RESEARCH ETHICS IN THE CONTEXT OF A DEVELOPING COUNTRY: PERSPECTIVES FROM PAKISTAN

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Abstract

The overarching rationale of research ethics guidance is that human participants should not be exploited when contributing to the good of science and society. Two essential requisites for this are that human participants consent voluntarily after being informed about a research trial and that benefits and risks are distributed fairly. With the increasingly global practice of biomedical research, fulfilling these requisites creates challenges in some contexts.

I examine the challenges of applying these ethical requirements when patients are enrolled into research trials in Pakistan, with reference to the moral reasoning employed by researchers to negotiate these challenges. Using insights obtained from interviewing physicians conducting research and patients in tertiary-care hospitals, and from observing the interactions between these physician-researchers and patients in the context of research trial enrolment, I demonstrate how the socio-cultural environment in which research is carried out shapes the practice of ethics in important ways. I present the issue of informed consent as the core challenge. I also examine the implications for research of the researchers' view that their primary duty is that of a physician.

The researchers determine the amount of information patients receive about research, guided in this by their sense of duty and influenced by their communication skills, time constraints and patients' education status. The process of decision-making is affected by such factors as the patients' gender, education level, financial independence and the role of other actors such as the spouse, relatives and the researcher. Commonly, a joint decision is reached after mutual consultation within the family, but sometimes patients may delegate or accept decisions made by the family, and occasionally the family's interest is inconsistent with the best health interest of the patient. This raises ethical challenges. When recording consent, a written consent is obtained because sponsors and guidelines require it and researchers prefer it. This emphasis on a written consent raises ethical challenges with regard to the ethical principle of respect for persons. I also argue that following the ethical principles of justice and equity are essential to avoiding exploitation when conducting research.

Complex issues arise when guidance and local norms are at variance, or there is disagreement between local norms and fundamental rights. Their resolution requires sensitivity to, and awareness of, the context. Importantly, it is the commitment of those conducting research and at the interface with patients that determines the ethics of research. I conclude that upholding the spirit of the guidelines is more important than procedural intransigence.

CONTENTS

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I dedicate this thesis to my late mother –Zarina Yazdani Khan and my father - G Yazdani Khan - for instilling in me the

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This project is thus not a sole achievement; it is collective and I rejoice in that.

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Statement of Authorship

This thesis is the result of my own work, except where otherwise indicated. All other sources are acknowledged. It contains approximately 77, 500 words, excluding, footnotes, bibliography and appendices.

Introduction

Biomedical research is integral to improving health-care and its results can save lives, as I know from personal experience. As an intern in a government paediatric hospital in Pakistan, I treated hundreds of infants with acute diarrhoea using oral rehydration salts (ORS), without which infant mortality would have been very high. Researchers went on to improve and introduce zinc and low osmolarity ORS which further improved treatment. Later, working as a registrar in haematology, I administered chemotherapy and saw its effects on improving prognosis for some patients. Were it not for research into new treatments these lives would not have been saved.

In the development of a new or improved intervention, it is usually necessary that its efficacy is tested on human beings. At this stage “the scientific merit of a project must be matched by the ethical merit of the work” (Benatar 2002). Ethics has tempered medical practice and medical research ever since medicine has been practiced but there have been instances when ethics was disregarded and human participants were exploited with fatal consequences. The experiments conducted during World War II are a reminder that, despite guidelines setting out key requirements for conducting research on human participants, fundamental principles of human rights and ethics can be ignored or considered unnecessary. When human participants are considered as “other” they may be stripped of the protection afforded by the established guidelines. Research must therefore be guided not only by sound scientific principles but also by fundamental principles

of human dignity and ethics (Benatar and Singer 2000; Benatar 2000; Annas and Grodin 2008; Bhutta 2002).

There is rapid transnational movement of medical knowledge and an increasing amount of research is being conducted between countries by international collaborators and locally. The expressed aim of funding organizations is to find affordable treatments for diseases affecting the populations of low and middle-income countries, and to improve their quality of life and well-being, as well as to expand scientific knowledge (Gates-foundation 2012; MRC-UK 2012; INDOX 2010; Wellcome-Trust 2012; EGE 2003). In addition, the growth of pharmaceutical sales is driving an unprecedented search for human subjects, particularly in low and middle-income countries (Petryna 2005, 2009; Gitanjali 2011; Glickman et al. 2009).

To avoid exploitation of human participants, two important ethical considerations are: obtaining an informed consent from patients to enrol in research *and* justice in distribution of benefits and burdens (Emanuel, Wendler, and Grady 2000, 2008), included in it is fair selection of research participants (Belmont 1979). Trials in developing countries raise concerns about whether consent is meaningful when obtained from patients with low literacy and poor understanding of medical research (Lynoe, Chowdhury, and Ekstrom 2001; Bhutta 2004 a; Macklin 2003 ; Hill et al. 2008). There are also concerns about meaningful consent where it is not given autonomously (Alvarez-Castillo 2002; Ezeome and Marshall 2009; Gupta, Goel, and Bhoi 2006) or is given as consequence of economic constraints and patients' ignorance of their rights (Abbas 2007; Bhutta 2002). Patients

in developing countries are also at risk of exploitation from being enrolled in research that has little or no benefit to themselves but greater benefit to others (Sirinivasan and Loff 2006; Alvarez-Castillo 2002; Benatar and Singer 2010; Benatar 2000, 2001; Macklin 2003 ; Igoumenidis and Zyga 2011). The guidelines were considered "sufficiently vague to allow for virtually any method of obtaining consent", such that the informed and voluntary aspect of that consent was questionable (IJsselmuiden and Faden 1992:830).

Although research ethics guidelines have been revised in line with the globalization of research, their application continues to create challenges in developing countries. This has led to a debate on whether the requirements stipulated in these guidelines are applicable wherever research on human participants is conducted (Macklin 1999a) or need to be adapted to conform to the contexts where research is conducted (Chattopadhyay and DeVries 2012). For instance a standard requirement of these guidelines is "autonomous decision-making" but fulfilling this requirement is challenging in many international settings, where cultural norms require persons considered more authoritative to make decisions on behalf of others (Kass, Maman, and Atkinson 2005). An emphasis on a written consent appears to reflect cultural insensitivity (Emanuel et al. 2004), and as such would be seen as a form of "ethical imperialism" (Bhutta 2001). In either case a dogmatic approach to following ethics guidelines and (or) local norms can result in unethical practices.

This indicates the need for applying the requirements of ethics guidelines in a manner that is culturally appropriate for the specific

research context but which is simultaneously ethical - that is, guided by moral reasoning rather than arbitrarily interpreted for pragmatic ends (Benatar 2002; Schuklenk 2004) - such that contextualized interpretation upholds the "true spirit" of research ethics guidelines (Bhutta 2002), while respecting local ethical values (Chattopadhyay and DeVries 2008). However, local practice may or may not conform to stated ethics requirements, and should be taken account of in ways that protect participants from exploitation (Bhutta 2001, 2002, 2004 a; Benatar and Singer 2000; Benatar 2004; Tangwa 2004). Thus, "one should respect practices within other cultures that pose no threat to health and safety, but reject those that infringe on universally agreed human rights"(Benatar and Fleischer 2007 :620), otherwise the ethical merit of the research enterprise will be undermined.

Since ethics guidelines do not land into a vacuum, they must be grounded in the lived reality of individuals (Chattopadhyay and DeVries 2012), therefore taking account of the context in which the guidelines will be applied is a moral requirement (Benatar and Singer 2000). Such an approach entails an interpretation of ethics guidelines that is empirically informed by an understanding of local norms and practices, and the reasons that underpin them. Knowing the practical realities of research in action would also facilitate decisions about which guidelines are relevant and applicable, or in need of amendments (Chan and Wendler 2010; Molyneux and Geissler 2008).

There is also a need for forming or redrafting effective local ethics guidelines (Bhutta 2002). For example, the Indian Council of Medical Research (ICMR) has developed its own research ethics guidelines in

which twelve principles specifically suited to local context are elaborated (ICMR 2006). In many contexts, however, the current understanding of indigenous ethical practice is superficial (Fox and Swazey 2008; Nie 2007; Hyder and Wali 2006; Bhutta 2004 a) and there are calls for empirical research to enhance this understanding (Macer 1999; Veatch 2003).

The research presented in this thesis aims to provide such an understanding from Pakistan. My thesis rests on the empirical findings regarding informed consent and justice in research in tertiary-care teaching hospitals of Lahore, Pakistan. While empirical research on these issues has been forthcoming from other developing countries, research ethics has not been an area of focus in Pakistan (Hyder and Nadeem 2001).

My objectives in this thesis are twofold. First, I seek to provide an empirical understanding of the context of research practice by describing the views, experiences and practices of researchers and patients enrolled in research. This exploration of "indigenous" practice and the realities molding it fills a gap in the research evidence, because no such work has been conducted on physician-researchers and patients enrolled in research, in Pakistan. Second, my presentation and analysis of these local views, experiences and practices seeks to highlight the ethical issues that arise, to examine how these are managed, to reflect on the implications and examine the relationship between research ethics guidance and local practice.

I begin in Chapter 1 by examining the research ethics guidelines and their evolution. My main emphasis here is on informed consent and responsive research, two of the requisites for avoiding exploitation. The chapter also reviews literature from developing countries in general and Pakistan in particular, to point to the need for a better understanding of local researchers' and patients' perspectives on research enrolment.

In Chapter 2, I discuss the methods I used in order to obtain "a respectful understanding of local categories, local narratives and local practices"(Kleinman 1999:79) of research enrolment. My main data collection methods comprised interviews and observation of researchers and patients at tertiary-care hospitals. Since my researcher-participants were clinical doctors who conducted research in addition to their clinical work, I refer to them throughout this thesis as physician-researchers. My patient-participants were those who were enrolled in research trials being conducted at the time of my interviews; I refer to them as patients.

In chapters 3-6, I present the findings of my data analysis. Concerns regarding informed consent emerged as the predominant issue and therefore constitute the main storyline of my thesis. I tell this story by following the chronological stages through which consent was obtained.

Chapter 3 describes some of the issues that arise when physician-researchers provide information to patients with varied levels of understanding. The chapter presents physician-researchers' views

about patients' understanding of information and patients' perceptions of their understanding, supplemented by my observations of the interactions between the two. It also shows how various contextual factors such as education, time available for consultations, and physician-researchers' attitudes towards patients' information needs affect the provision of information.

In Chapter 4, I examine the process of coming to a decision, describing physician-researchers' and patients' views on the various types of decision making I identify. The chapter analyses the role of the physician-researchers, of the family and of gender in the decision-making process, and highlights the particular challenges associated with recruiting women into research trials.

In Chapter 5, I present findings, from the physician-researchers' and patients' viewpoints, related to the purpose of obtaining a written consent, and its implications in a population with low literacy.

In Chapter 6, I present two further themes that emerged as important for the physician-researchers. One was the primacy of their role as physicians, which for them raised the issue of responsive research. The other concerned challenges for them as physicians presented by variations in the local conception of patients' autonomy.

In Chapter 7, I discuss the ethical issues identified in chapter 2-6, and summarized in the concluding remarks of those chapters, in the light of comparative literature from developing countries and the requirements of research ethics guidance

My concluding chapter presents a summary of my analysis. This confirms the view that an insistence on procedural requirement of the guidelines can result in ethically untenable practices but that adopting locally acceptable practices can also be ethically problematic. I suggest that incongruity between local practice and the requirements of the guidelines can be minimized if the guidelines are interpreted not literally but so that the intention of the guidelines is retained and their spirit realized. This should be the broad aim of using empirically informed understanding of context to interpret ethics guidance.

Chapter 1

Literature Review

This thesis examines some of the challenges in developing country contexts of applying international guidelines for the ethical conduct of biomedical research on human subjects. On the basis of fieldwork with physician-researchers and patients involved in research trials in Pakistan, I examine issues relating to two main requirements for conducting ethical research: the requirement that a voluntary, informed consent is obtained from research participants and the requirement that research is responsive to the health needs of patients and populations from which research participants are drawn.

In this chapter, I review the ethics guidance relating to informed consent and conducting responsive research and I identify the key challenges of implementing these requirements that have so far been documented in the research ethics literature from the developing world, including Pakistan. I begin by introducing the most influential international ethics guidelines in use today and the international frameworks formulated to assist in the interpretation of these guidelines. The central section of the chapter draws on this corpus of guidelines and frameworks to present the core requirements for informed consent and responsive research and identifies the challenges of implementing these requirements in the developing world. The final section examines the requirements for ethical research as stated in national guidelines formulated in Pakistan and

reviews the literature on these requirements and their implementation in the context of the nascent field of research ethics in Pakistan. This section demonstrates the need for a better understanding of the circumstances in which patients are enrolled into research trials in Pakistan so that the ethics guidance can be more effectively adapted to local needs. It also establishes the context in which I present the findings of my research.

1.1 International research ethics guidelines

Concerns for patients' wellbeing and rights have long been an integral part of medical practice and health-care professionals have been bound by ethical codes and oaths since Hippocrates. It was not, however, until the nineteenth century, when experimental methods were used with patients, that medical practice became clearly distinguished from experimentation (Vollmann and Winau 1996; Jonsen 1998). The enthusiasm for experimentation may have advanced science but appalling stories of abuse were reported, resulting in the experimental spirit being tempered with a "roughly defined ethic" (Jonsen 1998:132).

The first ethical standard in the form of a Directive on Human Experimentation was formulated in Prussia in 1900 (Vollmann and Winau 1996; Fluss 2004). This forbade all non-therapeutic experimentation unless "the person concerned has …declared unequivocally that he consents to the intervention…on the basis of a proper explanation…" (Jonsen 1998:133). This guidance foreshadowed the present day requirements for informed consent and

enumerates clear directives concerning the general, technical and ethical standards to which research should conform.

