate individuals exposed to contagious diseases to prevent further spread in the community. These measures must apply to individuals despite their will. Justifications for these policies usually rely on Mill’s work ‘on Liberty’. Mill’s theory of justice explicitly opposes compulsion except in very limited circumstances. He claims “the sole end for which mankind are warranted, individually or collectively, in interfering with the liberty of any of their number is self-protection” (Mill 1859, chapter 1). According to this rationale, although a society is better off if people are free to make their own choices and when individual autonomy is promoted, state is justified in limiting individual autonomy to prevent harm to others.

### ***Voluntary and mandatory vaccination programmes***

In non-emergency situations, vaccinations are a typical example of preventive public health measures aimed to protect public safety. There are different ways by which vaccination programmes are implemented: in some programmes individual freedom is severely constrained while others are compatible with personal autonomy. The first category involves mandatory programmes in which

individuals are required to be vaccinated, unless they qualify for an exemption (for health or religious reasons), and where there are financial penalties for those who do not comply. Such measures usually apply as a condition in order individuals to have access in certain sectors such as public school (Hodge and Gostin 2001) or to perform certain professions (health workers) (Berg 2012). The second category includes incentivised or voluntary programmes. In incentivized programmes vaccinations are optional but individuals who comply receive some reward, usually financial. In voluntary programmes complying or not complying involves no penalties or incentives (Nuffield Council on Bioethics 2007). In the case where vaccination is optional or voluntary individuals are able to choose, and thus their personal autonomy is not restricted<sup>107</sup>.

Different arguments for the justification of mandatory vaccination programmes have been put forward. First of all, it is argued that this measure can be relied on hypothetical consent; members of the public understand and accept that vaccination is an appropriate mechanism to prevent contagious diseases. Since population immunity is an important collective benefit, both organized work of society in establishing vaccination schemes and collective action by a community in participating to achieve high levels of vaccination coverage are needed. However, as in preventive interventions in general, a vaccination programme may bring much benefit to the population but relatively small personal benefit for each individual (Rose 1981). Advocates of this measure reply that even in such cases an argument of hypothetical consent remains valid because from the perspective of the individual, the harms of vaccination may outweigh the risks of the disease if herd immunity is achieved.

Yet, the main justification for vaccination programmes that impose important limitations of purely voluntary behaviour is that the consequences of decisions about vaccinations affect not only the people who are considering whether or not to receive a vaccination, but also others. Quasi-mandatory and mandatory approaches shift the emphasis away from protecting the interests of the individual, towards providing benefits to others (Friedman 1970). Another principle on which

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<sup>107</sup> This policy is often compared to ‘nudges’ by Thaler and Sustein (2008).

this measure may rely is fairness. Fairness is a principle that is considered to outweigh personal autonomy in the case of non-voluntary public health interventions in general. As already stated, in Mill's account it could be legitimate to make certain forms of treatment compulsory when the risk of transmission and the severity of the disease is high. O' Neill argues the same could be argued in cases where there is a safe and effective vaccination programme and vulnerable individuals who cannot be vaccinated need to be protected. Mandatory vaccination in those cases is considered legitimate and justifies exposing some individuals to public health burdens for other people's benefit to produce the herd immunity. According to this rationale those who do not have a serious reason to opt out (medical reason) should not put the other members of the population in danger by acting irresponsibly. Therefore, a public health intervention could also be justified relying on considerations of fairness even if it imposes unequal burdens on different members of a population. An example of a public health intervention of this kind is children's vaccination against rubella for the protection of pregnant women and their fetuses (Miller et al. 1997).

Mandatory vaccination programmes however are generally considered controversial measures and are usually implemented in the case of highly contagious diseases (e.g. smallpox) or as a condition for a particular group of people to have access to certain benefits (access to a private school). In contrast to environmental interventions, the use of vaccinations to achieve herd immunity constitutes an example where personal autonomy plays a more important role. Vaccination is a clinical intervention that directly applies to the individual and which in certain cases may have significant implications for one's health (therefore concerns for protection of bodily integrity may apply in this case). For these reasons opting out in non-voluntary vaccination programmes is generally permitted when individuals health may be at risk or when they have other serious reasons to opt out. Moreover, although individual freedom is more restricted in mandatory vaccinations compared to voluntary vaccination programmes, the right of individual to be informed remains, as individuals need to be aware of the risks and benefits of a vaccination, in case they have medical (or religious) reasons to refuse the intervention, and not only to achieve better compliance.

***Organ donation***<sup>108</sup>

Although vaccination programmes in non-emergency situations may offer both direct and indirect benefit to those involved, other policies such as testing all incoming patients for HIV or harvesting organs from healthy deceased persons for transplantation are implemented in order to benefit others. The notion of presumed or tacit consent is often used to justify such policies. The underlying thought is to reverse the usual default assumption about what is permissible and make those who disagree with those policies to opt out. However, even such decisions are considered consistent with a person's sovereignty because those who explicitly indicate their opposition can easily opt out (Sunstein and Thaler 2008).

Opponents of presumed consent argue that it is wrong to presume consent when consent is not explicitly given and when no relevant conventions clarify that silence expresses agreement (Harmon 1990; Brownsword 2004; Beauchamp and Childress 2008; Dworkin 1988). These objections seem to interpret 'presumed consent' as meaning that presumably, individuals have given actual tacit consent and note that it goes too far to assume that, just because a patient fails to carry with them a directive forbidding organ harvesting in the event of death, they can be assumed to be consenting (Eyal 2011). However, advocates of this policy contend that an alternative interpretation is also possible according to which individuals would have presumably consented to the intervention if, under the current circumstances, they were decisionally-capacitated. This view is based on the fact that there is no special information that indicates that the patient would not consent to such policies (Eyal 2011).

According to the advocates of the policy, members of a community are morally obliged to provide other persons with objects of lifesaving value when no cost to themselves is required (Beauchamp 2013). Yet, such public health measures do

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<sup>108</sup> The reason I discuss the organ and tissue procurement policy here is because it provides a useful example of how obligations of social beneficence may be given more attention in public health policy than in the traditional bioethics framework. As I explain in the next chapter an argument for social beneficence may also apply for the justification of certain cluster studies where individual consent is not possible.

not need to be justified in terms of consent. It could also be argued that sometimes, certain values defeat individuals' consent rights. Since the basic reason for having the default be consent instead of non-consent is the considerable benefit to the organ recipient, it could also be argued that when the general benefits are large enough, and the cost for the individual low enough, to permit forgoing informed consent altogether is well justified. Therefore we may believe that consent is important for various reasons (for instance to protect personal autonomy) but argue that such measures should be implemented without seeking individual consent because other values should take priority in terms of promotion of social good.

The organ and tissue procurement policy provides a useful example of how obligations of social beneficence may be given more attention in public health policy than in the traditional bioethics framework. While in the past an absolute right of autonomy was the norm and consent by a decedent before death (or by the family after death) was the only way by which this intervention would be considered as legitimate, the scarcity of organs and tissues and the inefficiency of the system have prompted a reform of the current system aiming at creating more space for social beneficence (Beauchamp 2013).

***The use of an individual's medical information in public surveillance***

Another case where individual consent is not considered necessary in public health policy is in the use of personal medical data for public health purposes, for instance to report an infectious disease, and in the collection of medical information to assess population disease burden (incidence and prevalence of the disease). Although there is a common feature between these public health interventions (public health surveillance and data collection from health records) and clinical care interventions as in both cases information needs to be revealed in order better outcomes to be achieved (in the clinical care setting, patients share medical information to receive better treatment while in public health practice information is shared in order public health to be protected) in the first case an individual's information is revealed irrespectively of their wishes.

The reason that informed consent is not considered relevant in this public health

measure is that the same justifications that require informed consent in the clinical context do not apply in this area. First of all, it is argued that this type of information should not be considered as a property of the individual because it does not include all information about their medical record but relevant information necessary to achieve the particular aim. Moreover, fewer concerns for the protection of individual autonomy may arise, as in such measures non-intervention is involved and thus individual bodily integrity is not at stake. In addition, in most cases such information is anonymised which means that there is less need to protect individual autonomy or personal integrity. When information is not linked to identity, rights based justifications for control of personal information are not considered applicable.

Even if we considered medical information obtained for public health purposes as individual property, it is reasonable to expect that certain uses of such information without informed consent may be permissible. It could be argued that such information should be available without consent because the protection of other principles and rights are more important when determining population level disease burden. However, safeguards to protect individual interests must apply, such as confidentiality.

In certain circumstances, however, there is need to collect identifiable surveillance data, for instance in the mandatory reporting of contagious diseases. The reason that information is not anonymous in such cases is that other individuals, who may be exposed to the disease, should be notified by public health authorities. Similarly then to other preventive measures, collecting identifiable information without obtaining consent is justified in order to prevent harm to others.

There are several objections to the collection and use of surveillance data, in particular regarding consent (Verity and Nicoll 2002). However, advocates of this policy argue that the rights of others not to be harmed may take priority over an individual's right to refuse a procedure such as collecting surveillance data in a non-anonymised way. The competing value of public health that sometimes needs to override personal privacy is recognized by the law, which is strongly rooted in personal autonomy. In Article 8 of the European Convention on Human Rights,

for instance, it is stated that the right to respect for private and family life is limited by the interests of public health and the rights and freedoms of others. Moreover given that certain considerations are satisfied, the Data Protection Act (1998) recognises ‘health purposes’ as a justification for the use of sensitive personal data without the need for consent (Nuffield Council on Bioethics 2007). The main justifications for such measures is that the same standards for seeking individual consent cannot be adopted for public health policies, as this would have considerable social consequences; a significant amount of important healthcare data might not be accessible and effective control of highly infectious diseases would not be possible.

### ***Justifications for restricting individual choice***

The main justification for restrictions of personal autonomy in the public health context often relies on the classical ‘harm principle’. This is because an individual’s actions may significantly affect others and measures for equal standards of protection should apply. However, as already discussed in the examples above, further justifications for which a public health measure that restricts personal autonomy may also be possible; for instance the importance to reduce health inequalities, the duty to protect vulnerable groups of the population or duties of social beneficence when the cost for the individual is relatively small. As the reasons for which a state may intervene in a public health context and restrict individual autonomy will vary depending on the context (to ensure public safety, to achieve general welfare and social justice and others), different justifications may apply for defending the obligations of individuals to restrict their freedom to public health powers. In certain cases these obligations may rely on arguments of fairness, in others on the duty not to harm others, while in other cases an argument for political obligation to the community where individuals live to accept certain public health interventions may apply. It seems then that more than a single justification may be possible for the exercise of the state authority in the public health context and the corresponding obligations of the individuals to submit to this authority and limit their freedom. In chapter 8 I discuss which of these justifications may apply when different public health interventions are used for research purposes.

### 7.2.2 | Procedural justice approach

Much of the discussion in the bioethics literature aims to establish personal autonomy and individual consent as the cornerstones of biomedical ethics irrespectively of whether a medical intervention is aimed at benefiting the person concerned (as in the case of clinical care) or whether it is aimed primarily at benefiting others (as in non-beneficial studies). However, many of the issues raised by public health measures differ from those usually addressed in medical research. The principal aim of public health policy is to promote people's capability to be healthy, and not simply to promote respect for the autonomous deliberation of individuals or the provision of a greater opportunity to make choices. Moreover, in the public health area complex questions are raised about the relationship between the state and the individuals that are affected by its policies, and the duties that individuals have towards each other. The question of what weight consent can carry in these cases, and when it is, and is not, required is an important issue, which cannot be adequately addressed by relying on the principles of the clinical context.

Moreover, while in the clinical context individual consent is considered necessary to authorise the implementation of a procedure, for public health interventions, which do not involve considerable risks, a different kind of consent underlies their legitimacy. A 'procedural justice' approach that uses conventional democratic decision-making processes may be sufficient to give an authorisation to implement a certain policy. Thus, although individuals are denied the right to make individual decisions regarding interventions that affect them, they retain the right to be informed, the right to have a say and the right to be heard. Health authorities are obliged to disclose information concerning public health interventions, especially when a procedural justice approach involves the public. For this reason transparency is considered a main element of the procedural justice approach, as evidence on the reasons and rationales for which a given intervention may reduce some choice of individuals or bring inconvenience is necessary.

Another important element of the procedural justice approach is that those affected acknowledge the intervention as being helpful in meeting health needs



fairly. Involvement of individuals and stakeholder groups in decision-making processes is important in order opportunities to challenge interventions in preparation and in practice to be given. When individual consent is not necessary, and thus can be replaced with a procedural justice approach, procedural justice arrangements can form an appropriate means of reconciling different preferences within a population (these procedures typically involve: publishing plans for programmes in formats that are suitable for the public; a period of consultation; and a response to the issues raised during the consultation (Nuffield Council on Bioethics 2007). Thus although final policies may not meet with everyone's approval, there needs to be clear justification in reducing individual choices (Nuffield Council on Bioethics 2007).

### **7.2.3 | Adjusting the consent requirement on the level of risk and degree of intrusion in public health practice**

Although public health requires interventions that involve restrictions of choice, a straightforward argument in favour of state public health intervention to limit personal freedom and to restrict the right of individuals to control the application of interventions that may affect them is not possible. There are many different examples of how individual liberties are treated in health policy: in certain cases it may be impossible and pointless to obtain individual consent from all those affected (e.g. in environmental interventions, safety standards), other cases are more similar with the exceptions of the consent requirement in the clinical context (e.g. in emergency situations) and finally there are cases where although obtaining consent is possible its use should be limited because other moral principles are considered more important to personal autonomy, such as the duty of justice or the duty of social beneficence (e.g. in organ donation, mandatory vaccinations). Since different reasons for restricting individual choice and different standards for consent requirements may apply in various circumstances, it seems that a unique solution to the difficulties of obtaining informed consent in population-based interventions is not possible.

Yet, it is evident from the examples discussed above that the nature of the intervention and the level of risk involved, are morally relevant factors when considering the role of informed consent in the public health context. Based on

the discussion above, it seems that when an intervention is not directly applied to a particular individual (as in medical procedures) but at community level the requirement to obtain individual consent is weaker. When nonintrusive public health measures are implemented at community or practice level (e.g. for the provision of health-conducive environments, safety regulations), obtaining informed consent from each person affected by the interventions may be infeasible and certainly impractical. However, because of the low level of risk involved, personal autonomy is not threatened and thus a requirement to obtain individual consent is not considered as relevant. Yet, in such cases other measures for the protection of individual interests need to be implemented (e.g. community consultation for the evaluation and designing of public health interventions, and safeguards such as anonymising data in the use of patients' healthcare data for public health surveillance), to ensure that despite lack of consent individual interests are still protected.

Other measures may concern medical interventions and need to be implemented directly to the individual, for instance vaccinations, preventive medical testing for HIV, organ procurement. In the examples discussed earlier it is evident that although informed consent is practically possible, some individual-level interventions may be implemented without seeking consent from those affected, in order to benefit others (organ donation from the deceased) or to protect others from harm (medical testing for HIV). Social beneficence may justify restriction of personal choice in a public health policy when the cost for the individual is low and the expected benefit is considerable (e.g. organ donation from healthy deceased individuals). In other cases, protection from harm may justify even higher risk imposed to individuals (as in mandatory vaccination to limit the spread of serious contagious diseases to vulnerable groups). Yet, it is important to note that although, individual freedom is constrained in all these cases personal autonomy is not completely limited. In non-emergency individual level interventions, individuals may be assumed to agree with the policy but they still are offered the option to opt out (and thus they maintain the right to authorize whether an intervention would directly apply on them). When the aim of the policy is to benefit others, as in the case of organ donation, opting out is easy.

When the aim of the policy is to prevent harm to others, as in mandatory vaccination, opting out may need to rely on serious reasons such as risk of compromising a person's bodily integrity.