1.1.1 Nuremberg Code

The Nuremberg Trials at the end of World War II included "The Doctors' Trial" in which Nazi physicians who had conducted experiments on prisoners and ethnic and religious minorities were prosecuted. Evidence at The Trial showed that Nazi physicians had blatantly violated the principle of "do no harm", despite the Reich Minister of Interior's 1931 guidelines on innovative therapy and scientific experimentation, which were more extensive than the subsequent Nuremberg Code and other declarations (Vollmann and Winau 1996; Jonsen 1998). The "Nazification" of medical values had resulted in researchers viewing their "experimental subjects as having lives of lesser value" (Weindling 2008 :20).

The Trial ended in 1947 and the ensuing Nuremberg Code delineated ten basic principles for ethically, morally and legally sound experimentation (Jonsen 2000; Brody 1998). Based on principles of natural law and human rights that were believed to have universal application, the Nuremberg Code is by far the most influential document underpinning present day international ethics guidelines for biomedical research involving human participants. It laid down the foundation for informed consent by asserting that "the voluntary consent of the human subjects is absolutely essential" (Annas and Grodin 2008:139; Shuster 1997). For a research subject to be able to exercise free power of choice they should have sufficient knowledge

and understanding of the research and its associated risks such that he or she can make an informed decision.

1.1.2 Declaration of Helsinki

In 1949, the newly formed World Medical Association (WMA) adopted the International Code of Medical Ethics. This code aimed at ensuring the independence of physicians to work to highest possible standards of ethical behaviour, serve humanity and raise the standard of professional conduct (WMA 2008a). In 1964 the WMA adopted the "Principles for those in Research and Experimentation" on human subjects as a Declaration, known as the Declaration of Helsinki, formerly passed as a resolution in 1954. The focus of the Declaration was on the responsibilities of the physician-researcher and the assessment of risks, following revelations that ethical errors in the conduct of experiments on human participants had increased in number and variety (see Beecher 1966). The 1975 revision strengthened the protection for research participants and is considered the classical text of the Declaration (Ashcroft 2008).

The Declaration provides a concise code of ethics for physicians involved in medical research and is widely accepted as the cornerstone of ethical guidelines. It has become ingrained in the international culture of research ethics with several countries endorsing or emulating the Declaration in their research guidelines (Ashcroft 2008; Fluss 2004; Lurie and Greco 2005; Brody 1998).

The Declaration endorses informed consent and though it allows for consultation with the family the decision to enroll must be made

willingly by the research participant. It focuses on the responsibilities of the physician-researcher and on the protection of research participants such that risks and harms are minimized and benefits enhanced. This focus is an attempt to avoid exploitation; as Macklin writes, “arguably, the entire declaration can be seen as an attempt to protect human subjects from exploitation” (Macklin 2004:107). The Declaration is a “living” rather than a static document, and is reviewed and revised regularly (Williams 2008; Forster, Emanuel, and Grady 2001).

From 1996 – 2000, there was heated debate over paragraphs 29 and 30, which are now revised as paragraphs 32 and 33 in the 2008 version (WMA 2008), concerning the use of inert placebo for patients in the control group of a trial and the provision of the proven intervention to trial participants, especially in trials conducted in the developing countries. The debate was essentially on the harms and risks that trial participants are exposed to and became a moot point following short regimen AZT (Azidothymidine) trials to prevent mother to child transmission of HIV/AIDS in sub–Saharan Africa.

The issue with the use of placebo as a control was whether the control group should be given the “best proven” (ACTG-076) or the “best available” treatment, or rather – given that, as in many developing countries, there was no available treatment- whether the control group should be given the more costly and established ACTG-076 treatment or no treatment (the placebo) (see Ashcroft 2008; Malik and Ghafoor 2012). In 1996, a clause permitting the use of placebos in trials where no proven diagnostic or therapeutic intervention exists was introduced

into the revision of the Declaration and retained in the 2000 revision. Then in 2002, following concerns that paragraph 29 had been variously interpreted (Macklin 2009), the WMA added a note that was subsequently integrated into paragraph 29 clarifying the ethical acceptability of placebo-controlled trials, even if proven therapy is available, for "minor conditions" or "for compelling and scientifically sound methodological reasons". Critics objected that this clarification's appeal to scientific methodology could expose patients to "predictable serious or irreversible harm" (Macklin 2009:3) and that its subsequent integration into paragraph 29 paves the way for arbitrary interpretations, propelled by economic considerations rather than scientific methodology (Schuklenk 2000, 2004). Feminist bioethicists too object that allowing placebo controls, and the possibility that participants will be denied access to the benefits of the research after it has been completed, will "perpetuate global health inequalities" (Eckenwiler et al. 2008:166).

The issue of providing a proven intervention to trial participants after the trial is over arises from the ethical requirement of responsive research, which entails that the trial is relevant to the health needs of the local population, that participants are selected fairly on the basis of their appropriateness to answer the research question, and that there is a "reasonable likelihood" of that population benefitting from the research (WMA 2008, [Paragraph 17]). One aspect of this is that research results should be translated into accessible care for that community (Benatar and Singer 2000). The Declaration specifically entitles patients enrolled in research to share the benefits - either the

proven intervention or other appropriate benefits (WMA 2008, [Paragraph 33]).

In the short term AZT trial, it was said that providing the established treatment (ACTG-076) to the control group would not be responsive, as ACTG-076 would not become the standard of care in the developing world (Halsey et al. 1997; Crouch and Arras 1998). The trial was responsive in that the disease investigated was a priority for the local population and participants were selected appropriately, but it is argued that accepting the local standard of care, which in most contexts was no treatment, when treatment could be made available, knowingly failed to minimize the known risk of serious harms to the women-participants (Levine 1998 ; Angell 1997; Lurie and Wolfe 1997).[1]

What the "responsiveness principle" entails can be illustrated by two contrasting trials, the Meningococcal Meningitis vaccine trials in sub-Saharan Africa and the *Gadchiroli* trial in India. The Meningococcal Meningitis Vaccine trials were not "responsive". Although a safe and effective childhood vaccine against group A meningococcal meningitis was developed, children in sub-Saharan Africa were not vaccinated against meningococcal meningitis, resulting in an epidemic of meningitis (Robbins et al. 1997). Conversely, the *Gadchiroli* trial of the effectiveness of Home-Based Neonatal Care (HBNC) was

1 See also Annas and Grodin 1998; Michels and Rothman 2003; Schuklenk 1998. Others argued that conducting placebo controlled trials is better because it would provide convincing evidence that the short regimen AZT is better than placebo and validate its provision in the developing countries (Varmus and Satcher 1997; Wendler, Emanuel, and Lie 2004; Resnik 1998).

responsive.[2] The intervention was administered to all neonates suspected of sepsis in the intervention villages and at the end of the trial the researchers implemented this proven intervention as standard care in the intervention villages and in another 250 districts through government development plans (Bang 2010).

The overarching theme of the Declaration is the integrity of the physician to promote respect for all human subjects, to be responsible for protecting their health and rights and to act in patients' best interest by conducting ethical research (WMA 2008, [Paragraph 3,4,11 and 16]). That is, the integrity of a vigilant investigator is essential to conducting ethical research (Jonsen 1998).[3]

1.1.3 CIOMS guidelines

Since research activity has increased in developing countries, the "application of ethical principles formulated in the industrialized countries requires careful consideration and adaptation" (Idanpaan-Heikkila and Fluss 2008:168). Guidelines formulated by the Council for International Organizations of Medical Sciences (CIOMS) aim to advise how the ethical requirements set out in the 1975 version of the Declaration of Helsinki can be effectively applied in the cultural and socioeconomic conditions of low-resource countries (CIOMS 2002; Fluss 2004). The ethical principles underpinning CIOMS guidance are

2 In the Gadchiroli trial, the community–based health workers were trained to manage birth asphyxia, low birth weight, diagnose and treat sepsis with antibiotics, which were oral Trimethoprim-Sulphamethoxazole and intramuscular injections of Gentamicin, twice daily. This regimen resulted in a 60% reduction in neonatal mortality (Bang et al. 2005).

3 This echoes Henry K Beecher's words: "the ethical approach to experimentation in man has several components…the first being informed consent…[the second being] the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator" (Beecher 1966:1360).

respect for persons, beneficence (stating that the prescription of “do no harm”, is sometimes expressed as “non-maleficence”), and justice. In its preamble CIOMS obligates professionals with a dual role of physician and researcher to “protect the rights and welfare of the patient-subject”(CIOMS 2002).

CIOMS details 21 guidelines relating to: ethical justification; scientific validity; ethical review; informed consent procedures; vulnerabilities of individuals and communities, including women, children and incapable patients; equity regarding burdens and benefits; reasonable availability; choice of control; safeguarding confidentiality and obligations of external sponsors to provide health-care (CIOMS 2002). CIOMS also provides commentary explaining the terms and scope of each guideline, underscoring the imperative for physician-researchers to protect the rights and welfare of patient-subjects (Idanpaan-Heikkila and Fluss 2008).

On consent, CIOMS emphasizes that obtaining informed consent is a process, not an event, and therefore adequate time should be set aside for providing information (CIOMS 2002, [Guideline 4]). With regards to the responsiveness principle, it urges reviewers of the ethics of research proposals to consider whether the research responds to the health needs and priorities of the host country (CIOMS 2002, [Guideline 3 and 10]) and whether the proven intervention is made “reasonably available” to the local population (CIOMS 2002, [Guidelines 10 and 21]).

The CIOMS guidelines directly address the need to protect vulnerable individuals (CIOMS 2002, [Guideline 13]). Vulnerable people include the illiterate, the mentally disabled or cognitively impaired, those with life threatening illnesses, non-native language speakers, pregnant women, nursing-home residents, employees prisoners, university students and wards of state (Smith-Tyler 2007). The CIOMS also includes women as vulnerable individuals because in some parts of the world they are socially conditioned to submit to authority (CIOMS 2002, [Guideline 16]). The commentary by CIOMS recommends that such women consult or seek permission from husbands if they wish, but states that "a strict requirement of authorization of spouse" violates the principle of respect for persons (CIOMS 2002, [Guideline 16, commentary]), which is one of the core principles on which the guidelines are formulated.

In summary, present day research ethics guidelines are the outcome of an evolutionary process triggered by the need to sharpen ethical oversight by generating new or revised guidelines after each scandal of medical research in order to protect research subjects and avoid exploitation (Emanuel et al. 2004; Levine 1988). Informed consent and responsive research are both foundational to present day guidelines. However, Annas and Grodin write that globalization of research may have made the realization of informed consent difficult (Annas and Grodin 2008). Although the onus has shifted from the researcher to participants for decision making, the guidelines place the responsibility on researchers to be mindful of their obligation towards their patient-subjects (WMA 2008; CIOMS 2002). Benatar adds that

researchers be guided by moral reasoning when interpreting the guidelines in different socio-cultural and economic contexts (Benatar 2002).

1.2 International research ethics frameworks

In addition to research ethics guidelines, ethical frameworks are an important source of guidance. I will discuss two such frameworks: The Belmont Report, which provides a "principled moral framework" (Beauchamp 2008:149) and a framework developed by Emanuel and colleagues (Emanuel, Wendler, and Grady 2000), which offers practical guidance for conducting and evaluating ethical research.

1.2.1 Belmont Report

The Belmont Report, published in 1979 by the National Commission for the protection of Human Subjects of Biomedical and Behavioral Research,[4] set out a framework of moral principles for conducting ethical research known as the Belmont Principles. The formulation of the Belmont Principles was catalyzed by the reports in 1972 of the Tuskegee syphilis study, in which 412 illiterate and impoverished African-American men[5] with untreated syphilis, and unable to access healthcare, had been observed for forty years against a control group of 204 disease-free men (Angell 1997). When the Tuskegee study began in 1932, there was no established treatment for syphilis. Penicillin as treatment for syphilis became available in 1944, but it was not provided to these men, and their informed consent for

4 The Belmont Report was approved by the National Commission in June 1978 and published in the Federal Register in April 1979 (Jonsen 1998).

[5] Some write 399 black men (Thomas and Quinn 1991; Gamble 1997; Fairchild and Bayer 1999). It is also termed the "40 year death-watch" (Jones 2008).

observing their disease progression was not obtained. The study - and its Guatemalan arm[6] – continued unchecked, the men being seen as experimental subjects - as "clinical material, not sick people", even though the Nuremberg Code had been written at the end of the War (Jones 2008:93).

1.2.1.i Belmont Principles

The National Commission conceived the principles listed below as applicable regardless of time or place (Beauchamp 2005; Beauchamp 2005). The Commission presumed that "no responsible research investigator could conduct research without reference to these principles, and these principles form the core of any policy worthy of the name 'research ethics'" (Beauchamp 2008:152). The Belmont Principles provide guidance for interpreting guidelines in varied socio-economic and cultural settings as well as for evaluating any particular research practice.

1.2.1 i.a Respect for persons

This principle includes two ethical convictions. First, to treat individuals as autonomous agents, respect their informed choices, and not override or obstruct these choices unless they harm others. Second, is to protect persons with diminished autonomy. These situations arise in circumstances where a person lacks the capacity for self-determination either because of illness or mental disability, or where a person's liberty is restricted (Belmont 1979). Such people are

[6] In 2010, a researcher carrying out a study on the Tuskegee archive discovered an arm of the Syphilis study which had been carried out in Guatemala. Between 1946 - 1948, the US Public Health Service infected Guatemalan prisoners, soldiers and mental patients, with venereal diseases and then tested the efficacy of penicillin in treating those diseases (McNeil 2010).

entitled to protection "by the consent of an authorized third party likely to appreciate their circumstances and who will look after their best interest" (Beauchamp 2008:151). The imperative is that respect is owed to all human beings by virtue of their intrinsic worth (Darwall 1977), regardless of their ability to act autonomously.

1.2.1 i.b Beneficence

This principle requires making efforts to secure the wellbeing of persons. The principle of beneficence encompasses an obligation to "do no harm",[7] to remove harm and to do good. In the context of research, beneficence is understood as an obligation to refrain from intentionally causing harm to research participants, to minimize possible harms, maximize possible benefits, and, while protecting against risks of harms, being concerned about the loss of substantial benefits that might be gained from research (Belmont 1979).

1.2.1 i c Justice.

Justice is interpreted first as fair, equitable and appropriate treatment in the light of what is owed to or "deserved" by the research participants and reflects "fairness in distribution". In other words, the benefits and risks of research must be distributed fairly (Belmont 1979). There are several formulations for the just distribution of burdens and benefits, which identify substantive properties of distribution. First, to each an equal share; second, to each according to individual need; third, to each according to individual effort; fourth, to

[7] Beauchamp and Childress separate the obligation to "do no harm" from the principle of Beneficence and place it under the principle of Non–maleficence (Beauchamp and Childress 2001 :115).

each according to societal contribution and fifth, to each according to merit (Belmont 1979).[8]

Another aspect of justice in research is fair selection of participants - a requirement of the responsiveness principle. Participants should not be selected because of their compromised position or easy availability but because the disease under study is relevant to them and they will be among the beneficiaries of any subsequent application of that research (Belmont 1979). Historically, socially vulnerable groups have borne the burdens of research while the benefits have been utilized by the society at large or by those who can afford the proven intervention (Beauchamp 2008). Feminist ethicists draw attention to the injustice of "overrepresentation" in research trials of some groups, and of "underrepresentation" of other groups, observing that the principle of justice should "avoid both mistakes" (Sherwin 2005 :154).

1.2.2 Emanuel and Colleagues' framework

Emanuel and colleagues recently constructed a framework of ethical requirements for clinical research that is synthesized from codes, declarations and relevant literature (Emanuel, Wendler, and Grady 2000). This framework elaborates seven ethical requirements for research with the aim of ensuring that research participants are "not merely used but are treated with respect while they contribute to the social good" (Emanuel, Wendler, and Grady 2000:2701). The framework is not a formal ethics guidance but it provides practical

[8] In addition to these five formulations of justice Beauchamp and Childress add a sixth: "to each according to free-market exchanges" (Beauchamp and Childress 2001:228).

guidance on how the ethical principles discussed above can be fulfilled and "help in ethical development, implementation and review" of research (Emanuel, Wendler, and Grady 2000:2702).

In 2004, Emanuel and colleagues wrote that "an ethical framework for research in developing countries must provide more than broad principles" (Emanuel et al. 2004:930). To the seven requirements elaborated in 2000, they added an eighth principle of "collaborative partnership", and extended the requirement for "respect for participants" to include "respect for study communities" (Emanuel et al. 2004).[9]

In order to fulfil these eight principles practical guidance is elaborated through 31 benchmarks. The emphasis is on a contextual approach to the enrolment process reflecting local socio-economic circumstances and sensitive to local culture and language, entailing, in the true sense of collaboration, partnership with local researchers (Emanuel et al. 2004).

To assess the social impact of the research, evaluation should include a statement of who the beneficiaries will be and how will they benefit (Emanuel et al. 2004). Emanuel and colleagues extend respect for participants to include respect for study communities.[10] To enable

[9] Emanuel et al use the term "requirements" and "principles" interchangeably. Referring in 2000 to "seven requirements" (Emanuel, Wendler, and Grady 2000:2701), while in 2004 they refer to "7 principles" and add an "eighth principle" (Emanuel et al. 2004:930).

[10] The principle of "respect for community" is elaborated by Emanuel and Weijer, who argue that community ought to be accorded moral status for a number of reasons, while at the same time arguing for unifying all principles against oppressive practices of any community (see Emanuel and Weijer 2005:171-172).

responsive research the onus is on the community to ascertain whether the research meets their health needs.

In the requirement for collaborative partnership, one of the benchmarks is to "respect the community's values, culture, tradition and social practices" (Emanuel et al. 2004 :931). But respecting a community should not mean uncritical acceptance of "oppressive or coercive practices" (Emanuel et al. 2004:932),[11] because, some cultural practices and community norms could perpetuate oppression and violate fundamental rights of some persons resulting in serious consequences for their health (Macklin 1999a, 2003). One formulation of justice is distributive justice; another is the elimination of domination (Weijer 1999; Emanuel and Weijer 2005) , in which case, "all the relevant values including respect for persons, beneficence, justice, and respect for communities, must be used in the assessment of potential oppression" (Weijer and Emanuel 2000:1144).

1.3 Ethical requirements for conducting research

As a result of these developments since the Second World War, a degree of consensus has been achieved such that research must satisfy several conditions, in order to be considered ethical. Most importantly research should be scientifically valid, otherwise it is unethical, because if valid and reliable data are not generated research will be of no value (Emanuel et al. 2004).

[11] Similarly, Benatar writes that it necessary to avoid either uncritical acceptance of the moral perspectives of all cultures as equally valid, or "rejecting them all as invalid" (Benatar 2004:576).

Although research is conducted to gain knowledge which can be used to improve healthcare and research participants are a necessary means to obtain that knowledge, participants are susceptible to harm and exploitation (Grady 2006). Obtaining an informed voluntary consent, apart from showing respect for persons, is one way of avoiding exploitation, *and* the other is by avoiding unfair distribution of burdens and benefits (Emanuel, Wendler, and Grady 2008).

In many parts of the world, poverty, illiteracy, a fractured health care system and a lack or limited understanding of scientific research makes patients particularly vulnerable to exploitation by conducting research that is of no or little benefit to the participants but of greater benefit to others (Benatar 2001, 2000; Annas and Grodin 1998; Glantz et al. 1998; Emanuel et al. 2004). For conducting research in such populations the guidelines, along with informed consent, place particular emphasis on the responsiveness principle, which implies fair subject selection and fair distribution of benefits and risks, during and post-research (CIOMS 2002; WMA 2008).

In what follows I discuss the conditions that need to be fulfilled to meet the ethical requirements of informed consent, balancing potential benefits over risks, selecting participants fairly and providing the proven intervention, or other benefits, at the conclusion of the trial. Alongside, I also draw on relevant literature from developing countries to identify the particular challenges these requirements present.

1.3.1 Informed consent

> One gives an informed consent to an intervention if (and perhaps only if) one is competent to act, receives a thorough disclosure, comprehends the disclosure, acts voluntarily, and consents to the intervention (Beauchamp and Childress 2001:79).

A valid consent, then has three elements: “consent must be informed, voluntary and given by a competent person” (Brock 2008:607). Competence is an essential “presupposition or condition of the practice of obtaining informed consent” (Beauchamp and Childress 2001:80). Since adults are, in general, “presumed to be competent to decide unless determined otherwise” (Brock 2008:610), a detailed discussion of competence is not relevant to my study because my research participants were competent adults; here I focus on the process of informed consent.

Extending from the Nuremberg Code the importance of informed consent is closely related to the requirement that research participants, “to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them” (Belmont 1979), and their actions should not be subjected to controlling constraints by others (Beauchamp and Childress 2001).

Informed consent has an information component and a consent component. “The information component refers to disclosure of information and comprehension of what is disclosed” by the patient, followed by the consent component, which “refers to both a voluntary decision and an authorization” by the patient to proceed with the intervention (Beauchamp and Childress 2001:79).

There are two senses in which informed consent appears in the literature: in one sense – the ethical sense – it is an "*autonomous authorization"* by the research participant, who after reflection and careful thought authorizes the physician-researcher to initiate the intervention. In the second sense – the procedural sense - it is a requirement dictated by "*the social rules of consent* in institutions that must obtain legally or institutionally valid consent…" for effective authorization (Beauchamp and Childress 2001:78,emphasis in original). That is, informed consent is an ethical and a legal requirement for medical research (Brock 2008; Annas and Grodin 2008).

In what follows I will discuss the following elements: information, comprehension, research participant's voluntary decision to enrol and lastly the procedural requirement of documenting that consent.

1.3.1.i Information and comprehension (or understanding)

The Belmont Report (1979) examines three standards of information disclosure relating to practitioners, reasonable persons, and reasonable volunteers.[12] The "practitioners' standard" is a standard in which the professional community's customary practices determine adequate disclosure. The Belmont Report considers this inadequate since

[12] Beauchamp and Childress discuss the three standards of information disclosure in greater detail than the Belmont Report: the first, "professional practice" standard (the reasonable doctor standard) as judged by the medical community which they consider is of limited efficacy; the "reasonable person" standard, in which the patient determines the information needed but which has conceptual and practical difficulties; the "subjective standard", which they consider is the morally preferable standard but impractical (Beauchamp and Childress 2001:81-83).

research is conducted when a common understanding regarding the research intervention does not exist.

The “reasonable person” standard is where the patient (as a reasonable person) determines information disclosure and not the physician. The Belmont Report considers this insufficient since the information requirement of a person volunteering for research may differ from the information requirement of a reasonable patient (Belmont 1979).

The “reasonable volunteer standard” is where the nature and amount of information is enough to enable the person volunteering for research to know that the trial intervention is neither necessary for their care, nor is it fully understood, so that they can decide whether they want to participate or not (Belmont 1979).

The Belmont Report requires that sufficient information about “research procedures, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research”, be given (Belmont 1979). The researcher is responsible for providing this information and ascertaining that the information has been understood by the participant (Beauchamp 2008).

The international research ethics guidelines have some additional requirements to those in the Belmont Report. The Helsinki Declaration requires that besides adequate information on the topics specified by the Belmont report and listed in the preceding paragraph, the researcher should disclose possible conflicts of interest, funding

sources, the researcher's institutional affiliations, "any other relevant aspects of the study" and should inform participants that they are free to refuse or withdraw from the research (WMA 2008, [Paragraph 24]).

CIOMS requires all necessary information to be provided and is more extensive than other guidelines in specifying 26 items including the topics mentioned above and others such as fiscal, institutional and commercial interests of the researcher, the direct or expected benefits to participants and post-trial access to the intervention (CIOMS 2002, [Guidelines 4 and 5]).

Emanuel and colleagues write that research participants should receive relevant and accurate information about the purpose, procedures, benefits, risks and alternatives to research, and be informed that their confidentiality will be maintained, that they have a right to refuse or withdraw, that their well-being will be monitored and they will be informed of the research results (Emanuel, Wendler, and Grady 2000; Emanuel et al. 2004).

The informational requirement for informed consent requires not only that information is provided but also that this information is comprehensible. The context and the manner in which information is communicated also affect patient's comprehension. As an expression of respect for that person, the information to be provided must be adapted to the person's needs and capacity (Belmont 1979). The Helsinki Declaration requires that:

> Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver information…ensuring that the

> potential subject has understood the information….." (WMA 2008,[Paragraph 24]).

CIOMS stipulates that oral or written information is provided in the language that suits the individual's level of understanding and literacy, providing them the opportunity to ask questions and answering them honestly. The investigator is responsible for ensuring that the participant has "adequately understood the information" and for assessing comprehension of the research (CIOMS 2002, [Guideline 4, commentary]). Emanuel and colleagues add that information should be provided using local idioms and analogies that participants can understand, and where necessary involving the community and family (Emanuel et al. 2004).

Fulfilling all these requirements for information presents challenges in the developing world. A survey on information disclosure to patients in the USA and Nigeria enrolled in similar studies showed that 99% of US patients as compared to 72% of Nigerian patients were told of the study purpose (Marshall et al. 2006).

Patients receive information from researchers (or assigned persons) and usually also receive written information contained with, or in addition to the consent form. Literature from the developing countries shows that long jargon-filled consent forms give very little information that is relevant to patients (Cressey 2012). There is evidence of irregularities and deficiencies in obtaining consent. Cohen et al's review of 312 registered trials between 2004-2007 shows that informed consent was obtained in 58.6 % of the trials (Cohen et al.

2009).[13] However, Devasenapathy et al write that there is a risk that complex information and consent protocols will so "complicate the logistic issues" that clinicians in the developing world "will be driven away from clinical research" (Devasenapathy, Singh, and Prabhakaran 2009:298).[14]

Much research from the developing world shows the necessity of cultural sensitivity in obtaining informed consent and adapting informed consent procedure to local context,[15] in keeping with the principles of respect for person and community (Emanuel et al. 2004). Cash (2006) and Bhutta (2004 a) write that "understood consent" should replace informed consent so that researchers reflect on what information is essential for participants to understand before consenting rather than merely conveying information.

Researchers, evaluating a modified informed consent form to provide culturally appropriate information about research in South Africa, conclude that modifying information provision in this way and using the language of the trial participants enhances understanding of the proposed trial (Penn and Evans 2010). Others report that collaborating with local researchers to develop the consent document is also useful (Miller et al. 2007). Vallely et al developed informed consent procedures after community consultation in Mwanza (Tanzania) for an HIV prevention trial concluding, that an informed consent procedure that continues throughout the trial is useful (Vallely et al. 2010).

[13] See also Sarojini et al 2011.
[14] See also Lang et al 2011.
[15] See Barry 1988; Christakis 1998; Barry and Molyneux 1992; Shaibu 2007; Creed-Kanashiro et al.2005; Bull, Farsides, and Ayele 2012.

Involving local experts in creating standards and guidelines that are in tune with local ethical practices on the African continent upholds the principle of collaborative partnership (IJsselmuiden and Faden 1992; Fadare and Porteri 2010).