Although in public health settings individuals do not have the same control they have in the clinical context when they make decisions about their treatments, obtaining consent is crucial in legitimizing interventions when there are health risks to the individuals. Note for instance that even in mandatory vaccinations (in which there may be more than minimal risk to the individual involved) informed consent is still applicable. In general, it is argued that the acceptability of any policy should be considered in relation to the balance of risks and benefits, the potential of alternatives, and, in the case of harms involved, to the role of consent. (Nuffield Council on Bioethics 2007) However, since most public health measures do not concern medical interventions, risk is not the only factor that should be taken into account. To assess the acceptability and justification of different public health policies where individual consent is not possible we should also consider the degree at which the policy maker intervenes.

Different policy initiatives involve different degrees of invasiveness in relation to their particular goal; as there is a range of liberty-reducing legislative or regulatory measures that have been introduced by the state, a one-size-fits-all requirement of informed consent cannot serve most practical purposes. For this reason, the Nuffield Council on Bioethics has proposed an 'intervention ladder' to offer a tool for thinking about the acceptability and justification of different policy initiatives (Nuffield Council on Bioethics 2007). At one end is the least intrusive step: 'to do nothing', or at most monitor the situation, and at the other end what is presented as the most intrusive option, eliminating choice altogether (as in compulsory isolation). The Council states that all rungs on the ladder, including doing nothing, require justification but that in general, the higher the rung on the ladder at which the policy maker intervenes, the stronger the justification has to be<sup>109</sup>. Based on the Council's proposal, the 'intervention ladder', to analyse the

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<sup>109</sup> The Council explains that a more intrusive policy initiative is likely to be publicly acceptable only if there is a clear indication that it will produce the desired effect, and

moral acceptability of a public health measure, we could define broad categories of public health interventions as more or less intrusive and then identify broad categories of interventions that require robust consent in some cases and only minimal consent in others (Nuffield Council on Bioethics 2007, p. 41-3).

Taking the examples mentioned earlier into account, we could argue that to assess the acceptability and justification of different policy initiatives, where informed consent is not possible, we should focus on the degree of invasiveness (therefore the amount of freedom to be sacrificed) in relation to a particular goal (how this relates to the extent of the benefits across society). The same degree of freedom sacrifice cannot be considered acceptable for all public health purposes, for instance both to protect vulnerable groups from a serious epidemic and also to force individuals into leading healthy lives. Similarly, the aims and expected benefit of different research projects should determine the degree of freedom that would be acceptable to ask cluster members/ citizens to sacrifice, as I discuss in the next chapter.

### **7.3 | Some common points regarding the informed consent requirement between clinical research and public health interventions**

As it is obvious from the discussion above, informed consent is a requirement that legitimates certain actions, however in neither clinical research nor public health practice it constitutes an absolute requirement.

Both clinical research studies and public health measures refer to a diverse range of interventions and thus a straightforward argument regarding the importance of informed consent for all possible cases is not feasible. There is however a basic moral criterion based on which we can assess whether an intervention (in both the clinical and the public health context) can be morally justified, when individual consent is not possible; the level of risk involved<sup>110</sup>. In the previous section I

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that this can be weighed favourably against any loss of liberty that may result (paragraphs 3.37–3.38).

<sup>110</sup> Emergency situations are excepted from this rule. Despite the level of risk involved waiving the informed consent requirement is common in both clinical research and

argued for a comprehensive definition of risk taking into account a variety of factors that may threaten the moral values which informed consent is designed to protect (bodily integrity, personal autonomy, self-determination and others). I claimed that not only physical and psychological risk for the individual should be taken into account but also community risk, when for instance an intervention is not compatible with the cultural or social values of the community where the intervention is implemented or in which the affected individual belongs or when social, financial or other types of interests may be threatened. In the case of public health measures in particular where medical procedures are not involved, I claimed that the level of intrusion in the personal sphere should also be taken into account. I concluded that typically, when a competent adult does not give voluntary informed consent to an intervention in their body or private sphere, when the intervention is substantial, involves considerable risk or restriction of personal freedom and does not prevent severe harm to others, cannot be morally permissible, even if it aims to assist the individual or other people would benefit from it.

I also noted that on certain occasions in both the clinical and public health context where the need for robust informed consent is lesser (Miller 2010, p. 393) the informed consent requirement could be overridden by competing values, such as the advancement of scientific research (I referred to the example of data collection in public health area and the use of deceptive methods in clinical research). In such cases a waiver of consent may justify the conduct of a biomedical study and democratic procedures generate the permissibility of a public health measure. Finally, I argued that when no risk or minimal risk is involved and the intervention is considered or expected to be beneficial, individual consent may not be necessary (consent is not intrinsic valuable in such cases). I reviewed as a typical example of clinical research the comparison of the effectiveness of two widely used medical interventions and in the public health setting the evaluation of different models of care.

To illustrate how my previous arguments regarding the role of informed consent in both clinical research and public health policy may apply in cluster trials, let us consider a useful distinction that Spicker (2007) has made between the rights of participants in research. He distinguishes between particular rights and general human rights. He notes that participant rights are special to individuals by virtue of their relationship with the research investigator while general rights apply to everyone. Particular rights are negotiable and they mandate that researchers should behave with integrity towards their research subjects; if for instance they promise confidentiality, they should hold to it, and if they are conducting a study where confidentiality cannot be maintained, they should not be promising it (Israel 2004). Research participants also have general rights, human rights, for instance the right not to be exploited. These rights should not be compromised. Following Spicker's view, we could claim that individuals (whether they are considered as citizens or research subjects<sup>111</sup>) do not have a strong general right not to have their liberty or choices affected without their consent, contrasted to a right not to be submitted to risk of harm (with the exception of emergency situations) without their consent. In the first case lack of consent constitutes a particular right, which can be negotiated for low risk and beneficial interventions while in the latter case lack of authorisation to be submitted to substantial risk constitutes exploitation and thus violation of a general right (for this reason as I discuss in chapter 8 in such cases individuals should not be allowed to delegate their right to accept or refuse a risky intervention to their representatives).

Based on the arguments above, it follows that to decide on the appropriate informed consent standards that should be followed in a population-based health research implemented by cluster design (research which aims to improve population health but at the same time raises challenges for the protection of individual interests) it is important first to consider whether the study in question concerns a clinical or non-clinical activity<sup>112</sup>. Then based on the features of each

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<sup>111</sup> Both of these roles may be relevant in population-based research as I later explain.

<sup>112</sup> Clinical activities directly apply to individuals and thus are more likely to compromise the values (personal integrity, personal autonomy, the notion of self-ownership and others) which informed consent is designed to protect.

study we should define broad categories of research intervention by the level of risk involved (distinguish them as more or less or non-risky) and the level of intrusion involved (their impact on personal freedom). In this way we can identify broad types of cases that require robust consent, minimal consent or a waiver of consent when a study concerns a medical intervention or directly applies to individuals (and thus where individual choice is relevant), and cases where explicit individual consent is needed or a replacement of individual consent with a procedural justice approach when a study concerns an intervention that applies in practice or community level. In the next chapter I discuss solutions to problems related with our inability to obtain informed consent in cluster trials in detail, based on these distinctions.

## **7.4 | Conclusion**

The aim of this chapter was to explore the role of informed consent in clinical research and public health practice. I concluded that despite their differences (aims, nature of intervention involved and others) interventions in both clinical research and public health context may be morally justified when individual consent is not possible. I argued that a basic moral criterion for assessing the moral permissibility of an intervention in the absence of informed consent is the level of risk involved. I concluded that informed consent requirements in cluster trials should be adjusted to the level of risk involved relying on a more comprehensive definition of research risk to that found in current research ethics guidelines.

# Chapter 8

## **Revisiting the problem of informed consent in cluster trials: how should a cluster study proceed if informed consent is not possible?**

In chapter 1 I presented the reasons for which cluster design is used in health research; these may be related to the nature of the intervention and the aims of the study (interventions that cannot be rigorously tested through individual randomisation), the study methodology (e.g. our need to avoid contamination), administrative convenience (where special equipment and personnel are required) or other political and cultural causes (e.g. when there is no tradition of individual consent in the host country). In all these cases obtaining consent from research participants may be problematic (either because it is practically infeasible or because it is undesirable to take permission from each individual affected). The aim of this chapter is to suggest solutions to the question: how should a cluster study proceed if informed consent is not possible? Since the reasons for which informed consent may be problematic will significantly differ in practical and moral respects in different cluster studies, in order to successfully address this question this chapter is divided in four parts. In the first part (8.1.) I focus on moral challenges that derive from the distinct features of population-based research which haven't been adequately addressed in current guidelines and I suggest solutions; these problems are related to the nature of the intervention and the aims of the study. In part 8.2, I discuss problems that researchers may also encounter in other health designs, most of which have been extensively discussed



in the research ethics literature. In part 8.3 I discuss the reasons for which solutions to the informed consent problem presented in current discussions on cluster ethics are not satisfactory and in the last section (8.4) I discuss the procedures that should be followed to ensure that a cluster trial is morally legitimate to proceed despite the absence of informed consent and how my arguments relate to the earlier discussion about the Human Right to Health.

In the following paragraphs I also discuss solutions to the questions I presented in chapters 1 and 4 related with our inability to obtain individual consent in cluster trials: e.g. when is a cluster trial morally legitimate to be carried out despite the lack of individual consent? When does the inability to obtain individual informed consent violate the rights of participants to make their own decisions about their participation? Is consent required from the communities involved additionally to individual informed consent? If so who has the authority to speak on behalf of community and based on what criteria? In which cases should researchers refrain from using a cluster design?

## **8.1 | New moral challenges associated with the informed consent requirement in cluster research**

### **8.1.1 | New moral challenges related to the nature or level of intervention**

In this section I focus on health studies for which an RCT design would have been impossible (i.e. studies that involve interventions that cannot be rigorously tested through individual randomization). By examining examples of social, behavioural, and community-level interventions in public health, I will discuss cases where it is practically impossible or incompatible with the aims of the study to obtain individual consent on both logical and logistical grounds. Following the discussion in chapter 6 I will demonstrate how problems concerning cluster randomisation, cluster level interventions or cluster size are related to the distinct features of population-based interventions.

In the following paragraphs I review several population-based research interventions implemented by cluster design, which are repeatedly discussed in research reports and research ethics debates. An important moral feature of the

research interventions discussed below is that they involve minimal or insignificant risk or intrusion to personal freedom. I argue that in none of these studies seeking informed consent from participants is necessary. Moreover I argue that because of the common moral features between public health measures and population-based research, some of the reasons that justify limiting personal freedom for the general benefit in public health practice could also apply in population-based research implemented by cluster design, despite the fact that in the latter case individuals are exposed to experimental rather than established interventions.

### ***Environmental and other community level interventions***

First of all, let us consider logical reasons for which individual consent may be proved problematic in cluster trials. When an intervention is delivered at a community rather than an individual level, it is not possible to provide each individual affected with a choice: first because the implementation of an intervention across a whole community (cluster) means that it would be impossible to accommodate differing choices of every individual member and second because individuals who oppose to the intervention cannot opt out of the trial. Such studies usually concern environmental public health interventions, such as programs aimed at reducing the incidence of dengue fever (Vanlerberghe et al. 2009), water fluoridation, or mosquito vector controls. When small-size clusters are involved, seeking consent from each cluster member may in theory be possible. However, in such studies individuals cannot realistically exclude themselves from receiving the intervention, and thus seeking informed consent would be pointless as it would undermine the very purpose of consent (unless refusal or consent from individual cluster-member were deemed to constitute some sort of veto on the research program as a whole (Sim and Dawson 2012)).

There also may be logistical reasons for which informed consent would render a cluster study infeasible (Donner and Klar 2004; Vanlerberghe et al. 2009). Certain environmental, or behavioural and social population health interventions that need to be delivered at the cluster level may involve large geographical communities and areas. Because of the size of the study group, logistics (such as timing or difficulties to identify research participants) may suggest that obtaining consent

from all those affected could be very difficult or even impossible (National Bioethics Advisory Commission 1999). Although researchers may wish to be able to enrol in their studies only those individuals who consent, for pragmatic reasons they cannot identify or separate them from those who are not willing to participate (see for instance the example discussed in Chapter 1 of a CRT, which tested the effectiveness of a new insecticide in controlling malaria rates in rural Pakistan. Each of the nine study sectors contained approximately 2000 people living in 400 homes).

In current research ethics discussions as well as the MRC guidelines it is argued that in such cases the role of the guardian is key to the ethical conduct of the cluster trials as they could serve as proxy decision-makers. Moreover, in CIOMS guidelines it is stated that when an intervention is implemented at community level researchers should seek consent from community leaders. As I have already explained (in chapters 2 and 3) this approach is problematic, because none of these solutions constitutes a substitute of informed consent (I discussed this in chapter 3). Yet the fact that the suggested solutions are problematic does not indicate that such studies should not go ahead. As I have already argued when a population-based intervention needs to be implemented at group level and involves only minimal risk or interference with personal life, individual consent is not necessary (see discussion in Chapter 7).

When individual consent is not necessary for a research intervention to be conducted there is no need to search for valid substitutes of informed consent or other proposals that could bridge the legitimacy deficit for cluster-randomized trials. Environmental or community level research interventions that involve minimal or no risk could be decided at a higher level, as in the case of public health measures. The provision of WHO/CIOMS guidelines in the case of community-based research could inform research ethics guidelines concerning this kind of cluster research, even when a study does not target a politically or socially organized community<sup>113</sup>: “Where research is undertaken on a community

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<sup>113</sup> A possible tension between a scientific and lay definition of community is discussed in the Appendix.

basis - for example by experimental treatment of water supplies, by health services research ...individual consent on a person-to-person basis may not be feasible and the ultimate decision to undertake the research will rest with the responsible public health authority.” (2002, Guideline 10) In the category of low risk population-based research fall many cluster research interventions, such as, educational practice, data collection including interviews, medical records review and surveys (McRae et al. 2011) experimental treatment of water supplies or of new insecticides<sup>114</sup>, experimental treatment of new prophylactic or immunizing agents, and of nutritional adjuvants or substitutes.

### ***Surveillance and data collection procedures***

Another case of cluster research where informed consent is not possible, because of the size of the clusters involved, concerns the use of existing data on medical records and registries in epidemiological studies. As discussed in the previous chapter, for the legitimacy of such procedures in public health practice a requirement to obtain informed consent is considered irrelevant. These arguments could directly apply in cluster research in cases where there is no a clear line between public health surveillance and public health research interventions (given that specific safeguards apply)<sup>115</sup>. The main however justification for not requiring individual consent in surveillance and data collection procedures in general is the fact that research data are anonymised and thus that there is no considerable risk involved.

In certain cases however, it may be necessary to collect identifiable private information for research purposes. Taking into account that research intervention is applied at the level of a practice and that it does not affect patient care or other important values we could argue that even for such studies a waiver of consent could be appropriate when the study would not be possible otherwise. An additional reason for which we could consider informed consent as irrelevant in

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<sup>114</sup> When insecticides have undergone prior safety and efficacy testing (Rowland et al. 2000) do not constitute additional risks for the participants.

<sup>115</sup> The same rule also applies in RCT design. There are no different standards for seeking consent where there is not difference between routine and experimental care as I discussed in chapter 7 (when comparing the efficacy of two licensed therapies).

such cases is the fact that the risk involved is a technical matter that few individuals could assess reliably (i.e. in observation studies of an electronic health records the risk is considered to be the breach of data security and confidentiality which extends the capacities of most people (Eyal 2011)). As I have already argued informed consent is not an absolute ethical standard, but a means of securing respect for other, more basic values or aims. Given that specific protections are taken, we could argue that seeking consent from participants is not necessary because a requirement to obtain individual consent could not improve such protections further. These conclusions are compatible with the CIOMS provision: “when the research design involves no more than minimal risk and a requirement of individual consent would make the conduct of the research impracticable (for example where the research involves only excerpting data from subjects’ records) the ethical review committee may waive some or all of the elements of informed consent” (CIOMS 2002, Guideline 5).

In general much of the information collected in epidemiological surveillance studies is beneficial to community health (Gostin 1991). Yet, although cluster member interests may not be directly affected in surveillance and data collection procedures, we should not neglect the risk that certain epidemiological surveillance studies may involve in undermining the dignity of a cluster or community. Though individual interests may not be at risk (especially when collected data are anonymised) the rights of host populations to express their views concerning the collection, use and dissemination of their data when the risk of stigmatization is present should be well recognized and protected (for instance in HIV/AIDS trials or genomic research involving aboriginal or indigenous groups (Bankert and Amdur 2006, p. 137)). Such provision is missing from CIOMS guidelines, which suggests that there is pressing need for guidance on how community or group interests should be protected when such studies are carried out (I discuss this further in 8.4).

### ***Health services and knowledge translation research***

Obtaining informed consent in cluster research may be problematic because of the nature of the intervention. In Health services and knowledge translation

research<sup>116</sup>, individual consent may be practically impossible because the results of the study cannot be applied selectively to individuals who are patients in the cluster. When cluster design is implemented to assess the effectiveness of alternative health policies and models of care<sup>117</sup> seeking consent from individual patients is practically difficult as whole health care units are randomized and the intervention is either administered to the health professionals (training or education) (Figueiras et al. 2006) or involves changes to the health care organization (Taljaard et al. 2009).

For this kind of studies where the immediate target of the intervention is not the cluster members (e.g. patients) but the practitioner (Hutton et al. 2008), we can argue that the interests of the individuals are not directly affected by the intervention. McRae et al. have claimed that a waiver of consent is justified in such cases because cluster members do not constitute research subjects in the strict sense and regulatory and ethical requirements for informed consent only apply to research subjects. Their view seems compatible with my conclusions in Chapter 7.

Not having the right of veto over all choices that affect an individual is most unusual in the context of health research. However that is perfectly in order in other areas of everyday life; for instance obeying the law, paying taxes or providing public services are not practices tailored to individual choice. Even within the sphere of medicine, individual consent is not normally considered necessary in relation to health care interventions when applied at a practice level, for instance, when introducing a change in a general treatment policy across a clinician's practice (or when a public health measure is implemented within a

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<sup>116</sup> Health services and knowledge translation CRTs commonly apply to health professionals and measure patient outcomes for the assessment of organizational change (McRae et al. 2011).

<sup>117</sup> As the outcomes of RCTs cannot be generalized to the broad population (vulnerable groups are usually excluded), and they do not provide information about performance under real-life conditions (Sabin et al. 2008) conventional randomized trials typically address 'efficacy' (performance in subjects most likely to respond favorably under optimal treatment conditions) rather than 'effectiveness' (performance under real-life conditions) to generalize the results of clinical trials to ordinary practice settings (Sabin et al. 2008).

community as I discussed earlier). As noted by Onora O’Neill, there are some public goods that we need to provide as a community that cannot be tailored to individual choice. “Clinical care itself has to be provided to standards and formats that are also largely fixed and uniform, and so cannot be treated as a matter for informed consent. The scaffolding of professional training, of institutional structures, of public funding, of physical facilities are all public goods. The public provision of health care can reflect democratic process, and thereby certain forms of collective choice; but its basic structures cannot be geared to individual choice.” (O’Neill, 2004, p. 1135) As Sim and Dawson point out, the fact that these interventions are not subject to individual agreement is not a matter of practicality. It rather reflects an acceptance that such measures, practices are legitimately decided at a higher level: “This may reflect a greater willingness to delegate decision making to professionals in respect of community-level interventions and a tacit acknowledgment on the part of patients that they lack the same central role in such decisions that they possess in relation to individual care” (Sim and Dawson 2012). Delegating these decisions to government institutions is essential so that general welfare can be achieved.

Cluster trials in such cases seem to share some of the features of everyday health care arena, when interventions are implemented at a practice level. Consent is irrelevant with the authorisation of an intervention and thus the acceptability of the intervention should be guided by other ethical considerations. This conclusion is compatible with the solution that MRC guidelines suggest; when the intervention is at the level of a practice and it does not affect patient care, it is provided that explicit consent from individuals is not necessary.

***Low research risk, participant rights and civic duties in population-based research***

Similarly to public health practice, when nonintrusive population-based research interventions are implemented at community or practice level, obtaining informed consent from each person affected by the interventions may be infeasible and certainly impractical. As explained in chapter 4, by obtaining informed consent we ensure that an individual has accepted the aims of the study and thus that it is legitimate to expose them to research risks for the general benefit. However, in

Chapter 7 I concluded that when research risk is minimal or insignificant participant interests are not compromised (taking into account that other safeguards also apply) and that a waiver of informed consent may be appropriate for both disease-based or population based research. Moreover, in the previous chapter, I argued that when an intervention in public health practice involves only minimal risk or intrusion in personal life, other morally relevant considerations than personal autonomy should take priority, such as the protection or improvement of population health. Based on the common moral features between population-based research and public health interventions we could argue that when a research population-based intervention does not interfere with important values of personal or community life, it is acceptable to require cluster members to sacrifice some freedom (and thus oblige them to participate in a trial from which they have no option to opt out) in order to secure certain social benefits; for instance to protect the most vulnerable members in the community by testing a new prophylactic agent.

We could also argue that by participating in low risk population-based research, cluster members are fulfilling their civic duty because of their contribution to a study which aims to correct health and social disparities and which is connected to social justice. This argument cannot be valid for disease-based research<sup>118</sup>, unless it aims to find treatments for diseases/conditions that affect the most vulnerable or disadvantaged groups of the population (e.g. medical research on children). As discussed in chapter 4, Rhodes argued that we all have a moral duty to participate in medical research and that valuable studies should not be restricted due to low recruitment rates. However, in clinical studies, low recruitment rates often concern non-beneficial trials or high-risk research (for which consent would otherwise be necessary) (Bromwich and Rid 2015) and for which only few people would be eligible (participants in unique conditions are needed who are already in vulnerable position because of their disease; e.g. patients suffering from

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<sup>118</sup> As discussed in Chapter 6, there is a morally relevant difference between population-based and disease-based studies: a condition or disease is considered a population-based concern because the community, in which individuals live or belong to, is at risk of this condition or disease and not because of risk or vulnerabilities sustained by the individual members of these communities.



Alzheimer disease (Grill and Karlawish 2010)), whereas population-based research usually targets healthy individuals or those at risk of contracting a disease. Moreover, as discussed in Chapter 6 a distinct moral feature of population-based interventions is their commitment to social justice (which disease-based studies do not necessarily share). It follows then that the examples which advocates for a moral duty to participate in research refer to, such as jury service and taxation, could, as a general rule, serve as better moral analogies to population-based studies where everyone's contribution is necessary to achieve public or common good. Of course, a moral and civic duty to participate in population-based research would suggest that we should always assess the amount of freedom to be sacrificed and how this relates to the extent of the benefits across community and the needs of the host population in general.

In the previous chapter I also argued that minimal risk should not be defined as commensurate with the risks of daily life of people living in risky environments, rejecting in this way the idea of relative risk (discussed in Chapter 5). I claimed that research risk should be defined more broadly and include not only health interests but also welfare interests and community interests such as financial interests, cultural values and legal interests of the populations targeted by research projects (ensuring in this way that health research is not considered as an isolated activity but within the broader socio-political context in which it takes place). I also suggested the use of an 'intervention ladder' in order to define broad categories of research intervention as more or less risky and intrusive and so to identify cluster randomized trials where robust individual consent is required and those studies where seeking informed consent from individuals is less important or irrelevant. Having examined possible risks for both the individuals and their communities in the examples of cluster research described in 8.1.1. I concluded that lack of individual consent does not make any of these studies problematic because it does not violate the basic rights of participants who are deprived of their particular right to choose. We can conclude that the examples of cluster research described above could serve as paradigms of the "less risky and intrusive" category of health research and that they could be used to help health investigators to assess whether seeking individual consent in their study is

necessary.

***Instrumental reasons for obtaining consent in low risk research***

The examples discussed so far concern cluster-cluster studies where seeking informed consent is infeasible but also unnecessary. However, in contrast to what is often assumed, cluster-cluster trials do not necessarily raise consent issues. In certain cluster-cluster health studies individual consent is possible (i.e. easy to obtain) yet unnecessary. When research risk is low and the study is implemented at a community level, lack of informed consent will not affect the moral integrity of the study but researchers may consider important to obtain consent from individual participants, for instance to ensure compliance or preserve trust (although these aims may also be achieved through other means).

Let us consider for instance a community education approach to public health studied in slums areas in Mumbai where geographical communities were the units of randomisation and intervention<sup>119</sup>. A cluster-cluster study was conducted by SNEHA, where cluster members were given the opportunity to voluntarily participate in the study by visiting the health centre in their area. Based on the previous discussion, individual consent was not necessary, since by visiting the health centres individuals were able to show their support or disapproval of the proposed intervention and easily opt out if they disagreed with the aims of the study. However, researchers asked for cluster members' approval. Community members were asked whether they agreed with the opening of a health centre in their community as well as their intentions to visit the centre. Researchers decision to seek individual consent for the intervention in this study may illustrate that there might be another, instrumental, reason for which individual consent should be obtained. By using informed consent processes investigators' work was better known and that increased the chances of the members of community to support and participate in the study. As some participants<sup>120</sup> stated:

*So I said if it is about people's health, then definitely I would support. It is also an*

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<sup>119</sup> For more information about the study see the Appendix.

<sup>120</sup> A description of data collection, data analysis, etc. is given in the methodology section.

*issue of my health, my children's health. I understand that this is a kind of serving people (female resident, 29 yrs, intervention area).*

*Yes, this study should happen. Someone will benefit from it (female resident, intervention area).*

*Yes, such research should happen because we stay in slums. There are many problems here: diseases, dirt, unhygienic conditions. Research is important to solve these problems (female resident, 45 yrs, control area).*

*When you do such work the support of the entire community is needed. When there is support from the community, then good work can be done (male resident, 51 yrs, intervention area).*

*Yes, I thought that it was good. If not for my benefit then at least for someone else's benefit. This should happen. Even if I do not benefit and the area doesn't benefit, at least you (the researchers) will benefit (female resident, 45 yrs, intervention area).*

It follows then that when the success of a health study highly relies on participants' willingness to adhere with and support the tested intervention, obtaining consent may not be morally necessary but practically important for health investigators to achieve better results.

### **8.1.2 | New moral challenges related to the level of randomisation**

Obtaining individual consent for randomization may be problematic in both individual-cluster and cluster-cluster trials. Some authors have raised concerns that our inability to obtain consent before randomization violates subjects' autonomy rights (Weijer et al. 2011; Donner et al. 2004), while others have suggested that some form of representative mechanism can be allowed to consent for entry of the cluster into a study, provided that careful safeguards are taken and the study is conducted in a transparent manner (Sabin et al. 2008).

Individual consent to randomization is not feasible in individual-cluster trials because random assignment often occurs before individuals are identified or approached (McRae et al. 2011). According to Edwards et al (1999), autonomy in

such cases is lost unless the individual has a democratic choice of who the guardian is and some right to consultation by the guardian. As I have already discussed, however, a guardian's or gatekeeper's consent is not truly equivalent to individual consent and there are certain difficulties with accepting the role of proxy consent in such cases (chapter 3). Nonetheless, lack of individual consent is considered less problematic in individual-cluster trials as consent can be obtained after randomisation and those who do not wish to participate in the study can easily opt out. Individual freedom, choices or rights are not restricted in that case. According to McRae et al (2011) trials where researchers seek individual consent from cluster members at the earliest opportunity and before the start of intervention or data-collection procedures are not problematic. In this way, cluster members can still adopt the ends of the study as their own (agree or deny to be exposed to risk for other people's benefit) and thus the moral purpose of informed consent is fulfilled. Based on their suggestion we can conclude that not seeking consent for randomisation is not problematic, as long as consent from cluster members is obtained before they are exposed to risk. In individual-cluster research not obtaining consent for randomization can be justified because it is the risk of intervention that might undermine individual dignity for social benefit.

However, although McRae et al are right to argue that individual rights are not compromised because of the inability of research participants to consent to randomisation, they fail to explain why (McRae et al. 2011; Donner and Klar 2004) such concern is not valid in the first place. In contrast to conventional clinical research where informed consent is generally considered in terms of a dyadic relationship and constitutes an agreement between clinical investigator and research subject, in cluster trials consent to randomisation concerns a community or group rather than individual decision, because there is no accepted way of allowing some cluster members' decisions to influence the chances of others participating. In short, informed consent cannot be obtained for randomisation purposes because a decision regarding cluster randomisation cannot be decided at individual level.

Cluster-cluster trials as already discussed are more complex. Individual consent is logically impossible before an intervention is assigned to individuals and

individuals often cannot opt out of the trial (in such cases a decision is made for both randomization and participation). Having argued that the use of gatekeeper does not provide a satisfactory solution for addressing the problem of individual consent (same reasons that apply for problems with randomization in individual-cluster trials also apply here) and given the fact that cluster members cannot consent before receiving the intervention, an alternative solution is to argue for a waiver of the consent requirement for randomization purposes. According to the Common Rule the requirement of informed consent can be waived when research does not involve more than minimal risk, the waiver will not adversely affect subjects' rights and welfare, the research could not practicably be carried out without the waiver and, whenever appropriate, the subjects are provided with additional pertinent information after participation. Since in cluster-cluster trials a decision has to be taken for both cluster randomisation and intervention, the same reasons that would justify waiving individual consent for cluster intervention should also justify waiving consent for research randomisation.

As I have already noted, the Common Rule, as well as other research ethics guidelines and regulations, rely on individualized ethical principles and for this reason they are not appropriate to provide solutions to moral challenges associated with the features of population-based interventions. The conclusions however in which I reached in my analysis in the previous chapters are compatible with the provision found in Common Rule. Yet, it is important to note that research ethics guidelines need to incorporate a more comprehensive definition of risk (they should also involve risks for the community or cluster, such as stigmatization), in order to take into account different types of health studies and provide clear guidance to research committees and investigators.

## **8.2 | Common moral problems associated with the consent requirement in cluster research**

In this part I discuss cases of cluster randomized research where obtaining consent is considered problematic for methodological or cultural reasons. In all these cases seeking informed consent is undesirable either because it would undermine the scientific validity of the study or because it would make the research process very

slow and difficult or culturally controversial. The problems I discuss below are no different to problems raised in RCTs.

### **8.2.1 | Methodological problems with obtaining informed consent in cluster trials**

Obtaining individual consent in cluster trials may be problematic for methodological reasons. In certain cases although consent to intervention is in principle feasible, as well as the option to opt out, the consent requirement is viewed as undesirable. Seeking informed consent in certain studies may lead to contamination (which the use of a cluster design aimed to avoid at first place<sup>121</sup>), when a cluster trial examines a behavioural or educational intervention<sup>122</sup> (Eldridge et al. 2005, Glanz et al. 1996), to scientific errors (when it is not possible to answer important scientific questions) or to the recruitment of unrepresentative sample (Hutton et al. 2008; Canadian Institutes of Health Research 2011).<sup>123</sup> In all such cases the methodological integrity of the study would be undermined. This is a common problem in both RCTs and CRTs. As stated in Helsinki Code II, some studies would be vitiated if participants were asked to consent.

Methodological problems associated with the consent requirement are typical problems in social research in general, and thus not only related to the research design. One of the most basic axioms in social research is that the methods used (e.g. the presence of a researcher) may alter the behaviour of research subjects

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<sup>121</sup> As I explained in Chapter 1 there may be also methodological reasons for using cluster design, when randomization at the individual level may not avoid contamination. For instance, researchers studying the change of social behaviour or the transmission of knowledge may choose to randomise participants at the level of a GP practice or town to avoid social interaction between the participants in close proximity, which will contaminate the study (Taljaard et al. 2009).

<sup>122</sup> So that those in the control group will not observe and adopt the activities in the experimental group (McRae 2011). This raises methodological challenges at the level of design and methodological analysis (Althabe et al. 2008) as it would undermine the ability of the study to answer the relevant research question. Interventional research without consent is also justified when deception must be used to produce scientific valid data. Much social and behavioural research relies on studies in which participants are deceived about the purpose of the research.

<sup>123</sup> Researchers often face the same problems in ordinary trials (RCTs). A common practice to resolve these problems is to withhold information from the control groups.