In vulnerable communities in India, where levels of illiteracy and poverty are high, cultural barriers and paternalism on the part of researchers has meant the practical application of the principle of informed consent falls short of the requirements in the guidelines. Patra and Sleeboom-Faulkner conclude that this is mainly as a consequence of researchers not understanding the importance of informed consent or considering it an extra burden on their limited resources, including time. They emphasize the need to take more time explaining the advantages and disadvantages of participating in a trial to potential participants and to take the views of those who participate in the decision-making procedure into account (Patra and Sleeboom-Faulkner 2009).

A number of studies show that it is necessary to improve procedures for fulfilling the requirements of the guidelines for obtaining consent from participants in the developing world.[16] It is generally considered that a one-off meeting with the researcher is insufficient for participants to comprehend research (Britz and Roux-Kemp 2012). A study from Chile reports that women, including non-literate women, highly value being fully informed about the research and efforts made

16 Andoh 2008; Anya 2003; Bhan, Majd and Adejumo 2006; Newton and Appiah-Poku 2007; Rajaraman et al 2011; Van Loon and Lindegger 2009; Moodley, Pather and Myer 2005; Préziosi et al. 1997; Nabulsi, Khalil, and Makhoul 2011; Joubert et al. 2003; Bento, Hardy, and Osis 2008; Chaisson et al 2011.

to make the information understandable (Sánchez et al. 2001). Another study from Haiti shows that three, 30-40 minute information sessions with a counsellor over 7-10 days significantly improved participants' comprehension (Fitzgerald et al. 2002). According to Miller et al (2007), and Woodsong and Karim (2005), providing information in private and comfortable settings and allowing participants to discuss and ask questions is useful in improving understanding. What this suggests in practice is that fully informed consent may not be achievable within the constraints of the real world situations in which consent is obtained in many developing country settings – this is something I explore in depth later in this thesis.

Many writers note that literacy has an important effect on understanding.[17] People who are illiterate are vulnerable and require protection:

> Those who are unable to protect their own interest, because they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their interests, then means of protecting their rights and welfare must be strictly applied (CIOMS 2002, [Guideline 13]).

Researchers conducted an empirical study in Ghana to ascertain if women enrolled in a Vitamin A randomized control trial were aware that they could be receiving placebo. The results show that women with primary and secondary or higher education were 1.5 and 2 times respectively more likely to know that not all capsules contain Vitamin A than women with no education (Hill et al. 2008).

[17] Lynoe, Chowdhury, and Ekstrom 2001; Muthuswamy 2005; Ezeome and Marshall 2009; Kumar et al. 2012; Krosin et al. 2006; Manafa, Lindegger, and Ijsselmuiden 2007; Nienaber 2010; Patra and Sleeboom-Faulkner 2009; Mystakidou et al. 2009. Newton and Appiah-Poku 2007; Tindana, Kass, and Akweongo 2006; Britz and Roux-Kemp 2012; Zong 2008.

A study from Thailand on patients receiving Interleukin-2 shows that 73% joined the study voluntarily and 99% had a good understanding of the information. Only one of these 141 participants was non-literate, 39 had less than 12 years of education while the rest had qualifications ranging from high school to professional level (Pace et al. 2005). Younger and educated women were more likely to enrol in a trial in Egypt and understood the consent form easily (Aboulghar 2011). Conversely Bhansali et al report from India that patient's educational status and economic background did not influence their comprehension of the information in the consent forms (Bhansali et al. 2009).

Another factor highlighted in a considerable body of literature is that patient's unfamiliarity with, and difficulty in, understanding scientific concepts influences their comprehension of research.[18] This may dissuade researchers from disclosing all the information about research to patients (Newton and Appiah-Poku 2007). Some writers consider that a lack of equivalent terminology for scientific terms in the local language is a major hurdle, in obtaining informed consent.[19]

1.3.1.ii Voluntariness

After information has been communicated, patients go through a decision-making process. It is important that participants consent freely without coercion - that is without an overt threat of harm - and

[18] Kass, Maman, and Atkinson 2005; Sarkar et al. 2010; Khalil et al. 2007; Krosin et al. 2006; Nienaber 2010; Banerjee and Baker 2012; Jegede 2009; Kamuya, Marsh, and Molyneux 2011; Lema, Mbondo, and Kamau 2009; Mystakidou et al. 2009; Marshall 2008; Moodley, Pather, and Myer 2005; Ekunwe and Kessel 1984; Dawson and Kass 2005; Macklin 2003; Sumathipala et al. 2010.

[19] Molyneux, Peshu, and Marsh 2004; Dawson and Kass 2005; Mystakidou et al. 2009; Adams et al. 2005.

undue influence. The Belmont Report acknowledges that it may be impossible to demarcate the boundary between justifiable persuasion and undue influence (Belmont 1979). Undue influence usually, constitutes:

> … actions as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled (Belmont 1979).

Similarly the Helsinki Declaration requires that participation of subjects in research is voluntary, consultation with family or community leaders is accepted, but no competent individual can be enrolled unless they freely agree (WMA 2008, [Paragraph 22]). CIOMS too, requires an individual who has considered the information to arrive at a decision without "coercion, undue influence or inducement, or intimidation" and also acknowledges the borderline between undue influence and justifiable persuasion is vague (CIOMS 2002, [Guideline 6]). It recognizes that in some cultures permission is required from "a community leader, a council of elders, or another designated authority" but while these customs must be respected, such permission should not substitute an individual informed consent (CIOMS 2002, [Guideline 4, commentary]). Similarly, a benchmark in Emanuel et al's framework includes implementing supplementary community and familial consent procedures where culturally appropriate, but states that negotiating "spheres of consent" is only to

gain "permission to invite individuals to participate" and not a substitute for an individual's decision (Emanuel et al. 2004:934).[20]

There has been much discussion of autonomous decision-making. Childress writes that autonomy can be understood to work at two levels: first-order autonomy would be where "decisions about the rightness or wrongness about particular modes of conduct" are the domain of the individual themselves (Childress 1990:13). That is, the person themselves *will* and act on that will. In keeping with this the person may yield their first–order autonomy and this:

> Abdication of first-order autonomy appears to involve heteronomy, that is, rule by others. However, if a person autonomously chooses to yield first- order decision-making to a professional ..., that person has exercised what may be called second-order autonomy…..in this case respect for their second-order autonomy is central, even though their first-order choices are heteronomous (Childress 1990:13).

Hence second-order autonomy would be when the person chooses to delegate decision-making to others, either the physician or the family.[21] Many studies from developing countries show that most patients depend on the family or physician-researchers to decide for them.[22] In a survey from southwest Nigeria over 50% of female

[20] See also Kass et al 2005.

[21] Beauchamp and Childress in defence of the universal application of the principle of respect for autonomy write that this form of autonomy does not abandon or supplant the commitment to respecting individual's autonomy; in fact this recommendation accepts that the choice is still the patient's. "Even if the patient delegates the right to choose to others it is still the patient's autonomous choice" (Beauchamp and Childress 2001:62). Others, critical of the universal application of the principle of respect for autonomy term this as "acrobatics of language"(Chattopadhyay and DeVries 2012:6).

[22] Masiye et al. 2008; DeCosta et al. 2004; Yousuf et al. 2007; Barry and Molyneux 1992; Gitanjali et al. 2003; Molyneux, Peshu, and Marsh 2004; Shaibu 2007; Dawson and Kass 2005; Patra and Sleeboom-Faulkner 2009; Kumar et al. 2012; Marshall et al. 2006; Molyneux et al. 2005; Gikonyo et al. 2008; Mumtaz and Salway 2009; Marshall 2008; 2006; Xiaomei 2006;2009; Rashad, Phipps, and Haith-Cooper 2004; Sariola and Simpson 2011; Tindana, Kass, and Akweongo 2006; Tekola et al. 2009; Marsh et al. 2011 .

participants obtained permission from their husbands (Osamor and Kass 2012). Frimpong-Mansoh argues for a reformulation of informed consent so that it reflects socially connected relationality, as that is the reality of social life - in which people are not isolated solitary individuals (Frimpong-Mansoh 2008). Sherman et al reiterate the importance of tailoring consent procedure to the circumstances of the Peruvian Amazon community in which gender dynamics and social structure affect the consent procedure, as does the limited flexibility of the regulations' requirements (Sherman et al. 2012).

However, relationality may affect person's voluntariness for enrolling into trials. Interfamily and gendered relationships affect women's participation in research. For example some women in an Indian trial did not enrol because they were not in a position to make independent decision (Gitanjali et al. 2003).[23] In a trial in Chile some women withdrew because of "pressure from partners" (Sánchez et al. 2001:407). Literature from Kenya (Ngare 2007), Nigeria (Bhan, Majd, and Adejumo 2006; Osamor and Kass 2012) and Uganda (Loue, Okello, and Kawuma 1996) shows that women refuse participation if their husbands do not permit. In a trial involving children in Kenya, mothers considered it the norm for the father to decide, hence in expecting decisions about a child's participation in research to be made by the father, mothers are simply following their social obligations (Kamuya, Marsh, and Molyneux 2011). Conversely, a collaborative randomized trial in India concludes that, practical constraints notwithstanding, a respectful approach to a complete

[23] See also DeCosta et al 2004; Agrawal, Goel, and Lal 2012.

informed consent process can be achieved, leading to individual decision-making and respect for the family (Geller et al. 2006; 2004).

Given that there is tension between respecting the traditional "spheres of consent", to use Emanuel and colleagues' term, and promoting individual decision-making in patriarchal societies, there are calls for researching ways to promote decision-making capacity (Tekola et al. 2009). In her work on the Batswana people, Shaibu experienced incongruity between the "Western ethic" and the local cultural values with respect to confidentiality as well as autonomy and realizes that both autonomy and confidentiality were collective, although confined to the family (Shaibu 2007).

Consent guidelines rest on a "Western" standard of privacy, which presuppose an individual identity, separate from that of the family. Yet, Monshi and Zieglmayer write that in the Sri Lankan context this is only peripherally recognized where close and hierarchical family relationships ensure the family makes a person's life decisions. By adapting the consent method to the context enabled them to respect the sense of privacy and the emotional needs of their participants, better (Monshi and Zieglmayer 2004). Another study from Sri Lanka shows that decision-making is not individualistic but family-centered and a seamless integration of the international requirement and local practice is challenging (see Sariola and Simpson 2011).

This raises the question whether individual decision-making, with all its attendant requirements of privacy and confidentiality, is workable in some parts of the world. A study conducted in Dhaka showed that

in cases of married women enrolled in research, 76% of researchers considered it is essential to consult the husbands for consent (Hossain et al. 2008). Similarly in rural India, although 84% of trial participants said that the decision to participate in a trial would be their own, only 36.8% made the decision independently (DeCosta et al. 2004).

Such findings have led some to argue that "autonomy" in local ethics exists in the context of family or community rather than an individual (DeVries, Rott, and Paruchuri 2011; Xiaomei 2006; Kaelin 2009). Others, however, state that while extended family and community leaders may act as an additional protective mechanism, they cannot replace an individual informed consent that recognizes an individual person's fundamental rights (Elsayed and Kass 2007; Bhutta 2004 a, 2002). For this there are calls "to create avenues for vulnerable people to genuinely and meaningfully exercise their right to freely decide" (Alvarez-Castillo 2002:27).[24] Voluntariness, and in turn, consent can also be affected by patient's ideas about how a particular research project may or may not benefit them.[25]

1.3.1.iii Documenting consent

Whilst not usually highlighted as an ethical requirement of valid consent. In the sense that informed consent is a procedural requirement determined by institutional rules (Beauchamp and Childress 2001), the guidance requires it to be documented, preferably in writing. Thus the Helsinki Declaration, as general rule, requires

24 See also Nussbaum 2000;2008.

25 Molyneux, Peshu, and Marsh 2004; Kass, Maman, and Atkinson 2005; Lema, Mbondo, and Kamau. 2009; Bhutta 2004; Shah et al. 2010; Sanmukhani and Tripathi 2011; Wazaify, Khalil, and Silverman 2009; Taiwo and Kass 2009; Krosin et al. 2006; Lema 2009.

consent to be expressed in writing and signed by the participant. But if consent cannot be "expressed in writing" then a "non-written consent must be formally documented and witnessed" (WMA 2008, [Paragraph 24]; see also CIOMS 2002, [Guideline 4, commentary]). However, CIOMS also requires that sponsors and investigators must obtain a signed form as evidence of informed consent (CIOMS 2002, [Guideline 6]). Conversely, a benchmark in Emanuel et al's framework is that consent should be obtained in a culturally and linguistically appropriate format and since obtaining written consent may be culturally insensitive in some communities then consent may need to be obtained in some other, more culturally appropriate manner, as long as it is voluntary and can be verified by an independent observer (Emanuel et al. 2004).

The literature on documenting consent in developing countries shows that it is important to be sensitive to non-literate participants. Salaam and Brown, who conducted research in Nigeria, advise researchers to be considerate to non-literate participants who may not understand the requirement of written consent (Salaam and Brown 2012). Hyder and Wali, analysing components of a study on informed consent in the developing world,[26] report that researchers strongly believe in obtaining informed consent from participants but argue for flexibility in the process and documentation of consent (Hyder and Wali 2006). Shakoor et al reiterate the same from Dhaka (Shakoor et al. 2009).

[26] The National Bioethics Advisory Commission (NBAC) commissioned this study.

In a questionnaire survey from Nigeria on the opinions and attitudes of surgeons towards informed consent, 68.4% of surgeons consider consent to be of medico-legal importance while 10.5% consider it important for satisfying the surgeon's conscience. The authors conclude that the process of obtaining consent goes beyond acquiring a patient's signature on the form and is also an opportunity for doctors to convey concern for the well being of the patient (Irabor and Omonzejele 2009). A study from Ethiopia, reports on the need for developing informed consent from the local cultural perspective, though participants supported the concept of informed consent, most did not favour written consent (Tekola et al. 2009). Nonetheless, most trials in the developing countries report obtaining written consent from trial participants (see Mukkannavar et al. 2012; Agnandji et al. 2012; Akhtar et al. 2013).