(Olsen et al, 2004). Although there are many different ways to address this problem, when the aim of the study requires the researcher to minimise the impact of the research process on behaviour, consent should not be obtained (assuming that a waiver of consent is morally justified), as the study needs to be minimally obtrusive and concealed to avoid the possibility of generalisation (Spicker 2007).

Difficulties with obtaining individual consent for methodological reasons are common to all zalen<sup>124</sup> randomised trials. In RCTs it is generally accepted that an ethics committee should approve a consent procedure that does not include all consent elements or a waiver of the requirement to obtain consent, when the risk is minimal (McRae et al. 2011). As Edwards et al have argued when “Informing the controls fully about the experimental arm(s) is likely to produce the very effect that randomizing by cluster was designed to avoid – that is, prompting controls to adopt the treatment(s) under investigation, one option is to withhold information about the novel treatment from controls, on the grounds that they are getting conventional care and are therefore in the same position as people outside the experiment” (Edwards et al. 1999). Dawson and Gerrard (2006) have argued that the threshold for informed consent being overridden in such cases must be very high. Based on the ethical analysis in Chapter 5, we could argue that not obtaining consent or even refraining from informing controls in such cases is not against participants’ interests if two conditions apply: first participants are not made worse off by not receiving the experimental intervention<sup>125</sup> and second if a research ethics committee confirms that by waiving a consent requirement community values or individual interests are not compromised (thus that all values which informed consent is designed to protect are respected).

As the consent process may substantially lead to study bias in outcomes and participant selection, the reasons for arguing for a waiver of individual consent should be different to those that apply in the cases I described in (8.1). To justify, then, the conduct of a cluster trial despite the absence of individual consent in

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<sup>124</sup> In the zalen design participants are randomised before consent to participate has been sought (Torgerson and Roland 1998).

<sup>125</sup> I have rejected the idea of ethical relativism in assessing risk thresholds.

such cases, we need to argue that scientific validity takes priority over the moral requirement of consent. Following the discussion on individual consent in clinical studies (in chapter 7) we could argue that the requirement for individual consent might be overridden in cluster health research where several factors, essential for the conduct of a study (e.g. scientific question or administrative difficulties<sup>126</sup>) are incompatible with the consent requirement. Similarly to RCTs in such cases, an independent committee should assess the validity of the reasons for which informed consent is not desirable and whether a waiver of consent could be justified for the trial to go ahead (Hutton 2001).

Since the severity of moral concerns related with our inability to obtain consent will vary from situation to situation, it should be noted that when research risk is greater then the requirement for consent becomes stronger. Although it is essential to ensure that a study has a methodologically sound design, which can produce valid findings and bring about therapeutic benefits, it is also essential to make sure that methodological demands are not considered as a means of avoiding inconvenient ethical requirements, when those are necessary. Especially, when vulnerable populations are to be involved cost or convenience alone are not sufficient criteria to permit a study. According to the moral principle of respect for persons and their communities, discussed in Chapter 5 (which also suggests that vulnerable groups should have additional protections) we should ensure that key questions concerning the risk involved, selection criteria and post trial access<sup>127</sup> are answered before the conduct of a health study, and thus cluster randomized study in which consent is not possible, is permitted.

We can conclude that although a cluster design may facilitate the conduct of a valuable health research when researchers are faced with financial, methodological, administrative and other methodological difficulties that would practically render a research project problematic by a conventional design, the

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<sup>126</sup> As I discussed in Chapter 1, a conventional design in developing nation settings where special equipment or personnel are required would make the trial organisation and implementation very complicated (Taljaard et al. 2009). Cluster design may be administratively cheaper or more convenient (MRC 2002, p. 4).

<sup>127</sup> When for instance a safe and efficacious vaccine is tested to HIV patients in endemic areas because of the greater incidence of infection.



conditions under which informed consent could be omitted must be considered first. If a waiver of consent is not viewed as appropriate, using a research design where consent is not possible should not be morally accepted, even if a trial is expected to be very beneficial<sup>128</sup>. In International Ethical Guidelines for Biomedical Research Involving Human Subjects the conditions for a waiver of consent are described; it is stated: “when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable, the ethical review committee may waive some or all of the elements of informed consent” (CIOMS 2002, Guideline 4). It is clear that exposing research subjects to risks for the benefit of others without their consent can only be justified if those risks are insignificant. When a study involves more than minimal risk, an alternative design should be considered where at least individuals could freely decide whether they wish to receive the intervention or not (Sim and Dawson 2012) and researchers should find alternative ways of planning of study procedures and execution (for instance blind randomisation) (Puffer et al. 2003).

### **8.2.2 | Cultural reasons for not seeking consent in cluster research**

I have discussed so far a series of moral and practical reasons for which the informed consent requirement may be problematic in cluster-randomized trials and the conditions under which cluster studies can be morally acceptable despite the absence of consent. Let us now consider whether compatibility with customary religious or cultural practice should be taken into account when deciding the level and type of consent for research purposes.

Another reason for which cluster design may be used in health research is when there is no local tradition of informed consent in the host country and researchers are obliged to obtain permission from local authorities or community leaders. As Taljaard et al. (2009) observe, in developing countries consent should be sought from the head of a village/community before investigators approach or contact individuals.

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<sup>128</sup> This should not only apply to the control group as discussed earlier but to all research participants and clusters.

Difficulties with informed consent procedures are common in health research conducted in developing countries. Although informed consent in general is not sufficient to protect a research participant against abuse (it is an ideal that does not always work in practice), because of the difficulties with comprehension of research information and so on, when a study is conducted in a foreign country things may be even more complicated. Considering lack of access to treatments, poor health, the role of inducements, the inequality of power and resources between sponsor and host countries and culturally and linguistic differences between researchers and potential participants (Ekunwe and Kessel 1984), the complexity of consent forms may not only fail to protect participants from abuse but even fail to ensure that participants have genuinely adopted the aims of the study. In certain cases consent requirements may confuse participants especially when it is not common in their local culture individuals to be asked for consent related to health issues; for instance Rajiv Sakar and colleagues (2009) observe that obtaining consent in an intensive 3year surveillance study of diarrhoea in young children in India caused various problems in terms of understanding and undue inducements. As they state, despite a high compliance with the study protocol, retention of understanding about the research study was low over a long period of time. Although 89.4% of participants stated that the study was adequately explained during enrolment, only 43.2% could recall that it was on diarrhoea, while nearly half of the respondents said that they would not have participated if free medical treatment were not provided, despite the fact the free medical clinic was not offered at enrolment.

Moreover, in certain cases, whole communities may view with suspicion the intentions of researchers. Indigenous cultural beliefs concerning medical procedures such as blood testing, post-mortem examinations, and others, may be significantly different than those of researchers (Gostin 1991). Obtaining genuine consent, as it is considered in the medical context may also be problematic, because some communities are not familiar with the concept of medical research. In other cases, individuals may refuse to sign consent forms in concern that adverse consequences may follow (such as stigmatisation following a positive

HIV test) or because of false beliefs, for instance that in this way they sign away their basic rights (Nuffield Council on Bioethics 2005).

Although in developed countries regulations require that written informed consent is submitted even when research is conducted in different law and cultural settings (Regulations, 45 CFR 46, paragraph. 46. p. 116), obliging an illiterate person who speaks a different language and in whose culture personal autonomy plays no role or a less important role (Christakis 1988)<sup>129</sup> to conform may be very problematic. In cultures where a person is defined by her relations to others (Christakis 1988) and where there is less perception of conflict between a person and her society (Adityanjee 1986) decisions may be made in village meetings in consultation with the community and its leaders or village elders (Hall 1989). Moreover, in many places such as the Indian subcontinent and West Africa great respect is given to healers and elders (Hall 1989). As Henderson et al. observe in West Africa research participation is highly influenced by the opinion of tribal leader (Gostin 1999). They note that obedience to elders and village leaders is considered such an important cultural value that if permission has been given by a community or family representative, individual refusal may not arise.

It seems then that there are considerable problems of importing a voluntary informed consent concept in developing countries when their participation needs to be based on some culturally appropriate agreement. It could however be argued that despite difficulties in obtaining genuine informed consent or in following standard informed consent procedures, protecting participants from possible exploitation in developing settings is even more important (because of the vulnerabilities of developing populations). Some authors have argued that participant protection is possible when the application of special safeguards takes place (when for instance there is close monitoring, or when the study involves only minimal risk). But, how about informed consent? How should we proceed when research involves more than minimal risk? And in cases where low risk is involved are community leaders the right people to consent on behalf of

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<sup>129</sup> In some communities in developing countries the person is defined by their relations with others in their community.

community members?

The notion of consent on behalf of others is more common and embedded within some cultures in developing countries. However, situations where a community leader or a senior community member typically has the authority to decide on behalf of others, including their participation in research, seems the most problematic. In limited circumstances, in developed countries, the law permits a proxy to consent on behalf of children and adults who lack the capacity (Hill 1987) to consent to research. Proxy consent is consistent with the fundamental principle of respect for persons, which requires that when research is necessary, participants who have the capacity to consent should never be subjected to research without such consent. Some participants may choose to delegate to another person, the decision of whether to participate in research, for instance a patient may delegate this decision to their doctor. However, if such delegation has not taken place, obtaining consent on behalf of competent participants when individual consent is necessary, would mean that researchers have failed to treat all people as moral equals and follow ways that promote their dignity and wellbeing.

I have argued so far that consent given by a gatekeeper or guardian is not morally equivalent to proxy consent. Likewise it could be argued that a community leader should not be considered as a proxy decision-maker. First, although community leaders may be viewed as legitimate community representatives<sup>130</sup>, they may have the same difficulties with community members in understanding research information, be susceptible to inducements or even not be in a position to assess whether a study may harm individual rights and interests. A second and more important reason for which community leaders should not be considered as proxy decision-makers is because by giving consent on behalf of a cluster members the very purpose of consent would be undermined, as none of the elements of informed consent are present when consent on behalf of individuals is given: a cluster representative cannot decide based on specific information about risks and

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<sup>130</sup> Even if they are not elected as community representatives, community members may acknowledge them as such.

benefits for every single member of the cluster or ensure that the individuals voluntarily accept to participate; they cannot know the decision that each member would make nor meet all individual preferences. Therefore although respect for the cultural values of the host community should be secured, and the position of family or community leaders should be respected, community leaders' decisions and views about cluster participation should not be considered as a substitute of individual consent.

These conclusions seem to refute the provision of CIOMS Guidelines on Biomedical Research, according to which when an individual is not in a position to provide adequate consent, a proxy consent can be given by a trusted community leader<sup>131</sup> (WHO/CIOMS 2002). A possible objection to my argument could be that the principle of respect for persons and their communities, according to the human right to health approach (as discussed in Chapter 5), would require researchers to respect local social values and the culture of the host country. It could thus be argued that it would certainly be wrong to accept that a developed sponsor country has the right to set universal rights to which host countries should comply (ethical imperialism).

However adjusting the consent requirement on the basis of local values could lead to ethical relativism, which I have already rejected in Chapter 5 where I discussed a revised moral framework for research ethics. Although, the research ethics framework based on which my analysis has relied suggests that all those involved in research should understand and protect the values of host countries and their communities, following local values and customs is not sufficient in order the fundamental research ethics principles to be respected. For instance the principle of respect for persons and their communities requires that prospective individual participants, when competent, should be offered information regarding their participation and also consent, when consent is necessary. If obtaining individual consent is not necessary, then a waiver of consent by ethics committee is the most

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<sup>131</sup> This is another case where it is evident that existing provisions regarding the conduct of cluster consent are not adequate. As I have explained so far difficulties with obtaining individual consent due to methodological or cultural reasons should not be approached differently to difficulties presented in RCTs.

appropriate solution. If individual consent is necessary (because the risks of the trial are more than minimal and individuals should decide whether they wish to be subjected to those risks), then the trial should not go ahead (despite the fact that the host community may not find absence of individual consent in this case problematic). As already stated practical and methodological implications should not override ethical ones; if voluntary consent ought to be obtained, researchers should not implement a research design where consent is not possible.

These conclusions are consistent with Gostin's (1991) observations. He notes that it is false to equate cultural differences or literacy with the inability to make decisions. Researchers should provide information that is consistent with local language and culture and which is comprehensible for participants. Moreover, he points out that the fact that individuals have strong relationships with their families and community should not be considered as incompatible with the informed consent requirement. Giving respect to community or religious leaders means that they consider and evaluate as important the benefits to their society and not that they are not in a position to understand or decide whether they should participate in a health study or not <sup>132</sup>(Gostin 1991).

We can conclude that when community leaders are legitimate community representatives, they can represent the interests of their community (rather than the interests of individual members) and thus ensure a proposed research is consistent with the values and customs of their community. Thus the very term 'consent' should not be used in such cases since a community's legitimate representative cannot realistically consent on behalf of the entire community. A more appropriate term according to Gostin is 'community consensus' which suggests that community leaders represent the local perceptions in population-based research. As I discuss in more detail in the next part (8.4.), the best solution in such cases is for the research protocol to be approved by research committees in both sponsor and host countries to ensure that processes involved are culturally appropriate for the researched populations and thus that the principle of respect

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<sup>132</sup> This would also suggest that researchers have an additional reason to protect the interests of individual participant.

for persons and their communities is respected, before community leaders or cluster representatives are approached. This would ensure that communities are treated with respect and dignity and that researchers avoid any research activity that may harm, stigmatise or demean host communities and their members (according to the revised principle of respect for persons discussed in Chapter 5).

### **8.3 | Alternatives to the traditional model of informed consent in CRTs**

In the relatively limited literature on the ethics of cluster research (discussed in Chapter 2), there is not much clarity about the reasons for which informed consent in CRTs is morally challenging. Most discussions are based on the distinction between individual- cluster and cluster-cluster trials (Edwards et al.1999; Hutton 2001; Mc Rae et 2011) <sup>133</sup>, considering the latter category as more problematic, because of the inability of cluster members to consent to and opt out of the research intervention. As a result, current discussions on this matter have mainly been focused on solutions that would bridge the legitimacy deficit, relying on an individualised model of research ethics, such as cluster consent or other substitutes of individual consent e.g. hypothetical consent, as well as on possible ways by which difficulties with the implementation of such solutions can be overcome, e.g. the identification of multiple gatekeepers or guardians and others.

As I have already discussed not all difficulties associated with our inability to obtain consent can be addressed by finding an informed consent substitute, even if we accepted that some of the suggested solutions could successfully play that role. As discussed in section 8.1, when an intervention needs to apply at a cluster level it is impossible to accommodate differing choices of every cluster member. The question that needs to be answered in such cases is not whether individual consent is feasible (as discussed when a cluster-cluster trial involves small size clusters it is possible to obtain individual consent) but whether it is meaningful to seek informed consent in the first place.

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<sup>133</sup> Although this is an important distinction, it fails to take into account that difficulties with obtaining individual consent in CRTs do not only constitute a problem of practicality.

Moreover, in contrast to what has been suggested in the current research ethics literature (see discussion section in chapter 2 and 4.4 in chapter 4), a single justification for the whole spectrum of cluster research interventions that may restrict individual autonomy is difficult to defend<sup>134</sup>. Let us review some examples of the traditional model of informed consent discussed in chapter 2.

Some authors have suggested hypothetical consent as an alternative to actual consent when the latter is not possible. The problem with this suggestion is that even if we accepted that individual cluster members would agree to limit their personal freedom for the social benefit, we would still need to define the degree of restriction that would be acceptable for research purposes (under what conditions is it acceptable to rely on hypothetical consent?). For example the fact that individual cluster members may be willing to agree to certain restrictions on their personal liberty in order to achieve immune community, does not suggest that they would possibly agree to all possible research interventions testing different types of immunisation; their consent would be necessary for an actual vaccine to be tested on them.

Tacit consent has also been suggested as a solution to justify health research interventions where consent is not possible. Based on an individual's acquiescence to the government's rule and acceptance of the benefits of the society, one could claim that individuals tacitly give their consent to the research intervention<sup>135</sup>. However, as Hume states, mere residence in a jurisdiction is not enough for tacit consent, as the only option would be to leave the country (Wolff 1996). Rousseau makes an even stronger argument that that absence of true freedom to leave the country may not justify tacit consent to the state power. Residence then alone cannot justify why an individual must comply with

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<sup>134</sup> Advocates of a moral duty to participate in research have incorporated some of the justifications I discuss in the paragraphs below in their theory in order to defend a single moral justification for all health research studies (and in particular medical studies). Although some of them admit that certain studies are more risky than others (for instance John Harris) they believe that this fact does not suggest that a moral duty to participate in research is not defensible. In the following paragraphs I explain why this approach is false.

<sup>135</sup> This view is also implied in contractarian theories for the justification of a moral duty to participate in research.



population-based interventions that restrict personal freedom, especially if those interventions involve personal risk, which an individual cannot avoid.

Rejecting a consent requirement completely on the other hand would not be appropriate. Another attempt to justify health research, as discussed in Chapter 4, has relied on the utilitarian approach. According to this approach an individual has a duty to accept restrictions of personal freedom and obey the state when it maximizes the common good, as Jeremy Bentham would argue. But here again, the problem of fairness would arise since a course of action may favour the majority (host community) but be a great detriment to the minority (clusters or individual participants). Limiting individual informed consent in a public health context, and population-based research, when the risks are prevalent by making the utility comparisons, would be a dangerous route to take (and would certainly be incompatible with research ethics principles I discussed in Chapter 5).

### **8.3.1 | Cluster consent**

Let us now summarise the reasons for which cluster consent cannot provide a satisfactory solution to the problem of consent in cluster trials. As already stated, certain moral challenges presented in cluster research derive from the distinct features of population-based interventions while others are common to all types of health research. For all such problems associated with our inability to obtain individual consent in cluster trials a straightforward solution, such as cluster consent, cannot be appropriate. Although the distinction between individual-cluster and cluster-cluster trials could often help us identify difficulties associated with nature of the intervention, and thus with some of the distinct features of population based interventions, this distinction should not constitute definitive moral guidance on how problems related with our inability to obtain consent should be addressed (as discussed in previous paragraphs cluster-cluster trials may also raise problems that are not related to the nature or the level of the research intervention). Moreover, relying on a distinction between individual-cluster and cluster-cluster trials to access when researchers should seek consent from cluster members does not provide any guidance on when it is morally justified to use a cluster design or whether and when practical difficulties could override a consent requirement.

When problems associated with the consent requirement are common with those presented in clinical research, we can refer to current research ethics regulations for guidance (to assess whether a waiver of consent may be justified when individual consent is incompatible with the research question). In such cases seeking cluster consent would be pointless, because, as I have already argued, cluster consent does not constitute proxy consent. As Hutton (2001) points out, there is no feasible way to solicit informed consent from each member of a cluster for the cluster's participation in a CRT unless one is prepared to allow a single dissent to block entry.

Cluster consent may be problematic even when difficulties with the consent requirement are related to the specific features of population-based studies. Though a cluster representation mechanism is considered the consensus position in such cases, not much attention has been given on the conditions under which it is morally appropriate to use this mechanism<sup>136</sup>. As already discussed, when a competent adult does not give voluntary informed consent to an intervention in their body or private sphere, when the intervention is substantial, involves considerable risk or restriction of personal freedom and does not prevent severe harm to others, the conduct of the study should not be permitted. In such cases, consent does not constitute a particular right, which can be negotiated in order to allow other competing values to be satisfied. A decision to accept or refuse a risky health intervention cannot be delegated to a cluster representative, even if they have the authority to make such decisions (even if they were elected for this particular role). It is obvious then that another reason for which a gatekeeper or guardian itself should not be considered the resolution of every dilemma or collective action concerning cluster research, is that not all cluster trials involve interventions that justify autonomously waiveable informed consent rights.

However, even if we restrict the role of cluster consent only to studies that involve minimal risk for the participants, it is not clear what safeguards should apply in order to ensure that a decision is made in a transparent and democratic manner

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<sup>136</sup> With the exception of the work done by McRae et al (2011) which however does not depart from the traditional model of informed consent.

(for instance to ensure that a cluster gatekeeper has not been induced to make a decision that is against the best interests of the community, i.e. when a study may lead to stigmatisation) given the imbalance in the power between host and sponsor countries.

As already discussed these decisions are particularly important in collaborative health research in poor settings, where participation may be the only way by which cluster members as patients can have access to health benefits. Given that legal cluster representatives are usually not elected to take decisions concerning community health, their authority to take up such role is especially questionable when a study, for instance, involves medical procedures rather than educational programmes or consultation<sup>137</sup>.

Moreover, as discussed in chapter 3, the use of a representative mechanism for the entry of a cluster into the trial may present moral challenges, as it is often unclear who, if anyone, has the right to speak for a given cluster. There is often not a legitimate community representative that can represent cluster member rights or protect their interests. For instance, the elders of a village may not have formal legal authority to represent their people, although they may be viewed as cultural, religious or community leaders. As already discussed in such cases researchers have a moral obligation to respect local cultures and ask for community consensus (thus a more appropriate term would be ‘cluster consensus’ instead of ‘cluster consent’) but they should not conceive community leaders’ views as taken on behalf of the individuals in the cluster. Delegating to community leaders the authority to consent on behalf of the cluster would be significantly problematic in cases where cultural practices are not widely supported by everyone who is

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<sup>137</sup> My aim here is not to argue that a decision on behalf of a cluster will never be appropriate; when for instance a person has been legally authorised to decide on behalf of their community whether a specific type of health research should be permitted (for instance for decisions concerning environmental health interventions in a particular geographical area), and given that the study only involves minimal risk, then it could be argued that giving permission or withholding permission on behalf of their cluster does not compromise participant interests in an obvious way. However, the existence of a legitimate cluster representative elected to fulfill this particular role in cluster research in a developing setting would be an ideal case and thus should not be used as a guidance on how consent problems should be resolved in cluster research in general.

subject to them (e.g. unpopular practices with people who did not have the power to change them) (Nuffield Council on Bioethics 2005).

Finally, cluster consent may be problematic even when it is given only for randomization purposes and even when only minimal or no risk is involved and cluster members are able to opt out of the trial. Let us for instance look at the views of the participants<sup>138</sup> of the community-based study in Mumbai aimed at the improvement of health and nutrition of women through community resource centres<sup>139</sup>. The findings of the survey demonstrate that there is no point in seeking cluster consent when cluster members do not acknowledge a gatekeeper's authority to decide whether their community should be enrolled in a health study.

The transcripts yielded five main themes describing participants' views regarding representation in cluster research: gatekeepers were not considered as community representatives; community leaders should not serve as community representatives; gatekeepers lacked understanding of the purpose of cluster consent; gatekeepers were not interested in the aims of the study; and decision-making should rely on community consultation.

***Gatekeepers were not identified as community representatives***

The results showed that the gatekeeper (i.e. an individual who consented for the opening of a health centre in their area) was not identified as the person who could represent community interests and values. The gatekeepers were identified only by few residents as the ones who could be consulted by the researchers about the needs and problems of their area, while most people stated that researchers should have asked a different person referring to a stakeholder of a higher post:

*The person who has a small office here, the social worker, he can provide proper information [about our community]. He is an old resident, he can tell how this community was, how it has improved (male resident, 35 yrs).*

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<sup>138</sup> For more information regarding the methodology of the qualitative study see the methodology section.

<sup>139</sup> For more information about the health study see the methodology section (setting) and the Appendix.

*In our community, there is one person [who can take that role]. The vice president (of our committee) (male resident, 28 yrs, intervention area).*

*The person who is in charge of the mosque (male resident, 45 yrs, intervention area).*

***Community leaders should not serve as community representatives***

Most of the respondents claimed that corporators (elected community leaders who also served as gatekeepers) should not be considered as community representatives because they exclude community members from decision-making processes and neglect their needs.

*That is how Yusuf bhai (corporator) decides. He chooses a few people and arranges a meeting. These people are not from our community. They are rich people 'important people'. He takes their opinion because they can help. These individuals are members of mosque committee, a secretary... (female resident, 25yrs, intervention area).*

*The corporator decides everything by himself. Meetings don't happen. Whatever decisions are taken, are taken from outside and we do not get to know them here (female resident, 30yrs, intervention area).*

*The corporators think too high of themselves. They do not feel they need to consult people. This is why they never ask us before making decisions. This should not happen but who will listen? No one will listen to people with no influence or power. The only right way to make a decision is when everyone is consulted in the community (female resident, 29 yrs, intervention area).*

Although it was clear that in most areas the corporator (elected community representative) was considered to have the political authority to make decisions for the improvement of their area, the majority of respondents said that they were not happy with the selection of the corporator (of the elected community leader) as a community representative. In few cases participants were strongly opposed to the decision of researchers to ask their corporators to consent for cluster randomisation.

*If I knew she took the decision, I would not have allowed the researchers to set up a centre here (female resident, 40 yrs, intervention area).*

Most of the respondents stated that their corporator (elected community leader) should not be considered as community representative because residents are not happy with their work. A few people raised concerns about the corporator's skills and qualities:

*We got tired of telling the nagar sevak (corporator) about the sanitation issue. He has not done anything yet. Two years now...not even for this road that needs to be fixed. The corporator had told us that as soon as he wins the elections he would repair the roads and drainage in our area... we have been tired of filling applications and making requests for these things. There are still no roads here and children are dying. For all these things he does not have time (female resident, 40yrs, intervention area).*

*I am that old and no nagar sevak [corporator] has ever come to see what the problem is here...big or small, is not important. When there is a problem in the community, people will discuss it and raise money to resolve it. No one talks to the corporator. Even if we raise the issue, his personal assistant would tell us he is not in the office. We never have a chance to talk to him (female resident, 45 yrs, intervention area).*

*The nagar savak (corporator) whom we elected...we worked very hard, we put so much effort and made him win. He did not do anything after winning the election. We gave hope on him. Now we only rely on ourselves (female resident, 39yrs, intervention area).*

*The corporators are not educated people. So if you ask them what is this paper about, they do not know... they will just put a signature and that's it (female resident, 40yrs, intervention area).*

*The first thing he said he would do after winning is a bathroom. ...We elected him and he insults us this way (female resident, 36 yrs, control area).*

***Gatekeepers were not interested in the aims of the study***

It is interesting that none of the gatekeepers (individuals who gave cluster consent for the opening of a health centre in their area) was interested in learning about the aims of the study in which their cluster was involved:

*They did not give any information. They just took my signature...they just said they were doing some survey. I did not ask what the survey was about. We do not have our own problems here? Why should I get involved in other people's matters? So having this in mind I did not bother to find about the issue (female resident, intervention area).*

*There were some papers, which we read and signed. Whoever comes we consider them as guests. We place our trust on them and sign. Now how they will use that signature, this I do not know. If there will be some loss because of my signature, then we will have to tolerate this. But when we trust someone and sign, I do not think they will use our signature in a wrong way (male resident, 55 yrs).*

***Gatekeepers lacked understanding of the purpose of cluster consent***

Almost half of the gatekeepers who participated in the survey believed that by giving their consent they did not decide on behalf of their community but demonstrated their support to the research project.

*Whatever they are doing, let them do it through my signature (female, 45 yrs, intervention area).*

*No, when they took my signature, they did not tell me for what reason. They just took my signature and told me, when we will come back we will meet you (female resident, intervention area).*

*Whatever it is, I told them, is good for us. I do social work where. If there is any problem, I will take care of it (male resident, 45 yrs, intervention area).*

***Decision-making should rely on community consultation***

Consulting community members was considered as the right approach by which a decision regarding community matters should be made. All the respondents (residents, gatekeepers and politicians) stated that everyone's support is essential

when a decision about their area has to be taken. A collective decision-making process for community issues seemed to be endorsed even by those who were happy with the corporator's work.

*Everyone needs to be consulted. If one takes a decision then the people will not listen. If the work is for the improvement of the community, then they should ask everyone. One cannot decide on this alone* (female resident, 25 yrs, intervention area).

*If there is an issue about health, then our committee can decide. In our area most people gather together and we take everyone's view on the issue* (female resident, 40yrs, intervention area).

*Sometimes, the situation is such that there is need for everyone's support. Like when there is a water problem in our community or when there is a conflict somewhere. Everyone is called, we meet and we decide together* (female resident, 45 yrs, control area).

*We consult everyone in the community. We call a meeting with the most important people in the community. We discuss whether this is for our benefit or not and try to convince each other. Many people need to be convinced, otherwise we cannot take a decision* (male resident, politician).

*Regarding to the needs of our area, everyone's agreement is essential. Whether a problem concerns community hygiene or health, everyone should be consulted* (female resident, 25 yrs, intervention area).

*People's support is essential...why? Because everyone, together should take a decision. When a decision is taken by only one person, if a problem arises then that person will be responsible for everyone else* (female resident, 39 yrs, intervention area).

*The thing is that this is a slum area. And our opinion is that informing people is very important, regarding any decision. What often happens is that even if you do a good job, there always be people who will doubt your intentions* (male resident, 28 yrs, intervention area).



*We, the residents can only take that decision. Regarding health issues, Yusuf bhai is not responsible* (female resident, 32 yrs).

If we consider research participation as a community matter, we can argue that community consultation would have been a better approach to cluster consent in such case. Gallo and colleagues (2012) argue that researchers could understand the social dynamics of the group by consulting with the members of the cluster and their leaders and by asking them questions about the gatekeeper's role<sup>140</sup>. The results of this study showed that researchers should have ensured that group members understood and acknowledged gatekeepers' role to make such decisions and acknowledged their authority to do so before asking them to provide consent for randomization purposes. However, the fact that the particular study involved minimal risk and cluster members could voluntarily participate or opt out of the trial any time they wished, suggests that although obtaining cluster consent was not appropriate, it did not raise any moral concerns for the protection of the research subjects.

We can conclude that gatekeepers cannot protect or promote a cluster's interests by giving permission for a cluster to be enrolled in a trial, if they do not have legitimate authority to represent the individuals involved and if this authority does not extend to the decision at hand.

#### **8.4 | How should we proceed and what mechanisms should we use to ensure that cluster studies are ethically acceptable when informed consent is not possible?**

In the previous part I argued that cluster representation does not constitute a satisfactory solution to the problem of informed consent, for both moral and practical reasons, and that the decision for the conduct of a cluster randomised study should be in the responsibilities of a legitimate political authority<sup>141</sup> after

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<sup>140</sup> Gatekeepers are not necessarily group leaders.

<sup>141</sup> It is important however to consider that special attention should be paid to decisions that could lead to practices that exploit the cognitive weaknesses of citizens and act against their health interests. Corruption is an important factor that should be taken into

the study has been reviewed by an research ethics committee. Collaborative health research, which aims to improve the health status of a developing population, should be part of a country's policy, similarly to decisions concerning the implementation of public health measures<sup>142</sup>. As I discussed in Chapter 5, states have a duty to look after the important needs of their people individually and collectively. This duty ranges over obligations concerned with the provision of health care services and through public health measures and with securing certain social determinants of health. Studies that aim to address health inequalities and assist states to meet for their citizens their human right to health (clinical studies, public health studies, epidemiological studies and others) should be supported by their governments. Stakeholders within diverse democratic communities should be assisted in deciding which kinds of research should be fostered and supported, and which should be either rejected or reformed. For this reason it is essential that accessible standards are set for differentiating between studies that are morally acceptable and those that are not. This is the role that IRBs and RECs should fulfill.

#### **8.4.1 | The role of research ethics committees**

As noted by the Nuffield Council on Bioethics “An ethical analysis does not concern itself only with identifying and setting out appropriate general values and principles. It also has to concern itself with the institutions and procedures through which these principles are put into practice. The establishment and maintenance of research ethics committees is just as much an essential ingredient in the proper conduct of research related to health care as the functioning of political institutions is essential to the proper conduct of government.” (Nuffield Council on Bioethics 2005, Chapter 4). Research ethics committees are essential

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account when discussing the ethics of collaborative research. In certain cases a reason for which a state may fail to provide to its citizens basic conditions for their well-being and development may be by inappropriately restricting institutional spaces or neglecting basic social institutions. Corruption would certainly have implications in the conduct of health research, as it may fail to protect participants from exploitative practices and it may also constrain collaborative relationships between host and sponsoring countries.