In short, time constraints, local socio-cultural and economic factors including poverty, illiteracy, patriarchy and lack of scientific knowledge all affect the provision and understanding of information, decision-making and documentation of consent.

1.3.2 Assessing Risks and Benefits

The assessment of risks and benefits is a multistage activity of identifying and then assessing risks. The aim is to minimize risks to participants or assess whether benefits are sufficient to outweigh risks, consistent with a sound study design (Wendler and Miller 2008; Brody 1998). Beneficence guides this assessment (Belmont 1979). The wide spectrum of assessment includes risk of physical,

psychological, social and economical harms and the corresponding benefits (Belmont 1979; Emanuel and Miller 2001).

The Helsinki Declaration, in keeping with its aim that "the well-being of the individual research subject must take precedence over all other interests", mandates that risks and burdens to the individual and the community be carefully assessed (WMA 2008, [Paragraph 6 and 18]). CIOMS also requires potential benefits and risks to be reasonably balanced, and that the benefit from the intervention will be at least as advantageous as any available alternative (CIOMS 2002, [Guideline 8]). Emanuel and colleagues advise that risks to individual participants be minimized and potential benefits maximized (Emanuel, Wendler, and Grady 2000) but "if potential risks outweigh benefits to participants, the social value must justify these risks" and vulnerable populations must be protected (Emanuel et al. 2004:934). This assessment of social value should be guided by moral reasoning (Benatar 2002).

An example of granting an ethical sanction to research where social benefit may outweigh risks is the development of the Rotavirus vaccine. The use of this vaccine was halted in the United States due to childhood deaths from bowel intussusceptions. But in developing countries the benefits to the paediatric population far outweigh the risks; the 1 in 10,000 deaths by intussusceptions outweigh the number of deaths by acute diarrhoea, hence the benefits of vaccine may outweigh risks for children in developing countries (Weijer 2000).

The debate on the use of placebo for a control group is essentially about the harms that the control group will suffer if denied standard treatment. Literature from the developing world shows that although the use of placebo is restricted, especially in conditions where "serious harm" is anticipated (WMA 2008, [Paragraph 32]) the issue remains unsettled, resulting in contentious interpretations of paragraph 32 of the Helsinki Declaration (Macklin 2012; Malik and Ghafoor 2012). An example is the trial on Risperidone conducted in India in which the control group was given placebo. Patel, from the principle that "no participant must be harmed", argues that the control group in a trial must receive what is usual treatment in the circumstances (Patel 2006). The researchers, acknowledging that an effective treatment for acute mania is available, validated the use of placebo on grounds of "scientific methodology" (Mudur 2006). Patel asks whether depriving patients of standard treatment when they have a condition that may make them agitated and even psychotic is ethically tenable (Patel 2006).[27]

Benatar writes that the scientific merit of research must be met by the ethical merit of the enterprise (Benatar 2002). In view of this Bang et al, in the *Gadchiroli* trial, selected thirty–nine villages[28] as the intervention area and "compared" it with villages where government health-care services were administered and recorded mortality records

[27]This raised concerns about adequate safeguards ensuring that patients' interests are protected (Tharyan 2006).

[28]The Society for Education, Action and Research in Community Health (SEARCH) had an ongoing child health programme area (the 39 villages) and also a non-programme area where only demographic surveillance was done. The non-programme area was served by the government healthcare services. For the HBNC trial these areas were selected as "intervention" and "control" areas respectively. They were not selected anew for the sake of an experiment (Bang 2010).

in these non-intervention villages.[29] No "controls" were recruited from the intervention villages, nor were neonates observed as "controls" from the comparison villages, because it would have been both ethically wrong and practically difficult to observe the neonates in the control villages for morbidities without intervening. In view of the risks involved, all neonates suspected of sepsis in the intervention villages were administered the intervention regimen and children who did not respond to the HBNC regime were referred to the nearby hospital for available treatment (Bang et al. 2005 a).

1.3.3 Selecting participants fairly

There is broad agreement that justice and equity should guide the selection of participants, both at the social and at individual levels. Fairness demands that researchers should not offer potentially beneficial research to some participants and risky research to others (Belmont 1979), and this contravenes the responsiveness principle. Groups or individuals who are unable to consent freely, as a result of their socioeconomic conditions or their illness, should be protected against the danger of being involved in research that is of no benefit to them. Participants should be selected on their appropriateness to answer the research question and expediency should not be a motivating factor in enrolling underprivileged groups (Belmont 1979). An important benchmark for Emanuel and colleagues is that participants are selected to ensure valid science – the disease or "problem" is of significance to the population and patients are not

[29]This area was a demographic surveillance area where Bang et al recorded childbirths and deaths, usually a few weeks to a few months after the event had occurred (Bang 2010).

selected because of their "social subjugation" (Emanuel et al. 2004:933). Likewise, excluding patients for expediency is also unjust as it violates another aspect of justice, which is "*fair access to research*" (Beauchamp and Childress 2001:227 emphasis in original; see also Sherwin 2005).

CIOMS requires the same protection for vulnerable persons including women, but also states that denying research participation to women deprives them, as a class, of the benefits of new knowledge gained from research (CIOMS 2002, [Guideline 13 and 16]). The Helsinki Declaration states that disadvantaged and vulnerable populations should be enrolled only if the research is responsive to their health needs and it is likely that they will benefit from the research (WMA 2008, [Paragraph 17]). Socially vulnerable populations should not be "used" but, equally importantly, "populations that are underrepresented in medical research should be provided appropriate access to participation in research" (WMA 2008, [Paragraph 5]; see also CIOMS 2002,[Guideline 12]).

Literature from the developing countries raises concerns that the number of ethical misdemeanours is increasing as the number of trials increases (Mudur 2001; Sarojini et al. 2011). A Human Papilloma-Virus vaccine project was conducted on a vulnerable population in India where the stipulation that "everyone shall desist from research on tribal population, unless of specific benefit to them" [sic] was violated.[30] In addition, in many instances consent was obtained from

[30] Committee report on the HPV vaccine project see Sarojini et al 2011.

hostel wardens or headmasters on behalf of students in "*ashram paathshalas*" (residential schools) (Sarojini et al. 2011).[31]

In 1996, the Trovan drug trial was conducted in Kano (Nigeria), during the meningitis epidemic that occurred after the earlier recommendations for meningitis vaccination, with the vaccine trialed in sub-Saharan Africa, were disregarded. The epidemic afforded a trial site for expediting the approval of Trovan by the Food and Drug Administration (FDA) (Stephens 2000). The trial raised concerns about exploiting a vulnerable population who, because of illiteracy, poverty, and desperation for treatment, were unsure what they were consenting to. Apart from raising concerns about questionable consent, children who were not responding to Trovan were not given the available effective antibiotics, resulting in the deaths of eleven children and several who became deaf, blind or lame (Macklin 2003).[32]

Mudur writes of how patients in the developing countries can be used as 'guinea pigs' with reference to a cancer drug that was used on human participants in India without first being tested in animals (Mudur 2001); this raised concerns at John Hopkins, the university of the researcher who "collaborated" with an Indian counterpart (Baggla and Cassus 2001).

[31] See also Srinivasan 2011.

[32] The ill-effects of the Trovan trial left lingering doubts in the community as to the intentions of the pharmaceutical companies. Therefore, in 2003, the residents of Kano refused to have their children vaccinated for polio, fearing it was a plot to harm the children (Murray 2007).

1.3.4 At the conclusion of the trial

Ethical issues also arise in relation to the responsibilities of researchers to participants and research communities at the end of the research trial. Justice and beneficence tend to be key considerations in this debate, which is ongoing, over social justice and whether researchers and sponsors owe more than a minimum set of obligations to the participants and community (IJsselmuiden et al. 2010; Semplici 2012; Benatar and Singer 2000). The practical application of this is through one aspect of the responsiveness principle, which entitles patient-participants to post-trial provision of the proven intervention (WMA 2008,[Paragraph 33]). CIOMS adds that "the intervention or product, or knowledge generated, will be made reasonably available for the benefit of that population", determined on a case-by-case basis (CIOMS 2002, [Guideline 10])[33]. Of the 26 information items to be provided to participants one requires specifying whether, when and how the proven intervention will be provided to participants and whether they will be expected to pay (CIOMS 2002, [Guideline 5 at 12]).

The Belmont Report requires the advantages of the proven intervention to be provided to all, not only to those who can afford them, and that research should not be conducted on people unlikely to benefit from the subsequent applications of the research (Belmont 1979). To do otherwise raises the spectre of exploitation (Cleaton-Jones 1997; Wilmshurst 1997; Macklin 2004; Benatar 2001, 2000).

[33] See also Guideline 21 (CIOMS 2002).

Some argue that responsiveness has a broader scope than providing the proven intervention. It requires a "fair level" of benefits, taking into account how much, and not just what, parties to the transaction receive (Setouhy et al. 2004). This includes reasonable availability of the proven intervention *if* "affirmed by the countries themselves" (Countries 2002).[34]

Emanuel and colleagues, realizing that "very little can generate more resentment, mistrust, and sense of exploitation than unfair distribution of the benefits of collaboration," emphasize the need to enhance the social value of research with the collaborating partners (Emanuel et al. 2004:932). One of the benchmarks is that participants and communities receive benefits from the conduct and results of research through measures such as product development, health system improvement, dissemination of knowledge and long-term research collaboration (Emanuel et al. 2004). As a mark of respect for the participants, plans ought to be made regarding participants' care when the trial is over; these may require "creative strategies" by researchers for providing access to treatment (Emanuel, Wendler, and Grady 2008:131).

Literature from the developing world shows that reasonable availability in its "narrowest definition" indicates access to the proven intervention when the trial is over (Bhutta 2002:116). But Cohen et al's review of 312 trials registered between 2004 -2007 shows that almost no trial (99%) mentioned post-trial provision of the proven

[34] See also Setouhy et al 2004; London 2005, 2008 ; Gbadegesin and Wendler 2006; Emanuel 2008.

intervention (Cohen et al. 2009). Bhutta recommends negotiations by the research community on behalf of the impoverished and disenfranchised patients in developing countries for bringing about a change in local health-care (Bhutta 2002).

Some argue that although it is neither researchers' responsibility, nor in their power, to compensate for national health provision, they can act as a catalyst for change (Cash 2006; Singh 2011). An example was the *Gadchiroli* trial which introduced the proven intervention – HBNC – as standard care in the intervention villages and through the government in the other villages (Bang 2010). Another example is the Multidrug resistant TB (MDR-TB) trial conducted in Uganda: Singh writes that this trial was responsive as it researched a disease relevant to the community, initiated a treatment programme for the participants and inspired MDR-TB treatment policy reform in Uganda (Singh 2011). Trials conducted in Gambia on the Haemophilus influenza (Hib) vaccine, which led to a marked reduction in Hib Meningitis (Adegbola et al. 1999), and on the Hepatitis B vaccine (Group 1989), are other examples of collaboration between the local Ministry of Health and sponsors that ensured effective vaccines were made available to the population beyond the trial periods (Bhutta 2002).

Devasenapathy, Singh et al from India urge sponsors and researchers to assure minimum guarantees to research participants regarding "respect for the dignity of all participants, doing research on diseases that commonly affect the community, obtaining meaningful informed consent, translating evidence into accessible care and avoiding exploitation" (Devasenapathy, Singh, and Prabhakaran 2009:299).

Sastry, McGoon et al also consider it important to conduct trials in communities where the proven drug will be made available (Sastry, McGoon, and Gibbs 2010). Thatte and Bavdekar write that conducting research on issues irrelevant to local needs and failing to ensure post-trial access only increases the cynicism of local populations towards international research, so these issues need to be tackled efficiently (Thatte and Bavdekar 2008).

1.4 National guidelines and literature from Pakistan

Up to now I have examined research ethics guidance that is not specific to any geographic location and reviewed literature from developing countries in general. Now I summarize two brief sets of research ethics guidelines, one formulated by the Pakistan Medical and Dental Council (PMDC) and the other by the Pakistan Medical Research Council (PMRC). The PMDC was established in 1962, as a regulatory and registration authority for medical practitioners in Pakistan (PMDC 2001). The PMRC is an autonomous organization constituted by the Government of Pakistan in 1962 with the "mandate to promote, organize and coordinate medical research in Pakistan" (PMRC 2004 a). I also review existing literature on research ethics from Pakistan.

1.4.1 National research ethics guidelines from Pakistan

The research ethics guidelines of the PMDC exist as part of the broad code of ethics for physicians, first written in 1968 and since revised in 1974 and 2001. The PMDC code requires a physician to uphold the ethical principles of medical practice i.e. autonomy, beneficence, non-

maleficence, and justice (PMDC 2001, [9.2]). The research ethics section of this code consists of eight paragraphs and the last paragraph refers to the Helsinki Declaration stating (see Appendix J):

> The PMDC supports the resolutions and draws attention to the Declaration of Helsinki adopted by the 18th World Medical Assembly and revised by the 48th World Medical Assembly (PMDC 2001, [20.8]).

The PMRC established the National Bioethics Committee (NBC) in 2004, comprising a Clinical Ethics Committee and a Research Ethics Committee (REC). The remit of the REC is to review all research projects involving human subjects. It requires researchers to follow 14 general principles for the purpose of review (PMRC 2004 see Appendix K).

The PMDC requires researchers to provide adequate information to the participant about the aims, methods and any potential hazards and discomfort of the research (PMDC 2001, [20.2]). It requires a favourable balance between potential harms and benefits to patients (PMDC 2001, [20.0]). These requirements are similar to the Helsinki Declaration (WMA 2008, [Paragraph 24]) and CIOMS (2002, [Guidelines 4 and 5]) although the latter are more elaborate.