<sup>142</sup> The fact that political leaders may not be experts on the relevant issues in health research does not make their decision problematic as governments and other political authorities could use help of expert advisors (as in other areas for instance economics, law, foreign policy).

to ensure that health related research is abiding by various ethical principles and that reasonable limitations are imposed on research participation. In other words, the role of research ethics committees is to serve as guarantors that a cluster-randomised trial is morally justified and to provide overall ethical scrutiny of the study especially from the perspective of research participants and their communities.

Research ethics committees should first assess whether the use of a cluster design is appropriate for the study in question (whether a cluster-randomized design is a methodologically sound decision). If a proposed study protocol does not present clear reasons for which the consent requirement cannot be fulfilled, responsible committees should ensure that cluster-randomized trials are not merely used as a means of avoiding inconvenient ethical requirements. They must ask health investigators to clearly justify and present their reasons for not obtaining informed consent in those particular circumstances (for instance the possibility of answering an important proposed research question which is not compatible with the consent requirement) (Sim and Dawson 2012). When there are solid reasons for which a study is not compatible with the individual consent requirement, research committees should consider whether the study in question qualifies for a waiver of individual consent.

To decide which kind of health research should be supported and which rejected or reformed it is important that there is differentiation between reasonable and excessive risks. This is essential in order REC s and IRBs fulfil a ‘gate-keeping’ role for the protection of research participants and their communities as well as being capable of securing and preserving public trust (London 2006). One way to achieve this aim (as I argued in the previous chapter) is for research ethics guidelines to develop and implement risk-adapted consent standards, to classify risks to participants in categories (e.g. low, moderate, high) and specify risk-adapted consent standards for each category. Risk-adapted standards suggest that risk is an important factor that influences the informed consent process (as I have already explained in chapter 7 consent is more likely to be invalid as the risks of

research increase)<sup>143</sup> (Bromwich and Rid 2014). Bromwich and Rid (2014) have suggested that a collection of examples would cover the most common research interventions in medical research and that such examples could be used as paradigm to assess levels risk. Applying this suggestion in cluster research or health research in general, investigators and RECs could interpret which level of risk concerns the protocol under consideration and thus whether waiving an informed consent requirement could be justified. When a waiver of informed consent is justified, research ethics committees should ensure that appropriate safeguards for the protections of individual and community interests are satisfied (e.g. the privacy or confidentiality of medical and personal data).

Finally RCT should not be presumed as the paradigm method of health research for research ethics committees. Future revisions of research ethics guidelines and regulations are important in order take into account that alternative to RCT design research methods may also be preferable and useful (Sim and Dawson 2012).

#### **8.4.2 | Community involvement in cluster research**

Although research ethics committees and institutions research boards are well positioned to assess both the ethical and the scientific aspects of a cluster-randomised trial protocol, this does not mean that consultation with interested communities relevant to the proposed research cannot and should not occur.

Community consultation has been considered an important mechanism for the protection of group interests in health research and it is often described as a partnership between researchers and participant communities. It can be provided from research design to publication (i.e. consultation over protocol development, involvement in the conduct of research, dissemination of information, and publication of results) (Weijer and Emanuel 2000; Ross et al. 2010). Weijer and Emanuel (2000) note that the degree of this participation will depend on the

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<sup>143</sup> Some critics object that such classifications are complex and controversial (European Clinical Research Infrastructures Network 2010; Rid and Wendler 2010). However, the benefits of risk-adapted consent standards arguably outweigh the disadvantages in order to avoid a ‘one-size-fits-all’ approach to consent, which can unnecessarily delay or impede valuable research.

characteristics and the cohesiveness of the group (whether for instance a group has a common history or culture that should be protected). The aim of community consultation is to gain community input in the decision making process (Marshall and Berg 2006) by involving community in the development, review and oversight of a research study (Marshall and Berg 2006). There are various ways by which to conduct community consultation and involvement in research and different approaches on how to achieve this; such as conducting meetings with the communities, surveying relevant groups by telephone discussions, public notification mechanisms, identifying community leaders and others (Kudson et al. 2004; Marshall and Berg 2006). Plans for successful community engagement are stated in recent guidelines such as ‘Good Participatory Practice Guidelines’ for research on HIV prevention by United Nations Program on HIV/AIDS and involve community empowerment, capacity building and education (Berg 2006)<sup>144</sup>.

Having questioned the authority of gatekeepers, guardians and community leaders to protect cluster interests by providing cluster consent in most cases of cluster research in developing countries, we can claim that community values and beliefs, community reputation, social practices and tradition, and other cluster and community interests could be also protected when community representatives (gatekeepers, guardians and community leaders) are involved in cluster consultation. Cluster representatives may consult health investigators whether a research protocol, after it has been approved by a research ethics committee, is in line with the values and customs of the community or cluster (Bolton et al. 2003). Gatekeepers, guardians, and community leaders may also provide feedback and advice to researchers on the conduct of a study, for instance, provide insights as to the cultural appropriateness of different intervention activities.

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<sup>144</sup> Difficulties with these approaches have already been discussed in chapter 2: how a community is defined and who should speak on behalf of the community, who is the relevant representative (Marshall and Berg 2006). Despite these difficulties such initiatives should be encouraged as group interests are recognized as important and required protection.

When there is not a specific person or group of people who can undertake the role of representative (see for instance community-based study in Mumbai discussed earlier), community consultation may be realised by community advisory boards (CABs) where members from communities participate. This mechanism allows researchers to understand and assess the context in which different communities understand risks and benefits. As Sandra Crouse Quinn (2001) points out cluster consultation may be given in all stages of the research process that may involve community advisory boards. In this way both individual and community interests can be protected and a potential conflict between them is avoided.

### **8.4.3 | The role of information in cluster research**

According to Hutton (2001), trial information should be provided even in cases where a member of a cluster cannot opt out of the intervention (for instance, when an insecticide is sprayed throughout their village). It is argued that although providing information in those cases could either increase goodwill or a research subject's concern, a failure to inform a research subject might result in a sense of violation (Ashcroft 1998; Snowden et al. 1999). Based on the discussion above it is obvious that there is an additional reason for which information is necessary in cluster health research, even if individuals cannot opt out of the trial. In the previous chapter I argued that decisions concerning the implementation of public health practices and policies should rely on a procedural justice approach (an approach that focuses on fair, open and transparent procedures to ensure negotiation of substantive disagreement about, practices or policies (Nuffield Council on Bioethics 2007)) and explained that these procedures should be transparent, fair and inclusive (Nuffield Council on Bioethics 2007) Transparency in decision-making processes should also apply in research settings so that those affected recognize such decisions as being helpful in meeting health needs fairly<sup>145</sup>. For this reason the involvement of individual cluster members and

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<sup>145</sup> Although in certain cases a population-based research intervention may be more beneficial for some individuals than others (e.g. for the vulnerable members of the cluster), it is important that a government's decision to approve such study is viewed as fair by everyone. As discussed in Chapter 5, the human right to health approach suggests that the principle of beneficence should be restricted by the principle of justice and the principle of respect for persons (and their communities).

community representatives in decision-making processes (by for instance providing consultation concerning the design of the study) is important, as in this way research participants have the opportunity to challenge research interventions and raise their concerns (through focus groups or surveys or in other ways), especially where there is possibly mistrust on a research issue.

As I discussed in chapter 4 when informed consent from the participants cannot be obtained we need an alternative way of ensuring that participants/ cluster members agree with the aims of the study. As reducing choices requires justification in all policy decisions, procedural justice arrangements can form an appropriate means of reconciling different preferences within a community or cluster, even if the final decision does not meet with everyone's approval. If relevant consultants have strong negative reactions or endorse particular modifications, "those reactions or modifications have significant moral force and warrant respect and careful consideration" (Dickert and Sugarman 2005, p. 1124).

#### **8.4.4 | Achieving participant protection in cluster research at institutional and societal level**

Taking the provisions described above into account we could argue that in population based research, the protection of human participants is not limited to the individual level but it can also be realised and may even be more effective at the institutional and societal level<sup>146, 147</sup>.

Community involvement in cluster research may help to democratize health research by promoting public monitoring of research agendas. It could motivate community members to be involved in discussions regarding their local health needs and research priorities, distributions of research outcomes and level of

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<sup>146</sup> Even when a collaborative health research study is industry-funded, these safeguards should not be neglected. Although I have argued so far that states have the main responsibility to meet their citizens right to health, this does not absolve other parties, in particular the corporate sector, from their responsibilities. Pharmaceutical companies may have different motivations for pursuing social responsibility strategies, but it should be recognised that they have obligations in complying with relevant research laws and guidelines.

<sup>147</sup> Rhodes attempted to introduce that idea for medical research, which, however, proved problematic to apply in practice.

acceptable intrusion for the social good. Community engagement may promote an informed and engaged citizenry, ensure respect for divergent values that different communities may have, make research operations more comprehensive to the public involved, respect community priorities, and protect the interests of communities involved and their members (for instance in community advisory boards increased representation and involvement of diverse community members can be achieved). Finally, community involvement in research may promote researchers' and institutions' accountability and address the needs of their most disadvantaged populations more effectively.

## **8.5 | Conclusion**

The aim of this chapter was to suggest solutions to the moral challenges related with our inability to obtain informed consent in cluster research. I explained why solutions found in research ethics literature, such as cluster consent, are not adequate in meeting such challenges and argued that legitimate political authorities should take decisions regarding population-based research. I reviewed the role of research ethics committees and discussed the importance of community involvement in ensuring that a research proposal is consistent with both the principles of research ethics and the local values of researched communities.



## Conclusion

The aim of this thesis has been to explore and discuss the distinct ethical issues raised by the conduct of cluster randomised trials in developing countries and in particular those related to informed consent and representation. In contrast to ordinary randomised trials (RCTs), cluster randomised trials (CRTs) involve groups of individuals (clusters), rather than individuals themselves, and for this reason they present challenges on the nature and practice of informed consent. First of all, individuals (cluster members) can only participate in a study if their cluster is entered into a trial. Therefore, a decision regarding cluster randomisation is usually made before informed consent from cluster members is obtained. This raises important questions, such as: Who should make that decision? and Who has the right to decide on behalf of the cluster and based on what criteria? Considering that such decision may exclude individuals from receiving important benefits by participating in an, otherwise beneficial, study, answers to the questions above may have a significant impact on people's lives, especially in developing countries. In several cases, cluster studies may considerably differ to studies employed by conventional design, as consent may not be sought from all those affected by the intervention. In such cases, a decision needs to be made for both cluster randomisation and intervention, and therefore, it may not be possible for individuals to opt out of the study (for instance, when a large-scale trial tests new insecticides). Questions raised in such cases are: Is a trial legitimate to carry out, when individual informed consent is not possible? Does lack of individual informed consent violate the rights of the participants?

When individuals cannot decide for themselves whether they should participate or not, who should make that decision?

According to research ethics guidelines and regulations, obtaining informed consent is an essential ethical requirement for study participation in health research. By providing informed consent a competent person demonstrates that they freely give permission to be used for social benefit, based on an adequate understanding of information related to that decision. It is obvious then that cluster trials, because of their structural features do not fit within the existing research ethics framework. On the other hand, taking into account that the cluster design is an important methodological tool in health research, forbidding its use, because of the difficulties with obtaining informed consent, may be at significant cost.

Several solutions have been suggested to resolve the problem of consent in the limited literature on the ethics of cluster research. The use of gatekeepers, individuals who can serve as cluster representatives and consent on behalf of cluster members, has been the most popular suggestion (Edwards et al. 1999; MRC guidelines 2002; Hutton 2001; Donner and Klar 2000). However, as I explained, such a solution creates serious problems for the protection of both individual and cluster interests and should not be considered as a substitute of informed consent. I also discussed the views of Gallo et al. (2002) and the suggestions of the recent Ottawa statement (2013) for a more restricted role of gatekeepers in CRTs and the importance of cluster consultation in the absence of a legitimate cluster representative. I argued that these views cannot provide much guidance for those engaged in collaborative health research in developing countries, where clusters involve communities that lack political or social structures.

I concluded that, to decide whether and when it is acceptable to conduct a cluster study when informed consent is infeasible to obtain, we should first consider under what conditions we could morally accept the exposure of some individuals to research conditions without their consent for social benefit. By discussing the main arguments for the justification of health research based on the moral

approach normally taken in the research ethics literature, I examined the implications for cluster research where individual consent is absent. I concluded that none of them could serve as a default justification for limiting individual autonomy for research purposes, and that a different perspective needs to be adopted from the one commonly taken in respect to conventional randomised trials.

I argued that in order to meet moral challenges in cluster research a less individualistic research ethics framework should be adopted that takes into account the variety of health studies conducted in developing settings, as well as the broader socio-political context where collaborative health research takes place. I introduced the ‘human right to health’ approach and claimed that aim of collaborative health research should be to address health needs that cannot be feasibly or more efficiently met with existing knowledge and the resources of the host country. I argued that in contrast to current approaches for the justification of health research (precautionary approach, utilitarian approach, communitarian approach, contractarian approach and others) the suggested moral framework could provide better safeguards for the protection of participants and their communities in health research (by demonstrating the way in which inequalities in global health should be considered and addressed, the moral criteria based on which potential participants should be selected or not selected, and what should be considered as fair or appropriate distribution of benefits and risks). Moreover, I claimed that a human right to health approach could also support and encourage socially valuable research by taking into account a variety of health related studies conducted in developing settings (e.g. research into genetic determinants of disease, non-clinical research on finding better ways of delivering existing products and services, and others), which have not attracted much attention by existing clinically-centred guidelines and debates on research ethics. By presenting a revised version of the principles of Belmont Report based on the suggested research ethics framework, I argued that within this framework important moral issues in collaborative health research on risk assessment, exploitation, participant rights and researchers’ obligations could be better understood and addressed.

In contrast to current approaches on the ethics of cluster research, I argued that for all problems associated with our inability to obtain individual consent in cluster trials, a straightforward solution, such as ‘cluster consent’ or ‘community consultation’ is not appropriate. I suggested that a distinction between ‘population-based research’ (research that focuses on populations rather than individuals) and ‘disease-based research’ (research that aims to find treatment for particular diseases that affect individuals), introduced by Taylor and Johnson (2007), can help us better understand and address the ethical challenges raised in the cluster design and in particular the problem of informed consent. To provide then answers to the question: “How should we proceed when informed consent in a cluster study is not possible?”, we should distinguish between the cases where informed consent is problematic because of the distinct features of ‘population-based’ interventions (e.g. cases where the intervention needs to be tested at community level) and those where informed consent in CRTs may be problematic for reasons that investigators may encounter in other research designs (e.g. in order to avoid research bias). I noticed that a distinction between new and common problems with the consent requirement in CRTs is very important and should be part of the discussion on the ethics of cluster research.

Having argued that new challenges concerning our inability to obtain consent in cluster trials are related to the distinct features of ‘population-based’ interventions (which focus on populations rather than individuals), I examined the common morally relevant features of ‘population-based research’ interventions and public health measures. By reviewing the conditions under which it is morally legitimate to restrict personal freedom/autonomy for social benefit in different public health measures, I explored whether the same justifications could apply in similar interventions for research purposes. Moreover, I noticed that cluster trials, due to their experimental nature, inherit most of the ‘generic’ problems of health research, which have been widely discussed in the existing research ethics literature (e.g. research bias, cultural differences between host and sponsor countries), as well as some of the specific problems that investigators face in medical research when cluster trials involve clinical procedures (e.g. risk for bodily integrity). I claimed that, to successfully deal with the problem of informed

consent in CRTs, it is important to also examine the role of informed consent in clinical ethics. I then compared different standards for seeking informed consent in clinical research and public health settings and concluded that informed consent requirements in cluster trials should be adjusted to the level of risk involved. I contended that a more comprehensive definition of research risk than that found in current research ethics guidelines is needed in order to take into account different types of health studies that may be conducted in developing settings and to provide clear guidance to research committees and investigators. I claimed that research risk should be defined more broadly and include not only health interests but also welfare interests and community interests (such as financial interests, cultural values and legal interests of the populations targeted by research projects). I also proposed the use of an ‘intervention ladder’ in order to define broad categories of research intervention as more or less risky and intrusive and, in this way, to provide a method for identifying cluster randomised trials where robust individual consent is required and studies where seeking informed consent from individuals is less important or irrelevant.