The NBC of the PMRC elaborates fourteen “essentials” of informed consent (see Appendix K). The guidance to researchers for submission of protocols for review states:

> The human subjects in the project must participate willingly, having been informed about the research. Please provide all information that is likely to affect the person irrespective of age, gender, or literacy level of the subjects… (PMRC 2004, [4.0]).

The information to participants should include the purpose of research, procedure, risks, including psychological and social, and the duration of research. In addition it requires that research participants be informed of financial burdens that may be incurred by them and the benefits accrued to participants and society (PMRC 2004). The guidance also requires that participants should be informed "as to the availability of the product after discontinuation of the study"(PMRC 2004, [4.4])

The PMRC (2004) and the PMDC (2001) both require that the "human subject" should participate in the research project "willingly". Since the PMDC code addresses physicians, it invokes the physician's obligation towards patients and states that refusal to participate should not affect the care of a patient (PMDC 2001, [20.7]).

The PMDC writes that it is "essential" to obtain a written consent from patients enrolled in research (PMDC 2001, [20.2]), while the PMRC requires that the consent document is clearly written and/or orally explained so as to be understandable to subjects using local language wherever applicable, and "scientific, technical or medical terms must be plainly defined" (PMRC 2004, [4.14]).

To meet the requirements of responsive research the PMDC states that the findings from the research must be of sufficient importance (PMDC 2001, [20.0]), while the PMRC requires the researcher to share the benefits of research with the participants and society. It also requires researchers to advise participants if the intervention will be available at the end of the trial and whether it will be free or available

at what cost (PMRC 2004, [4.4]). Like the PMDC, the PMRC guidance requires compliance with the principles of the Helsinki Declaration (PMRC 2004, [9]).

1.4.2 Literature from Pakistan

1.4.2.i Informed consent

The literature from Pakistan on informed consent consists of the reflections and experiences of physician-ethicists and surveys on obtaining informed consent in clinical practice.

Bhutta, a physician-ethicist from Karachi, writes that understanding the nature of research is difficult in a population with low literacy and recommends that relevant information should be given in a manner that facilitates the understanding of research and helps dispel any "therapeutic misconception" (Bhutta 2004 a:774). Khan writes that a problem in Pakistan is that patients often do not question the purpose and benefits of research (Khan 2008). Amir et al reporting a survey conducted in Islamabad show that 98% of 200 patients in surgical practice acknowledged that consent was obtained from them before surgery, and though only 40.5% (81) understood the information, 93.5% (187) patients were satisfied with the process of informed consent (Amir, Rabbani, and Parvez 2009).

A study, from Lahore used survey and observational data to compare the clinical practice of obtaining informed consent in a private and a public hospital. It showed that the practice of obtaining informed consent was better in the private hospital compared to the public. The survey on 93 patients from each site showed that informed consent

was obtained from 47.8% of private hospital patients and from 9.7% of public hospital patients. The observations of the practice of informed consent show that in public hospitals informed consent was not taken from 90.3% patients or improperly taken from 6.5% patients. In the private hospital, informed consent was not taken from 53.3% patients or improperly taken from 45.7% patients (Humayun et al. 2008).

Jafarey and Farooqui, physician-ethicists from Karachi, used in-depth interviews, informal discussions and focus group discussions to report clinicians' perceptions of informed consent in clinical practice and highlight important issues, such as the role of the family and time constraints. However, they also draw attention to the need to include patients' views in any future study, especially in regards to the role of various players in the processes relating to consent and decision-making (Jafarey and Farooqui 2005).

Jafarey conducted an expanded form of interviewer-based questionnaire survey in Karachi, of the views of the public about the process of informed consent and decision making for research participation. This study raised several important issues. Many (39 % of 337) participants questioned the necessity of a "proper" i.e. written, signed documentation of consent. 53% of the participants felt that to enrol women, it is better to approach them through the husband or father and in case of a conflict of opinion with the family, they valued the male participants' opinion more highly than the woman's. A limitation cited by the author was that it did not probe deeply for the reasons behind these responses (see Jafarey 2006). Since the study

respondents had not participated in a research trial the findings illustrate the participants' theoretical views but do not reflect actual experience of consent and decision making.

Both the PMDC and the international guidelines require a written and signed consent form (PMDC 2001, [20.2]; CIOMS 2002; WMA 2008), which some physicians in Pakistan endorse. Reporting a national survey on obtaining informed consent for radiological examination, Haq et al write that informed consents' medico-legal importance is under-practiced and consent is not obtained in a formal way – i.e. in writing, as it should be (Haq et al. 2003). By contrast, Bhutta writes that an insistence on a written informed consent in an illiterate population is insensitive (Bhutta 2001).

1.4.2.ii Decision making

Moazzam, a physician-ethicist, writes about her experience as a paediatric surgeon in Karachi on how decisions for clinical interventions are made either by the family or the surgeon, sometimes both (Moazzam 2000). This is reiterated by Aslam et al (Aslam, Aftab, and Janjua 2005) and that in many cases (71% of 200 patients) the relative signs the consent form (Amir, Rabbani, and Parvez 2009). Khan concurs, stating that "it is common to get the consent form signed from the head of the family" along with stating that physicians and researchers accept this form of consent because they belong to the same culture (Khan 2008:83). Moazzam and Zaman identify a "moral" clash between "transcendental medical culture" and local family beliefs in clinical practice (Moazzam and Zaman 2003). According to Bhutta (2004 a), obtaining a truly informed consent is

especially difficult when the procedure is not in conformity with local cultural norms and realities; Upwall and Hashwani have the same opinion (Upwall and Hashwani 2001).

Ethicists from Pakistan exhort researchers and clinicians to act virtuously and be vigilant of their duty to obtain a truly informed and meaningful consent, given that patients in Pakistan, as in other South Asian societies, are vulnerable to exploitation due to poverty, illiteracy and ignorance (Jafarey and Moazam 2010a; Jafarey 2002, 2003; Khan 2008). Along with Sheikh (2008) and Bhutta (2002), these authors recommend enhancing local capacity for ethical practices, because, Khan writes, local researchers "have no concept of research ethics"(Khan 2008:83).

1.4.2.iii Trial responsibilities

Bhutta raises some specific issues of community participation, prior agreements for benefits of research to the local population and the standard of care. He emphasizes that the underlying socio-economic inequities need to be addressed and argues that the standard of care should be context dependent so as to facilitate locally relevant research (Bhutta 2002, 2004 b). Khan too emphasizes the need for a standard that is locally available, which may be different from the international standard (Khan 2006). However, the PMDC code states that placebo control should not be used if equally effective standard therapies exist (PMDC 2001, [20.0]).

In view of the fact that drug trials are on the rise in Pakistan, Moazzam writes that researchers should have a strong sense of moral

responsibility towards their research participants and safeguard the interest of their patients by ensuring that the proven intervention is provided to enrolled patients at the conclusion of the trial (Moazzam 2006, 2012). Although drug trials by pharmaceutical companies are necessary, it is important to achieve a balance between industrial policy and health policy, such that trials are responsive to the health care needs of the people in developing countries (Sheikh 2006). However, missing from the literature from Pakistan is any discussion of responsive research from the viewpoint of patient-participants and researchers.

1.4.3 The need for empirical research and analysis on research ethics in Pakistan.

My review of the literature suggests that whilst there has been much discussion of the ethical aspects of research in low-income settings, very little work has been carried out on research ethics in Pakistan. This is important because Pakistan is increasingly becoming the location for international medical research and also because, as the literature review above suggests, the interpretation and implementation of international research ethics requirements in particular contexts inevitably presents unique challenges. The requirement of informed consent, for example, plays out differently in important ways in different places – even if there is inevitably also much in common across low income settings. Whilst work has been done in many other settings, very little attention has as yet been given by researchers and policy makers to research ethics practice (Hyder

and Nadeem 2001) or to the views and practices of those who conduct research and those enrolled in research in the Pakistan setting.

Given the challenges of applying the ethical requirements of international guidance in developing countries, Bhutta argues that in a vulnerable population, such as in Pakistan, the design and implementation of the consent process should be carried out by "a knowledgeable and sympathetic researcher", who has a "full understanding of the local issues" (Bhutta 2004 a:776). This suggests the need for high quality empirical research to inform such work, and to enable the development of a guidance system that is situated in and suited to the local culture (Chattopadhyay and DeVries 2008).

Against this background my study aims to provide such an understanding of the local issues by exploring the views, experiences and practices of those at the interface with patient-participants. These are the physician-researchers who conduct research trials. It is equally important to know the views of patients enrolled in these research trials. I use the international guidelines as a heuristic to "home in" on local practices in order to reach a critical, contextual interpretation of the ethical requirements (Chan and Wendler 2010; Bhutta 2002), without attenuating the moral imperatives (Bhutta 2004 a; Benatar 2004; Benatar and Singer 2000; Tangwa 2004).

Chapter 2

Research Design

In this chapter, I discuss the design and conduct of the research undertaken for this study. I begin by outlining my research questions and rationale for the chosen method of data collection. I then describe the tools used for data collection and the challenges of entering the field. As I shall show, some of the difficulties I experienced with access to research sites and participants, and with obtaining consent from patient informants, revealed unevenness in local interpretations of international research ethics guidelines, and as such proved consistent with the central themes of the analysis in this thesis of the relationship between local practices and international guidelines. The final sections discuss the processes of data collection and analysis and reflect on the significance of the methodological challenges for the central themes of this thesis. I present my analysis of the research findings across the subsequent four chapters.

The aim of this project was to examine the challenges of applying ethical requirements elaborated in the international guidance literature for research when patients are recruited to research trials in Pakistan. Initially I chose to focus on the views, experiences and practices of doctors who recruit patients into research trials in the academic research environment of tertiary-care hospitals in Lahore. I refer to my interviewed doctors as physician-researchers (P-R) in the text. Since patients featured centrally in the narrated experiences of these

physician-researchers, I expanded my study to include patients already enrolled or about to be enrolled in these trials. My research focussed on the following questions:

1. What are the ethical issues that arise for physician-researchers when enrolling patients into research?

2. Why do these issues arise? Does the socio-cultural and economic environment have an effect?

3. How do physician-researchers manage these issues?

4. How in practice do physician-researchers manage and understand the boundary between research and clinical practice?

5. What is the patients' perspective on issues raised by physician-researchers regarding enrolment and research trial?

6. What is the relationship between international ethical requirement and local environment?

2.1 Choosing methods of data collection

In order to answer these questions, it was necessary to choose methods that would enable an understanding of "ethics in action" (TenHave and Lelie 1998:269). My aim was not to test a hypothesis using the experimental method of large-scale survey from which, in the manner of quantitative sociological research, a deductive conclusion is drawn (Burns and Grove 2005; Greenhalgh 2006; Mays and Pope 1999). Rather, my aim was to obtain a nuanced understanding of the contours of local practice and meaning surrounding the enrolment of patients

into research trials. As Chan and Wendler have observed, “sensitivity to context influences both how individuals ought to act and how their actions ought to be evaluated” (Chan and Wendler 2010:28). To reach such an understanding required a method that would maximize sensitivity to the contexts in which people act and evaluate their actions (Gordon et al. 2011). It was precisely these social contexts in which ethical actions and reasoning are shaped that I wished to delineate. Only by understanding these contexts, is it possible to reflect on the extent to which normatively derived ethical principles are applicable as practical ethics without further contextual interpretation (Gordon and Levin 2008).

I therefore chose to use in-depth interviews and observations, which are the most common sources of qualitative data, and to use “text-based, interactive [and] flexible] methods” of inductive analysis to interpret these data (Avis 2005:14). While qualitative research findings reflect the particular and unique qualities of real life situations (Koenig, Black, and Crawley 2003) and cannot be generalized; they can be extended to other similar circumstances and derive their strength in their validity, which can be ensured in several ways (Holloway 2005; Hammersley and Atkinson 2007c).

2.2 Preparatory to field entry

As a practicing doctor who had previously only conducted quantitative biomedical research, I needed training in qualitative social science methods prior to entering the field. I studied textbooks on qualitative research methods (Jacoby and Siminoff 2008; Creswell 2007 c; Holloway 2005; Hammersley and Atkinson 2007). I also attended an

intensive training workshop in qualitative research methodology and interviewing skills in Oxford, offered by what is now the Health Experiences Research Group.

2.2.1 Tools for data collection

2.2.1.i Interviews

I developed a broad list of questions, with associated prompts, in a "topic guide" or "interview guide" after discussion with my supervisors and reviewing relevant literature (Greenhalgh 2006:168; Sankar and Jones 2008:119). My open-ended questions initially defined a topic for my interviewees to elaborate on, in a way intended to reveal their own frameworks of meanings (Britten 1995). The guide was designed to elicit similar information from all interviewees while capturing each interviewee's unique perspective (see Sankar and Jones 2008).

I developed two interview guides, one in English for physician-researchers and one translated into Urdu for patients (Appendices A and B). I amended the interview guide for physician-researchers after conducting pilot interviews in Pakistan. I found that when I asked physician-researchers if they ever felt a patient's consent was not valid, they answered defensively: "We take written consent"; or, "We do not do anything without consent", as if they felt that I was judging them. So I changed the question to, "What issues arise when obtaining consent from patients?" I also found that when I asked about "ethical dilemmas", these physician-researchers did not know what I meant by

"dilemmas" so I changed the question to "What ethical problems/issues arise during research trials"?

In fact, refinement of the interview schedule was to continue beyond my preparation for the field. I discuss this here in order to show that my main data collection was a flexible and dynamic tool. As noted, my aim was to explore in depth my interviewees' perceptions of issues that raise ethical concerns, and for this I had chosen a semi-structured approach. During the main data gathering stage, this approach gave me the flexibility to compare across already-completed interviews and identify themes that warranted further exploration as ideas emerged from my experience in the field and from my preliminary analytic reflections on the data (Hammersley and Atkinson 2007c). This visiting back and forth between my questions and what my data were telling me helped me to proceed with a sharper focus of inquiry, as is recommended (Srivastava and Hopwood 2009).

I engaged with the data from the beginning by listening to the audio-recorded interviews on the day they were recorded. When these raised new topics and questions I added these to the interview guide and discussed these topics with subsequent interviewees if they did not raise them spontaneously themselves. For example, when I asked questions about the necessity of obtaining patients' consent to trial participation, physician-researchers' articulated their conceptions of patient autonomy. As a result, I added the following questions to the interview guide: "Why do you (P-R) want to take consent from patients?" and, "What is your (P-R) concept of (patient) autonomy"?

During the analysis of the initial interviews with physician-researchers, certain themes emerged that also warranted exploring with patients, so I modified the interview guide for patients to accommodate these. For example, initially I asked patients (in Urdu): "Were you, yourself willing to take part in the trial?" Then, after I had listened to physician-researchers narrating the complexity of patients' decision-making process, I realised I needed to probe further patients' perspective on decision making. I made some modifications to the questions and, to get a broader perspective, I expanded the number of topics to be discussed. The revised guide included questions about patients' understanding of research, about involving others in decision-making, and on whether consent should be in writing. I was fortunate to be able to re-interview, using the modified interview guide, eight patients whom I had interviewed earlier, to obtain their perspective on the additional topics.

2.2.1.ii Observations

Observations help in overcoming any discrepancy between what people say and what they do. They may make explicit an implicit practice or behaviour that participants may be unaware of, in a natural setting (Mays and Pope 1995). The typology of observations runs the gamut of complete participant to complete observer, with participant-as-observer and observer-as-participant between the two (Hammersley and Atkinson 2007b). I intended to be primarily an observer, and prepared for this role by negotiating with physician-researchers a way of being able to observe their consultations with patients, with patients' consent. I paid attention, from the time patients were called

into the room, to how patients were greeted, to whether or not there were others besides myself, the patient and the physician-researcher in the room, how and when research was discussed, how the physician-researchers interacted with patients, and whether the patient was accompanied and their consent was recorded.

2.2.2 Ethics approval

I obtained ethics approval in the U.K. from the University of Oxford's Research Ethics Committee (MSD/IDREC) in September 2008, the same month in which I had submitted by ethics application (Ref: MSD/IDREC/C1/2008/72). I obtained ethics approval in Pakistan from the National Bioethics Commission (NBC) in December 2009, more than a year after submitting my application (Ref: No.4-87/09/NBC-19? RDC/3912). I had not expected the approval from the NBC to take so long, or that it would require me to make a payment of ten thousand Pakistan rupees as fee for the reviewing process. It is reported that financial constraints limit the oversight activity of research councils (Thomas 2011), and CIOMS states: " ethical review committees may receive money for the activity of reviewing protocols"(CIOMS 2002, [Guideline 2]), but I had understood this to refer only to biomedical research protocols. In addition to the NBC approval, I had also to obtain local ethics approval at each of the individual research sites from which I enrolled research participants, as I describe below (2.4 Field entry).

2.3 Selecting research sites and participants

2.3.1 Selecting sites

I conducted my research at tertiary-care teaching hospitals in Lahore, the capital of the province of Punjab. I chose Lahore for practical reasons that facilitated data collection. First, Lahore offers large pool and variety of research sites connected with the main medical institutions. Three universities that oversee medical education are located in Lahore: the University of the Punjab, University of Health Sciences and the King Edward Medical University, and six of the eight hospitals that I chose as research sites have academic links with these universities. Second, logistic support was available to me in Lahore. Third, my professional experience with two of the selected sites facilitated my access.

Another advantage of choosing Lahore is that most of the physician-authors, and the published surveys, are from Karachi, so this is a study of perspectives of physician-researchers and patient-participants from another major city of Pakistan.

I found that although it is important to plan ahead the setting and actors in research, it is equally important to have a flexible approach, as other researchers have also noted (Gordon and Levin 2008; Creswell 2007 b; Sharkey and Larsen 2005). My research sites included sites A, B, C, D and E, which were government-run hospitals attached to institutions that train physicians, and sites F and G, which were trust hospitals where research and postgraduate training is conducted (Appendix F). Pakistan Medical Research Council (PMRC)

centres (H) were functioning as research cells in all the major government-run hospitals of Pakistan and were present at sites A, B and C. I also approached another institute of medical sciences (S) but, after three meetings and five months of email exchanges, my project was not approved there.

2.3.2 Selecting participants

Trials evaluating a medical intervention, usually a drug, are the most common from of research taking place in Pakistan (Moazzam 2006). Initially, in order to locate ongoing trials in Pakistan I visited the clinical trials registry at http://clinicaltrials.gov. From this I identified four ongoing trials that were actively recruiting patients in the hospitals of Lahore. These were Phase III, add-on, and Phase IV trials.

I conducted multisite research in order to obtain sufficient data and to represent a cross-section of physician-researchers and patients. Although I had selected my research sites before entering the field, once in the field I renegotiated some of them during the initial phase of data collection. There were only two physician-researchers at site C conducting the collaborative trial I had identified from the clinical trials registry, so I approached physician-researchers at site A conducting the same trial. Again, there were only two physician-researchers conducting this trial, and my access to patients was restricted. I was initially allowed to interview and observe patients' enrolment into the trial, but was later denied access.

I then approached other sites of research trials being conducted in Lahore. Some of these were listed in the clinical trials registry, and

some were not, but all were evaluating either a therapeutic and /or a diagnostic intervention. Some of the physician-researchers I interviewed introduced me to other physician-researchers conducting research trials. This form of purposeful sampling, called snowball sampling or chain referral, in which the initial participants identify other potential research participants, is a well established method in qualitative research (see Creswell 2007 b; Sankar and Jones 2008).

I kept an open mind about the number of participants to be included, because in a qualitative research project there is no hard and fast rule and considerable variation in sample size. A common theme is that this depends on when data saturation is reached. It has been suggested that an initial sample of ten cases followed by another three cases is necessary to see if any new theme is generated (see Baker and Edwards 2012). Guest et al (2006) report reaching saturation after twelve out of sixty interviews. I continued interviewing physician-researchers and patients until no new theme was added to my data. This theoretical saturation is an established practice in qualitative research (Creswell 2007 a; Sankar and Jones 2008). In addition I obtained copies of the consent booklets/forms of the research trials being conducted in these hospitals.

2.4 Field entry

2.4.1 Local ethics approval

Each of the individual institutions from which my research participants would be enrolled had its own requirements for granting ethics approval, even though CIOMS requires that a standard uniform review process be applied by all committees in a country (CIOMS 2002, [Guideline 2]). The process of gaining access at these different sites was very uneven, ranging from approval, to delays, to refusal.

Ethics clearance was straightforward at some sites. At three hospitals (sites A, D and E) I met the chairpersons of research ethics committees, who upon submission of my research protocol and the NBC approval letter gave me permission within a week. At sites B, G and H, the NBC approval letter was all that was asked for. Some hospitals (sites C and F) required that I present my project to the Institutional Review Board (IRB).

Delays were common at some sites. At site C, the IRB chairman, an eminent physician, questioned me about how I will disprove my null hypothesis and about the number of participants I will recruit to achieve statistically significant results. After being asked repeatedly about a null hypothesis, I replied that my null hypothesis is that the socio-cultural and economic environment does not affect ethics. To the question of sample size, I responded that it is not possible to commit to a sample size at this stage and I will continue to enroll participants until the data yields no new issues. After some discussions, I was informed that my research raises no ethical issues

but my null hypothesis is incorrect and I should determine the number of participants. I was also asked to submit my "questionnaire" to the committee for approval. Such a request is routine, but I was wary of submitting my topic guide, thinking that if potential interviewees viewed it then their interview responses would lack spontaneity, and that problems might arise if in interviews we discussed "unscheduled" topics that might arise in the conversation. Nonetheless, I was advised to submit the topic guide and was granted ethics approval for a year, at the end of which I was to reapply for an extension.

At site F, my research was approved after more than a year of negotiations. Initially, the ethics committee had stated that I should have a supervisor from their institution. I replied that I already had academic supervisors, suggested instead that someone might oversee my research, and received no reply. A year later, I resubmitted my research proposal with a request and all relevant papers – which were then not distributed to the ethics committee members – and presented my work at the scientific research committee. I received ethics approval on condition that I present at an IRB meeting too, which I did some months later.

Finally, at one site, (S) I was advised, after three meetings and five email exchanges my project required, for objectivity, "a minimum of three observers separately recording their findings" and my project was not approved.

2.4.2 Permission from gatekeepers

Apart from obtaining formal ethics approval from the IRBs, it was necessary to obtain permission from other "gatekeepers" at every institution from which I was to enrol participants. Thus I met Chief Executive Officers and relevant Heads of Departments. Some declined saying that there is no ongoing research in their department; others introduced me to physician-researchers in their department. I also met with the Principal Investigators (PI) of trials listed in the clinical registry and made contact with one hospital where I had previously worked. I used my contacts with physicians at other hospitals to physician-researchers conducting trials whom I could invite to be interviewed.

I was dependent in turn on physician-researchers conducting trials for access to patients enrolled in or about to be recruited into trials. I joined physician-researchers when they conducted their outpatient clinics, during which they consulted patients about either treatment or the research trial. The physician-researchers sought patients' permission for me to observe the interaction between physician-researchers and patient during clinics and for me to interview patients at some other time, in the hospital or elsewhere. The hospital administration knew that I would be conducting observations as well as interviews, and this was mentioned in the consent forms I provided to participants.

At sites A and C, I was initially allowed to interview and observe patients' enrolment into the trial at these sites (I observed Pts.U, T and

G) but my access was eventually blocked by non-local gatekeepers when I was told that the pharmaceutical company conducting the trial barred anyone from interviewing "its" patients. Here, the local physician-researchers would not act without seeking permission from the collaborators.

2.5 Gathering and storing data

Data were gathered in April 2009, from December 2009 to July 2010, and then in December 2010.

2.5.1 Obtaining consent

Before starting the interviews I informed all interviewees of the purpose of the interviews, about data storage and confidentiality. I maintain this confidentiality in this thesis by referring to individual patients (Pt.) and physician researchers (P-R) by a number (Appendix C).

At the time of completing my ethics approval form for Oxford's MSD/IDREC, I had committed to obtaining written consent from my participants. I had prepared consent forms in English for physician researchers (Appendix A) and in Urdu for patients (Appendix B). I explained to participants that signed consent was required to show that they understood the purpose of the interview.

However, in practice obtaining written consent created difficulties with some research participants. In the first place, there was the issue of allowing sufficient time for a consent, oral or written, to be fully informed. Occasionally, I asked patient-participants who would

otherwise have been excluded from my project to take the consent form home and ask someone to read and explain what was written in it. We then arranged an interview by telephone for a later date. More problematic, though, for some patients, was the matter of signed consent.

Physician-researchers and educated patients invariably read the consent form, asked a few questions, and signed it. With non-literate patients, I read out the information, or asked the accompanying relative to read it out. Then I asked the patient to ask their relative to write the patient's name and sign the form, if the patient agreed to participate. Some patients and accompanying relatives wanted me to write the patient's name on the form, which the accompanying relative countersigned.

Some women wanted their husbands to read and sign on their behalf, mostly because they were non-literate. On just one occasion, I asked three unaccompanied women who could not sign their names if they would allow me to photograph them instead. My thinking was that a photograph would be "proof" of my interaction with these women, and that it could be inferred from their allowing me to photograph them that they had also agreed, voluntarily, to be interviewed. The women consented to be photographed, but only, they said because I am a female.

2.5.2 Conducting interviews

I interviewed 40 physician-researchers and 41 patients. Of the 40 physician–researchers, 17 were women and 23 men. Of the 41

patients, 12 were men and 29 were women. The trials my interviewees were associated with were Phase III, add-on, active control or Phase IV drug and diagnostic trials.

The time available for interviewing physician-researchers was limited by the physician-researchers' clinical responsibilities, and sometimes patients or colleagues requiring immediate attention interrupted the interview. At these times, I would write down immediately what the interviewee had been saying, and this helped re-establish the connection in the thought process when the interview resumed. Sometimes I was unable to complete the interview in one sitting, and had to arrange for continuing the interview at a more convenient time and place; before restarting the interview, I would familiarize myself with the previously recorded interview. The nature of these interviews was such I was able to develop on points that emerged during the interview and explore them in detail. This "iterative approach", in which I attended closely to the responses of research participants, enhanced the richness and diversity of data (see Greenhalgh 2006). Two physician-researchers declined to be interviewed. Two others wanted to take the interview guide home, lacking time for an interview; one of them wrote her answers on the topic guide and the other sent short answers via email, but I exclude these data in my analysis.

Conducting interviews with patients was sometimes challenging because initially they answered in monosyllables or very briefly, followed by a long pause. To overcome this I would chat with them until they relaxed and then we commenced the interview. They were

also more reticent when interviewed at the hospital than elsewhere. This was partly because they were keen to return to the towns and villages they had come from after their consultations. It was also in part, an ecological effect of the hospital environment, the presence of physician-researchers affected patients' responses to my questions. It helped then to conduct the interview at a different location, as I discuss in the next section.

One physician-researcher and twelve patients were uncomfortable with being recorded, so I wrote down their responses. Sometime into their interviews the physician-researcher and one of the patients allowed me to turn on the recorder. Interviews with physician-researchers lasted 30-90 minutes. Interviews with patients initially lasted 20 minutes, but after I redesigned my topic guide they lasted 30-45 minutes.