I claimed that although the distinction between individual-cluster and cluster-cluster trials (introduced by Edwards et al. 1999, and adopted by MRC guidelines and debates on the ethics of cluster research) could often help us identify difficulties associated with the nature of the intervention, and thus with some of the distinct features of population based interventions, it should not constitute definitive moral guidance on how problems related to our inability to obtain consent should be addressed. Relying on a distinction between individual-cluster and cluster-cluster trials cannot provide any guidance on when it is morally justified to use a cluster design or whether and when practical difficulties could override a consent requirement. Moreover, I argued that in contrast to what has been suggested in the current research ethics literature, a single justification for the whole spectrum of cluster research interventions that potentially restrict individual autonomy is difficult to defend. In such case, the question that needs to be answered is not whether individual consent is feasible but whether it is morally relevant to seek informed consent in the first place.

To summarise, I suggested that to decide on the appropriate informed consent standards that should be followed in a CRT, it is important first to consider whether the study in question concerns a clinical or non-clinical activity. Then, according to the features of each study, we should define broad categories of research intervention based on (i) the level of risk involved (distinguishing them as more or less or non-risky) and (ii) the level of intrusion involved (their impact on personal freedom). In this way, we can identify (a) broad types of cases that require robust consent, minimal consent or a waiver of consent, when a study concerns a medical intervention or directly applies to individuals (and thus where individual choice is relevant); and (b) broad types of cases where explicit individual consent is needed or can be replaced following a procedural justice approach, when a study concerns an intervention that applies in practice or community level.

Based on the human right to health approach, I explained that the principle of respect for persons does not suggest that the consent requirement is paramount and noted that it is important to ensure that individuals and their communities are not excluded from studies that could help them address their needs and meet their basic rights. I concluded that lack of individual consent does not violate the basic rights of participants who are deprived of their particular right to choose in population-based studies, provided that minimal or insignificant risk is involved and that other safeguards also apply (e.g. a decision regarding post-trial access has been made in advance). I listed in the category of low risk ‘population-based research’ many cluster research interventions that are often carried out in developing settings, such as educational practices (when they are not controversial), medical records review and surveys, experimental treatment of water supplies or of new insecticides (when insecticides have undergone prior safety and efficacy testing), health services and knowledge translation research. I noted that individuals should never be forced to participate in studies that involve substantial interventions, interventions in their body or private sphere, or those that involve considerable risk or restriction of personal freedom (except from cases of emergency). I claimed that a decision to accept or refuse a risky health intervention should never be delegated.

I explained that difficulties with obtaining individual consent due to methodological or cultural reasons should not be approached differently to difficulties presented in RCTs and that although a cluster design may facilitate the conduct of a valuable health research when researchers are faced with financial, methodological, administrative and other similar difficulties, the conditions under which informed consent could be omitted must be considered first. I then discussed cases where seeking informed consent is necessary and when the consent requirement could be overridden by other competing moral values (such as respect for local culture). I concluded that local cultures should be respected but not transgress absolute moral principles.

Finally, I discussed the procedures that should be followed to ensure that a cluster trial is morally legitimate to proceed despite the absence of informed consent and how my arguments relate to the 'human right to health' approach. I argued that a decision regarding the conduct of research should be within the responsibilities of the legitimate political authorities of the host country (and not of cluster gatekeepers or community leaders) and that communities that lack pre-existing political and social structures should not be neglected in health research. I claimed that although consent may not be possible, the right of individuals and their communities to be involved in discussions regarding their local health needs and research priorities and level of acceptable intrusion for the social good, should not be disregarded. I discussed the importance of procedural justice arrangements in forming an appropriate means of reconciling different preferences within a community or cluster, when informed consent from the participants cannot be obtained and that strong negative reactions should be carefully considered, if a final decision cannot meet everyone's approval. Finally, I reviewed the role of research ethics committees in ensuring that a research proposal is consistent with both the principles of research ethics and the local needs and interests of researched communities. I concluded that collaborative health research, which aims to improve the health status of a developing population, should be part of a country's policy, similarly to decisions concerning the implementation of public health measures, and that human subjects should be protected at individual, social and institutional level.

# Appendix

## **Conflicting interests: possible tension between community and science**

Aim of this chapter is to examine the uncertainties in defining communities in relation to the scientific notion of the cluster in collaborative health research. By presenting the views of participants in a community-based CRT in Mumbai, India, we<sup>148</sup> investigate whether residents' sense of community matches with the scientific notion of the cluster, defined by the investigator as a geographic area, and explore the extent to which the cluster trial answers their needs. We then examine whether the possibility of a conceptual mismatch is likely to have methodological implications for the study. I argue that it is important to take social factors into account as well as statistical efficiency when choosing the size and type of clusters and designing a trial. One method of informing such design would be to use existing forums for community engagement to explore individuals' primary sense of community or social group and, where possible, to fit clusters around them.

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<sup>148</sup> The analysis in this chapter is based on a collaborative work between S. Lignou, S. Edwards, D. Osrin, S. Das, G. Alcock and J. Mistry (a multidisciplinary team with backgrounds in medicine, research ethics, social sciences and both quantitative and qualitative research methods). For more information please refer to the methodology section.



## A.1 | Introduction

The principle of respect for communities<sup>149</sup> and practices such as community engagement have become important ethical requirements for the empowerment of participant communities and the protection of group interests in international collaborative research, as well as for enhancing the quality of research, in both international guidelines and the bioethics literature (Hunter 2012). For instance, in the recent Ottawa Statement (2013) it is recommended that cluster consultation may ensure that the cluster randomized trial addresses local health needs and is conducted in accord with local values and customs (Gallo et al. 2012). This has happened without providing much guidance on a clear definition of ‘community’ and thus lacks useful direction for conducting community engagement or community consultation. As a result, researchers have employed a variety of definitions of community (external definitions), and utilized different practices and procedures, to secure the ethical conduct of their research (Ragin et al 2008).

The choice of clusters to recruit into trials may be influenced by a number of factors, including ease of recruitment and type of intervention to be evaluated. Clusters usually have geographical boundaries, although this is not always necessary. For statistical efficiency, it is important to keep the size of the cluster, in terms of participants, as small as is feasible to reduce the problems associated with intracluster correlation coefficient (ICC).

The importance of communities and their protection in strengthening the ethics of international collaborative research is increasingly highlighted (Weijer 2000), but there has been debate about the meaning of the term ‘community’ and its specific normative significance. As a result, a variety of definitions of community have been employed by researchers (for instance in public health programmes and policy ‘community’ is where prevention and intervention take place (Mac Queen et al. 2001) and different practices have been used to consult or engage communities (Ragin et al. 2008; Fleischman 2007; Israel et al 2005). In general,

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<sup>149</sup> According to this principle investigators have an obligation to respect communal values, protect and empower social institutions, and, where applicable, abide by the decisions of legitimate communal authorities (Weijer and Anderson 2002).

community indicates “a sense of belonging together” (Weber et al. 1978) and may refer to a group of people with common characteristics, such as race, religion, profession or living in the same locality (CDC/ATSDR 1997; Tindana et al. 2007; Ragin et al. 2008).

There are often important differences between internal and external definitions of community: the way in which the members of a community define it and the way in which it is defined by others (Anderson 1983). This dissonance can lead to dispute (Sharp and Foster 2007). As Marsh et al. (2011) noted, in international collaborative research, definitions of community are usually made externally, based on the aims and the context of a study (involving, for instance, groups of people with a certain disease or risk-factor, those served by a particular health facility, living in the same geographical locality or having a legitimately elected leadership (Goodman et al. 1993; Couzos et al. 2005; Vallely et al. 2007; Upshur et al. 2007; Cargo and Mercer 2008; Minkler et al. 2008; Ragin et al. 2008; Shagi et al. 2008). Non-theorists’ definitions of community have rarely been explored (Ragin et al. 2008; Shagi et al. 2008).

Previous studies have shown that participants’ definitions of community do not necessarily coincide with those used by scientists. For instance, in a community consultation for emergency research, the authors found that researchers considered ‘PAD Trial community’ to mean persons of a specific age, those with a potential for cardiac arrests and geography (building or units), while participants’ definitions of community varied as a function of the purpose of the definition and the demographics of the respondents (Ragin et al. 2008). Researchers in a recent vaccine trial found that participation established mechanisms for information sharing and created relationships between participants, but excluded other members of the same village (Marsh et al. 2011). Many discussions on protection of vulnerable groups in health research, and on guidelines for protection of indigenous communities in genomic research, have also been based on the fact that individuals’ rights and interests had been violated in the past by involuntary consideration of members of the groups studied (Sharp and Foster 2007).

A CRT involving slum settlements in Mumbai, India, presented us with an opportunity to consider some of these issues specifically in relation to cluster trials. Our objective was to examine the uncertainties in defining communities (by taking into account that there is a variety of definitions of community) in relation to the notion of the scientific cluster (taking into account that clusters are defined by methodological and practical concerns of the research proposal). We aimed to inform the idea of community in CRTs by developing an understanding of participants' definition of community and the factors that help shape their views. We investigated whether residents' sense of community matched the scientific notion of the cluster, defined by the investigators as a geographic area. We considered whether the possibility of mismatch was likely to have methodological implications for the study (beyond a simple statistical adjustment traditionally called intra-cluster correlation coefficient, ICC), as well as present ethical challenges such as stigmatization of vulnerable groups, potential social disharmony because of the interventions in the study and political difficulties for any cluster representative. If there were differences between scientific and lay views, a cluster trial might create social and political conflicts by artificially dividing pre-existing communities, or by forcing together different factions in the same cluster and offering interventions and shared resources only through coerced collaboration.

In examining participants' idea of community, we wanted to explore how, in practice, to determine what the concept of 'community' should be taken to mean substantially in different contexts (i.e., what are participants' particular conceptions of community in different studies being conducted and among different populations with different conceptions of community) and how should researchers take into account these conceptions in determining clusters in their studies.

## **A.2 | Results**

Many respondents did not immediately identify with the term 'community' and some struggled to understand the question, "when we talk about 'community' how do you think of it? What comes to your mind?" As a result, the interviewer sometimes prompted the respondent with the idea of community as being

geographically based, which invited a closed choice. This may have suggested that respondents were unsure of what constituted their community or that the idea of community did not always sit comfortably with those who live in mixed ethnic and racial groups where there might have been a history of discord. In addition to notions of community, which related directly to the scientific idea of a geographically bound cluster, respondents were asked specifically about community relations to help interpret their uncertainty, and for any additional functional conceptions of community.

The transcripts yielded four main themes describing notions of community people living in a locality, social cohesion, shared problems or projects, and the moral status of groups. While these ideas offered a mixed definition of community, the responses at least suggested a common denominator: a shared identity with others. On top of this idea, other different and sometimes inconsistent thoughts on community seemed to emerge, suggesting that respondents were using the term flexibly to suit their different needs and preconceptions.

### **A.2.1 | Community as people living in a locality**

Almost all respondents included a geographical element in their definitions. "... I consider everyone to be my community. The people who stay around, who stay in our area, they are only our community people (female resident, 39 yrs, intervention area)." Most defined their community as a group of people living in the same area, which conveyed a shared sense of 'localness' from their immediate environment:

*Community is one ... that which comprises local people - that's community (male resident, 28yrs, intervention area).*

*For me community is basically my surrounding, my people around me; that's community for me (corporator, area?<sup>150</sup>).*

Everyone said that community comprised their neighbours, regardless of religious, ethnic or caste differences. These responses were spontaneous and

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<sup>150</sup> Researchers are unsure of the respondents' location in which they lived.

suggest that the idea of living in a ‘mixed’ community required explanation. For example, one male resident in a control area said, “... here there are Maharashtrians, Mohammedans and people of other caste, religion and ethnicity. It’s a mixed community here.” Interestingly, few respondents included religion alone as the determining factor. Many thought that it was important to give explicit acceptance to the idea that people with different religious beliefs could stay together in one place. The double negative in a response such as “we are *not* from *different* communities” may have reflected a degree of ambivalence or the need to express a socially acceptable view:

*... be it Hindu, Muslim, Christian, we don't feel that we are from different communities. We all stay together, we become part of one community. Wherever we meet, we are known as being people from Z. So, we trust the community that stays here and stays together (male resident, 55 yrs, area?).*

As with religion, so with caste. Respondents explicitly and spontaneously rejected the view that community equated to caste, a view which they recognized might be common: “These caste-caste people say that this is my community ... It is not ... that I will consider people of my caste to be my community. Everyone is my community (female resident, 29 yrs, intervention area).” Here, community is broader, more embracing of society. Given that all respondents lived in Mumbai slums, the explicit desire to include people from other castes is interesting and may convey a sense of social aspiration by identifying, or even a wish to project a sense of social responsibility onto those more fortunate by claiming a common bond. It seemed acceptable, however, to identify with a place of origin. Some identified their communities as from Uttar Pradesh, some from Gujarat – a solidarity that was often accompanied by language differences - and some in terms of long duration of residence.

The boundaries of the geographical community were closer for some than for others, especially when additionally determined by social relationships:

*... the thing is, our area is divided ... This way if you come here and ask us, then we will tell you ... these two roads are divided. So in between these two roads, the 10 and 11 Road is there. If you come with people from there and then if you want some information, then why will we give you?* (female 40 yrs, intervention area).

The respondent, who lived in Road 13, said that she had refused to participate in a study in which the researchers were accompanied by people from Roads 11 and 12.

### **A.2.2 | Community in terms of social cohesion**

A few respondents included family in their responses about community. “My community is my children ... my family ... my own. That’s it (female resident, 25 yrs, intervention area).” The relative importance of different members of a social network may be reflected in the order in which the respondent listed them: children first, family second, and own people last, as if in concentric circles. The contrary view was that neighbours were part of the family:

*It’s a mixed community here. We think of everyone as being our brother and sister, relative, and accordingly we stay. Here, I do not have any relatives. They are all at different-different places. But the people of this mohalla (area), they are all my relatives* (female resident, 45 yrs, control area).

*The whole area, lane, is my friend. And relatives, no one is there* (male resident, 45 yrs, intervention area).

As well as conveying a feeling of closeness by identifying community with family, others emphasized the quality or harmonious nature of relationships based on communication and a common language, and gauged their perceived intimacy as analogous to family relations or to friends.

*[Our] Relation is very good with each other. For example, I met you now, so now you have become my Madam (I will address you as Madam). Now when we start talking gradually, then you will call me didi (sister) or I will*

*call you didi ... So that way we have the same relation in the area. We call some people chacha (paternal uncle), mama (maternal uncle), some we call khala (maternal aunt), some we call buwa (paternal aunt). This way the relation is like home ... Being related as friends is the best thing ...* (female resident, 29 yrs, intervention area).

This view was not ubiquitous. Some respondents said that residents of the same area had good, but not intimate, relations with each other, and could not be described as friends. Nevertheless, most respondents said that they lived in a united area where all residents had good relations with each other, regardless of their religious or caste differences, an avowal that we have already mentioned. “We maintain harmony with every religion. For us, this is our religion and the other religion is not. We maintain relations with people of other religions too (female resident, 32 yrs, area?).” Maintaining relations might sound a little less than heartfelt and the sweeping generalization to every religion might suggest reluctance to cause disquiet. One respondent used the metaphor of sharing a meal to convey the closeness of community relations and the social ritual of eating: “... Everyone ... used to sit and eat from the same plate. The Hindus, Christians everyone used to sit and eat from the same plate” (male resident, area?).

For some, the good relations between groups in their community contrasted with those in other areas.

*Now that everyone stays like one; like one. Now once again they had come, everyone ... Everyone stays like one here ... Everyone treats us nicely. The people in villages are different. Here no one will think that way* (female resident, 25 yrs, intervention area).

This is another example of defining one’s community in terms of what it is not. In this case, urban life was compared with rural life. Others compared long-term residents with newcomers. “But in our area, it was we Hindu, Muslim, people belonging to all the religions that are there, we united so that no person from

outside can come inside (female resident, 35 yrs, control area)” Or owner occupiers with rental tenants.<sup>151</sup>

Some respondents, however, believed that their area was not united. Distinctions were made between established residents and recent arrivals, with some effort to ascribe blame for deterioration in quality of life:

*The Muslims who have come from UP, Bihar, Bangladesh, they have made it very dirty. In this last five years this area has become completely dirty. But the Muslims who have come from Bangladesh, because of them there have been incidences of rape on small girls. Since then here the environment has become bad... since the last 10 years; ever since the Samajwadi Party has come to power, Abdul Hazim (president of Samajwadi party) ... since then the gangsterism ... lootmaar (vandalism) (male resident, area?).*

Violence was mentioned, and, again, blamed on another group, with the emphasis on the reasonableness of the respondent’s position:

*Now the children ... of this new, new generation, even for small matters they indulge in physical violence. But the old residents who are there, we first make them understand. If they don’t get convinced then even we ... the thing is, first of all we are not the kind of people who will indulge in physical violence. We just directly complain, dial the number (to police) (female resident, 36 yrs, control area).*

### **A.2.3 | Community in terms of shared problems or projects**

Some respondents said that being a member of a community meant helping neighbours when they were in need, especially when there was no immediate family living nearby. “I don’t have relatives here, but if something happens to me now, my entire house would be flooded with people (female resident, intervention area).” Less typical responses included helping each other as a corollary of being related like family: “As far as the community is concerned, where we stay, all the

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<sup>151</sup> However, not all of them believed that their area was divided.



local people, we stay like brothers. If they face some problem or if we face some problem then everyone will work together” (male resident, 51 yrs, intervention area).

Reflecting a view of community in terms of sharing health resources, many respondents mentioned the lack of a local government hospital, particularly for maternity services.

*At least a hospital should be there. Pregnant women who are there, in Govandi that is there, the nursing home. When it is time to give birth to a child, that time the woman is struggling between life and death ... Even the child's life is (at risk), and regarding health, everyone here ... thinks. Because when they give birth to kids, it is also important to think about them, isn't it? (female resident, 39 yrs, intervention area).*

Environmental conditions represented a shared experience that might draw people together and support their notion of community. Water supply – or the lack of it – was a common shared burden: “...the *nagar sevika* (corporator) here said water will be provided. The pipeline has been dug; pipes have been laid but only for show, to devour money as was the accumulation of waste.

*If you see the entire area surrounding ... the dirt that falls out of that vehicle keeps falling on the road. In that, our kids play. In that, our women walk. And in that, we have to walk. That is not something less; it is a big bundle of diseases that is given to Z by Municipal Corporation. Now, here the people seek employment. (Suppose) someone runs a welding factory here. Now if that vehicle has to be welded then its entire dirt will fall at that place. We cannot stop him. Because it is his employment, we cannot say no to him. In a way, he is helpless and we too are helpless. Because he has to earn his living, we suffer from diseases. Everyone staying in this area has to tolerate. So, all these things that are there, meaning this pollution, such big pollution, why is it in Z only? There are many things that one can say... (55 year old, man, gatekeeper, area?).*

*So here there are many poor people. Since it is a slum area it is a very poor locality. So here there are many diseases ... that are usually prevalent. Now if I open this (window) so much smell... will come from this dumping ground. That staying here ... is difficult ... difficult it is. Now here there are many diseases like TB, malaria, typhoid ... Now mainly here there is the smell, dumping ground is there; biomedical this has started.... the entire Mumbai's filth is there. The children here are not safe. Here there is smell, there is ... How can the children be safe? Always something or the other. In a year, every month we have to get medicines for our children (female resident, 39 yrs, intervention area).*

This having been said, shared problems did not necessarily lead to collective action to relieve them.

*These small diseases like fever happens to kids while playing in filth; these fodia (skin infections) occur in head, in hands, in legs. This continuously keeps happening to someone or the other. And nobody is ready to maintain cleanliness. If one person maintains cleanliness, then four people will come running to make it dirty. This is how it is here ... Here, make a wall from this side and from that side and in between, make a road. And the dustbins, the big ones that are there, keep two that side and two this side so that the filth does not happen. In this filth, the children go. How many times the mother will hit the kids saying "don't go, don't go, don't go?" How much can she do to keep the child home? Firstly, the area should be clean. If the place is clean, even the kids will stay clean. Health will also be good then. Health depends on the surroundings (female resident, 29 yrs, intervention area).*

In the face of such problems, many simply felt helpless to act and seemed to point the blame at the authorities for heaping societal problems on the same vulnerable groups.

*If you ask any person like me (meaning a resident of this area), then he will say that we are helpless. We stay in slums because we are helpless. (Since*

*the authorities here give permission to such companies, biomedical waste is brought and burnt here....Now, since 22, 30 years we have been tolerating this (garbage vehicles in our area). Due to this, there are various diseases. If you want to give all diseases in a particular area, then this is the way (male resident, 55 yrs, area?).*

#### **A.2.4 | Community in terms of moral status of groups**

Most respondents believed that both control and intervention areas should have access to intervention services being evaluated in the cluster trial. “We feel bad that one has been given and the other has not been given ... No, one should not do this. If one is giving, then give it to everyone little-little (female resident, intervention area).” Their views on fairness and study design were led by, and implicitly relied on, geographical notions of community as clusters. In one case, the trial was perceived as socially divisive unless the wider research community understood the reasons for it and the intervention might subsequently be applied to control areas.

*How will we feel ... then people will start fighting: that there it is this way, at our place there is nothing like this. Why this? This way everyone will start fighting.... I mean the ones who are understanding, they will keep quiet. Now that it has come there, then one day it will come here too: this way some people will think (female resident, 25 yrs, intervention area).*

One respondent talked about a queue for such services and the degree of effort those in the control areas had put into the project.

*... For example, you might say that only my lane will get the facilities that are there and that lane will not get. So what I would want is even that lane should get facilities. All the 10 areas should get ... I will feel. I will put so much effort that the area in which you get more support, so that our turn may come soon ... one thing that we will feel is that our turn should come soon (female resident, 36 yrs, control area).*

Implicit in these views is the sense of humanity and moral identification with those who are denied services: “This should not happen. For both the

communities, it should be the same ... In a society, everyone is equal ... The people there, humans are the same everywhere, aren't they? There is no difference between people. Even they eat grains, even we eat grains (female resident, 45 yrs, control area)" A minority said that it was important to them that their area would have partial access to the services. "If my area doesn't receive the services, then I will break Sudhir *bhai's* head. Because here, we people stay. We know that here such things are needed (female resident, 40 yrs, intervention area)."

### A.3 | Discussion

The term community seemed to have either a narrow or broad meaning for different respondents. For example, it was used to refer to all of Mumbai or a locality, or was understood in terms of religion (for example, all Muslims). It was also used to describe a group of people who lived in the same area and had something in common besides a shared sense of place, such as religion, ethnicity, dialect, proximity to one's house (residents of the same lane), or a specific relationship with each other (family, relatives).

The term was never used to distinguish people of the same caste, and this raises an important issue. Communalism – in terms of conflict between identity groups – is never far from Indian consciousness and casts a shadow over politics and society. Although caste has been abolished, social divisions persist and subpopulations are still classified according to caste and tribal status. Likewise, the potential for Hindu-Muslim conflict is an ever-present cultural trope that calls to mind a history of violence that extends to the present. The Mumbai riots of 1992-1993 were largely located in poorer areas and it may be that people felt a need to describe their communities as mutually tolerant, a counterpoint to both society's and their own concerns<sup>152</sup>. Finally, the notion of the slum is often used as a means of 'othering' its residents and has many pejorative connotations. One could propose a scenario in which our respondents were keen to emphasize their good relations with their neighbours – particularly in terms of caste and religion –

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<sup>152</sup> Although we did not want to give an interpretative authority with respect to participants' behaviours or statements, we considered that a distinction should be made between what people say about their conceptions of their community and who is in it and what do they actually hold.

and at the same time to reframe their slum dwelling status in terms of modern urbanity, tolerance, and fraternity.

About half of the respondents raised ideas of community additional to geography or locality, most of which were consistent. Some appeared inconsistent and might suggest that people felt that they belonged to more than one community, had multiple identities that either held simultaneously (as in family relations) or were drawn on singly, but were functionally dependent on the context or the question posed (for example, in response to questions about health problems or evaluation of fairness and clusters). Alternatively, they may have not had a clear view of what community is. There were no conflicting responses between individuals in the same area.

The fact that so many were sympathetic to a geographical definition of community means only that their sense of community seems compatible with the scientific notion of a cluster. Most respondents gave a geographical definition, and only two excluded their immediate neighbours. However, the boundaries of the locality, the extent of the community's reach (explicitly or implicitly identified by respondents) and the geographical areas covered by the corresponding clusters were often different. Ideas of geographical boundaries were different even within lay responses; for instance, one gave a narrow geographical definition, including only people who lived in her lane, while two others said that they considered as their community only the people who had been living in the area for many years. Only six people clearly defined their locality as their community and used phrases such as "this is a mixed community". More than a third were prompted to give a geographical definition (most of them had given an apparently inconsistent non-geographical definition before) and eventually agreed that the people in their area - their neighbours - were also their community.

The findings suggest that there was unlikely to be an obvious conflict between a lay and scientific view of community in the case of this particular cluster trial. The respondents seemed willing to agree with ideas of community, including scientific ones, once prompted, which might indicate that they were willing to internalize (or rationalize) their involvement in the trial. Some methodological

limitations of the study should be noted. When respondents were asked to define their community, half of them did not understand the question to begin with and the interviewer had to use examples. Either they were unfamiliar with the term and had not been asked to give a definition of community before, or the words that the translator was asked to use (*samaaj*, *basti*) and the original term 'community' do not have exactly the same meaning. However, by using examples and rephrasing questions we believe that responses and their translation did not bear a systematic misinterpretation of the respondents' views.

Existing research suggests that notions of community reflect a distinct set of values and governing structures (Weijer 1999), as well as sufficient social interaction and permanence to allow an individual to identify herself as a community member (Ragin et al 2008). Good relations between the residents of an area are not sufficient to claim that people with a shared sense of place constitute a community<sup>153</sup>. In particular, some respondents said that they did not have harmonious relations with their neighbours. This might have methodological implications for cluster design and for research governance, including the choice of cluster, statistical adjustment for similarity, and the roles of gatekeepers in proving cluster consultation or permission on behalf of the cluster.

A few people said that the reason that all residents lived in harmony, despite the fact that they lived so densely, was that they did not interfere with each other's lives. The intervention under test encouraged community members to discuss intimate personal issues such as family planning and domestic violence. It was, therefore, important that beneficiary definitions of community are respected, in order to prevent their having to discuss this sort of information with people they do not consider as members of their group. Responses to perceived causes of disease were also associated with geographical ideas such as environmental or living conditions and access to hospital facilities, and these resonate with the scientific notion of clusters and the need to address a shared problem. Many respondents thought that denying control clusters access to the trial intervention would be unfair, and often referred to clusters as communities, apparently

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<sup>153</sup> Although good relations are more likely to lead to active cooperation.

adopting a scientific view and suggesting they had sympathy with the wider society of included clusters.

Future research could investigate the potential for such mismatch in other, more controversial, CRTs in order to judge whether it is an issue worthy of ethics review. The question of what a community is and how well scientists are able to incorporate such a notion seems logical prior to any analysis of balancing the social value of a CRT against the risks and potential benefits to individuals within communities. Despite the comforting findings in our study, it is still conceivable that artificial division of communities or social groups (to achieve smaller numbers of individuals in each cluster) could lead to social and political conflicts.

### **A.3.1 | Potential social disharmony and mistrust**

A trial might create intra-community tensions between participants and non-participants or between intervention and control groups, linked to the provision of services and the nature of individual costs and benefits. This would undermine relations of trust and understanding between researchers and social groups that participate in research. Moreover, a potential disagreement between a lay and scientific view of community could have methodological implications, such as contamination (because of the proximity between the members of the group), and ultimately undermine the value of the study.

### **A.3.2 | Potential harms to individual members**

Differences between internal and external definitions of community may also affect the interests and rights of individual members of the social groups that participate in research. Researchers usually define social groups by the way they function socially, politically or morally as whole groups, or by their genetic or disease characteristics, but the perspectives of individual members may be different. An individual's membership may be voluntary (membership in a group may be important to an individual's sense of identity) (McMillan and Chavis 1986; Puddifoot 1995), but may also be involuntary (the benefits and harms of a group may affect an individual because she has been born and raised in it and not because she has chosen it) (Putnam, 2000). Determining who is and who is not a member of a group can be a matter of dispute (Sharp and Foster 2007). In CRTs,

this dispute may be problematic, especially in the case of cluster trials of interventions which cannot be administered individually (cluster-cluster trials), in which individual participants cannot opt out or are not offered the opportunity to consent. Potential harms to individual members, such as stigmatization and undue influence to participate, should be considered. In contrast, individuals may not be identified by researchers as members of a social group and may be denied the right to participate.

### **A.3.3 | Uncertainty of the role of the cluster representative**

The way cluster boundaries are defined in CRTs will also affect our approach to issues of representation. A cluster might include a well-defined group - for example, a village - with legitimate political authority that could represent and protect the group's interests and consult the researchers on group needs and values. However, a trial may include clusters with more than one well-defined group - for example, two or three villages - and offer shared resources and interventions through collaboration. If the groups have different values, needs and traditions, which cannot be reconciled, which group's interests should take priority? Is it morally justifiable for a trial to deliver what is objectively in the researchers' interests without taking into consideration the views and values of participant groups? Practical challenges concerning the resolution of disputes between different parties (especially when there is potential harm) should also be considered.

Since a variety of clusters are involved in CRTs, the degree to which group and community interests may be affected by a disagreement between scientific and lay views of community will vary. Social groups range from extremely heterogeneous to homogenous. They may consist of geographically dispersed populations or highly localized communities that share common sociocultural traditions and whose members interact frequently (Weijer & Emanuel 2000). Moreover, there are multiple types of relations between individuals and their groups or communities; for some individuals membership may be voluntary, and for others involuntary. Some individuals may have exclusive membership of a community, while others may be identified with several communities (Widdows and Cordell 2011). Different interests and goods will be affected in different types of



communities. For instance, a trial in which cohesive communities such as villages are divided into clusters may seriously affect the maintenance and integrity of their social structures and the solidarity and unity between their members, while a trial that randomizes hospital wards would not have the same implications. In the latter case, other common interests would be at stake for cluster members (the patients in the wards), such as their interests in the quality of the services that facilities provide (Sharp and Foster 2007). Finally, the degree and kinds of interests that could be affected by group participation in CRTs will also depend on the type of study. For instance, group-based interests are more likely to be substantially affected in a CRT that tests a new vaccine than in a knowledge-translation study.

#### **A.3.4 | A combination of the scientific and lay approach**

To prevent potential and theoretic conflicts becoming morally problematic, another type of community could be suggested, which is a combination of the scientific and the lay approach. This would respect residents' needs and values and would reduce the potential methodological difficulties of defining the boundaries of the cluster and of statistically adjusting for similarities within each cluster. By using existing forums for community engagement, researchers could explore what individuals' primary sense of community or social group comprises and, where possible, try to fit the clusters around them. The difference between this notion of community and the cluster is that it would also be based on people's values and needs and would not be an external definition for scientific purposes. It would also entail a normative process, meaning that it would presuppose that researchers know and respect the existing social relations and hierarchies and through this avoid intra-community tensions. Members of the community do not necessarily need to be close to all other members, but should be able to work together and in harmony with those who have the same health needs.

#### **A.4 | Conclusion**

The findings suggest that, while there might be challenges to drawing cluster boundaries in CRTs, it is unlikely to be problematic in the particular trial under study. Nevertheless, I argue that it is morally and politically important to take

social factors into account - as well as statistical efficiency - when choosing the size and type of clusters and designing a comparative trial. One method of informing such design would be to use existing community forums to understand what individuals' primary sense of community or social group comprises and, where possible, to fit the clusters around such perceptions.

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