2.5.2.i Interview location

Interviews with the physician-researchers were conducted in different locations within the hospitals. If the interviewee was a senior physician-researcher who was usually the PI on the trial, I invariably conducted the interview in their office, sometimes after initially having to postpone or reschedule the interview. The interview locations for junior physician-researchers were more scattered. I wanted to conduct the interview in a quiet place where we would not be disturbed during the interview but finding such a place was not easy, though not as difficult as looking for a place to interview patients. Occasionally, I would interview physician-researchers in the

doctors' office – a room next to the inpatient wards, which was an office for doctors who were on duty; at the time of the interview the other doctors would leave the room allowing me to conduct the interview (at site E and once at sites C and D). At other times, I used a vacant examination room in outpatients (at sites B, D, and G) or, more frequently, an empty side room by the wards (at sites B, C, D, and E). At site F, where the doctors were the clinical research officers with an office, I was able to interview them in their office; though only one interviewee (the officer-in-charge) had a separate cubicle the other two interviewees shared the office.

As regards interview locations for patients, finding space in a busy hospital was even more challenging. I conducted my initial interviews in the outpatient waiting area (most commonly in sites B, D and sometimes site E) and for this I would go at a time when, from experience, I realized that mostly trial patients, i.e. patients enrolled in that particular clinical trial would be present. Occasionally I could use an empty examination room (when available in sites B, C, D) in the outpatients department. At site (E) I was at times also allowed the use of the doctor's office or an empty "lecture room" For one of the sites (H at site B), an empty laboratory served as the interview location.

As the interviews with patients progressed, I realized that patients were giving short answers to questions about clinical research and informed consent when interviewed within the hospital environment. I decided to try to interview as many patients as possible outside the hospital setting, or at least a place away from the consultation rooms. From then on, I telephoned patients with whom I had exchanged

contact details at our first meeting, to arrange to talk with them at their homes or at some other time in the hospital. In these circumstances most patients talked more openly. Three patients came to my office for the interview; one of them (from site A, where my permission to interview patients was subsequently withdrawn) first sought prior permission to talk to me from their physician-researcher.

2.5.2.ii Data storage and transcription

I transferred all interview recordings to a computer on the day they were recorded. After transferring them, I listened to each interview, dated it and labeled it with a pseudonym, which I later replaced with a number for the interviewee. To prevent loss of identity of the interviewees during the analysis, I kept separately a list of names, pseudonyms, and numbers. Every week I copied all the data into a portable hard drive. I stored the written scripts of the eleven interviews with patients that were not recorded in a file.

Interview transcription took longer than planned, and was complex. I was unable to find a competent transcriber until after the interviews were complete. I discontinued with one of the four transcribers engaged initially because of her poor transcription and I retyped her transcripts because large portions of the interviews were missing. Two transcribers worked on interviews that were mostly in English and one transcribed interviews that were a mostly in mixture Urdu/Punjabi/English. Very few interviews had been entirely in either Urdu or entirely in English, with the result that transcription was time consuming because some sentences were typed in Roman Urdu and

some in English. The software available to the transcribers was either in Urdu (*Nastālique* script) or English and Roman Urdu transliteration for them was challenging, especially when the languages switched mid-sentence.

I translated all the interviews or interview portions in Urdu into English myself because a translation by someone who was not engaged in the interview is likely to miss something of essence. I had not realized how difficult this would be. The transliteration was not just unfamiliar to me but had been done by transcribers untrained in any system of Roman Urdu transliteration. Often, I had to return to the audio recordings to understand the Roman Urdu words because of the inconsistencies in the symbols that had been used to represent the sounds of the Urdu language.

2.5.3 Observations

Conducting systematic observations at different hospitals created varied challenges. At one site F the researchers talked to patients in a separate room, where only the patient, the researcher and myself were present; once we used an office where other research officers were working but not involved in the consultation. At site E we used the physician's office. At site C, I observed consultations, in the out-patient clinic, between a female physician-researcher and female patients, with their accompanying relatives, at which no other physician was present, and in which the relative, if male, was asked to leave the room if the patient was to be examined, unless a curtain was

drawn around the examination bed. Another consultation was observed in the doctor's office.

At sites B and D the consultation was usually conducted in the outpatients department, with other physicians and, sometimes, patients present. At least two doctors shared an outpatient consultation room, sitting facing each other. Patients were called in by the *nāib qāsid* (peon) and seated so that patients' backs were towards each other. After greeting the patient, the physician-researchers usually introduced me, by name, and saying that I am a researcher, and asked if they consented to my presence. The language used was Urdu or Punjabi, depending on the patient. None of the patients objected to my presence and I did not interfere in the consultations.

I maintained a field diary in which I kept notes of my observations of physician-researcher and patient interactions. Though overt research poses fewer ethical dilemmas, this may be offset by the group or individuals reacting to being observed and modifying their behaviour (Mays and Pope 1995). To minimize this I was discreet when noting the observations. As I was present for a relatively long period of time, I receded into the background and found it relatively easy to observe, though I was screened from viewing physical examinations of patients when the physician drew the curtain around the examination bed.

I realized early in my fieldwork that although the physician-researchers had my contact number to inform me when a consultation was booked for enrolling a prospective patient, they sometimes did not contact me beforehand. I knew that patients were recruited from the

outpatient clinics - and occasionally from inpatients – and that particular physician-researchers held their specific outpatient clinics on particular days, so I decided to "hang around" on these days, when enrolled patients were called for follow-up. At site E, for example, Tuesdays were for local research, Wednesdays and Thursday afternoons were for international trials. At site C, the days were Friday and Saturday. At site F, I would "hang around" on Monday and on Wednesday and Thursday mornings.

2.6 Data Analysis Procedure

Though analysis was ongoing while data were collected, the formal data analysis was carried out at the end of data collection, after all interviews were transcribed. Qualitative analysis relies on inductive reasoning to interpret and structure meanings derived from data (Thorne 2000). Data analysis begins with preparing and organizing the data, followed by reorganizing the data by "reducing" it into thematic categories through a process of coding and condensing the codes into broader themes (Creswell 2007 c; Holloway 2005). "The goals of the reduction phase are to (1) reduce the amount of raw data to that which is relevant to answering the research question(s); (2) break the data (both transcripts and memos) into more manageable themes and thematic segments; and (3) reorganize the data into categories in a way that addresses the research question(s)" (Forman and Damschroder 2008:48).

My supervisors, in Pakistan and the United Kingdom, guided me during data collection phase and during the analysis. To further prepare myself for analyzing the data, I attended a two-day course on

analyzing qualitative interviews held in Oxford, and two one-day training sessions on using NVivo 8, one before data collection and one after some interviews had been transcribed.

2.6.1 Interview data

2.6.1.i. Code manual

The strength of qualitative research lies in interpreting the data. Using a software programme for managing data analysis may have the advantage, according to Pope and Mays, of seeming "more technical" and making it relatively easy to coding large amounts of data and create code reports, but it does not do the interpretation and "all too often that creative turn is missing" (Pope and Mays 2009 :738). I used NVivo 8 initially but was more comfortable and felt more engaged with data when I analysed it manually and so soon returned to doing manual analysis. This also meant I could continue to analyse my data in a resource-constrained setting where the software was unavailable.

I listened to the audio recordings and read the transcripts simultaneously. This was necessary, initially to check the accuracy of the transcripts and develop a sense of the interview, and, as noted, to understand the Roman Urdu transliteration. Data analysis was an iterative process and required careful attention. After the initial stage, I re-read the transcripts, and listened to the recordings and highlighted, by changing the font color, passages in the transcripts that provided answers related to the interview topics.

On subsequent readings of and listening to the interviews, I highlighted more passages that added to or elaborated on passages highlighted previously. Then I read these highlighted passages and translated them into English, again listening to the recordings if necessary. While I encountered a response that was similar to responses by other interviewees, regardless of site, or my observations, I inserted a comment as a memo.

I read the translated passages from the transcripts, noting emergent themes as they arose in the margins of each passage. By using this open coding, based on thematic categories, I was able to develop a code manual, which I used to code the rest of the interviews. When an interview transcript was coded I wrote the interviewee's pseudonym and the relevant page number of the transcript containing the coded passage in the respective column of the code manual. This facilitated retrieval of the relevant passage from the transcript when, later, I produced code reports.

After developing the code manual, I connected various thematic categories and a framework emerged. The code manual was reanalyzed and dominant themes were identified as main themes, which became the "parent code" and the interconnected themes in the columns became "sub-codes". Later, if new themes emerged when more transcripts were coded, I added these themes to the code manual as sub-codes, either under the existing parent code, if it fitted into the framework, or as a new code. I went back to query the early interviews using these new sub-codes. After analysing about ten physician-researcher interviews and the same number of patients'

interviews, I felt I had reached data saturation; this is consistent with the findings of Guest et al (2006). In another report, seven of ten (70%) themes were evident within the first five interview transcripts, with the next four transcripts adding another two (20%) and the next five interviews adding only one (10%) new theme (Patrick et al. 2011).

2.6.1.ii Code reports

Once the code manual was formed and the codes condensed, the next stage was to reduce the data into code reports. This was time-consuming. From the code manual, for each parent code, a code report was generated which consisted of the parent code and sub-codes. I did this by picking out, from the columns of the sub-codes, participant's pseudonym and the page number of their interview transcript, and opening the transcript at that page. Then using Microsoft Word, I copied and pasted sections of the highlighted transcript that reflected that sub-code, into a document. Code reports were produced as a work- in- progress. By shifting the relevant passages from five or six coded interviews, at a time, to the respective code report, I was able to reorganize the data systematically and it was relatively easy to recognize patterns.

Coding categories were not static. If, when I read the code reports, new themes emerged within an already designated sub-code and it was apparent that there are distinctions between the two themes, then I separated them. The new theme became another sub-code and was

used for coding subsequent transcripts. I continued coding during the writing up process as well.

2.6.2 Observation data

I read my observations on the interaction between physician-researchers and patients, and noted the emerging theme or themes. I also used the themes listed in the code manual of the interview data to analyze the observations. I coded the observational data in a manner similar to the coding of the interview data, making connections between the sub-codes. When a similar theme from another observation was noticed I wrote a memo to remind me (see Sharkey and Larsen 2005).

Concluding remarks

In this section I reflect on some of the implications of my methods for the findings of my thesis. I focus in particular on my positioning in the field and my experiences with accessing research sites and participants, and obtaining consent.

As a Pakistani, Urdu-speaking female who had trained and previously worked as a medical doctor in Lahore I was connected with the culture of my research participants in general and the physician-researchers in particular. This also has its limitations. It was necessary for me to develop a critical awareness of my environment, to avoid making assumptions, and to try to treat the familiar setting as "anthropologically strange". Though I was of the same ethnic origin as my research participants, studying bioethics at a postgraduate level had sensitized me to the actions and behaviours that I might not

otherwise have considered ethically problematic. Kleinman writes: "were ethnographers better prepared in ethical reasoning they would be in a nearly ideal situation to project local moral issues into global ethical deliberations and vice versa" (Kleinman 1999:79). A positive aspect of my ethnic connection with my research participants was that we have languages in common; I spoke Urdu or English with physician-researchers, and Urdu and Punjabi and sometimes English with patients, which helped in ease of communication.

I was aware of the ethical implications of being introduced to patients by physician-researchers. This may have influenced patients to consent to my research. I was conducting research in a hospital setting, so patients may also have perceived my research to be part of the normal work of a hospital. I was also especially aware, with patients, of my role in the construction of knowledge, as being the medium through whom the narrative unfolds (Finlay 2002; Sharkey and Larsen 2005). While this raised opportunities for me, without necessarily benefitting patients, I was aware that I was offering patients the opportunity to talk, and some female patients said that talking about the emotional stresses they experienced during the trial was helpful.

My identity as a researcher did not necessarily facilitate access to some research sites or physician-researchers, however. Two physician-researchers were concerned that I might be monitoring the ethical conduct of their research. Although I reassured them that my research aimed to obtain an understanding of the issues and processes

involved in trial recruitment, and all information would be confidential, one of them declined to participate.

The difficulties I experienced in accessing sites also relate more broadly to the main theme of this research. My concern in this project was to detail the relationship between local ethical practices and guidelines for research involving human subjects. In particular, I wished to identify points where local practice departs from international guidelines, and to explore the reasons for this and the implications for ethical practice. When I entered the field, I experienced a striking lack of uniformity in ethics review procedures, which directly impacted my own access to research sites and participants. This was despite CIOMS that requires a standard review process to be applied by all committees in a country (CIOMS 2002, [Guideline 2]).

Accessibility can be a problem in any research endeavour, and not just at the initial phase of the research but throughout the research process; after gaining access, it is important to maintain the spontaneous flow of information (Gordon and Levin 2008; Hammersley and Atkinson 2007a). As stated earlier the dynamics in the field caused me to alter my participant sample. Had I only followed one collaborative drug trial, in which I interviewed four physician-researchers, and to be told that access is withdrawn after interviewing two patients and conducting three observations, I would have had a very limited data set. My preparation for fieldwork and my social connection in the field helped me pursue access to new research sites, by contacting physician-researchers on other trials earmarked from the clinical trials

registry, while I was negotiating access or waiting for permissions at other sites. This "judgemental" sampling helped me negotiate the unpredictability of access and take up the available research opportunities (Wallace 2005).

My research was the first employing qualitative methods to be conducted at most of these hospitals. The IRB members reviewing my project were mostly clinicians accustomed to reviewing clinical trials, and assessed my project on those grounds. Koenig and colleagues also found that medical professionals are familiar with clinical trials but lack knowledge about qualitative research and many of them consider qualitative research is not really scientific (Koenig, Black, and Crawley 2003).

The difficulties I encountered in obtaining written consents from some patients introduce a central theme of this thesis, which is the relationship between international ethics guidelines and local practices in processes of obtaining informed consent. Though I had received oral consent from all participants, I was acutely aware that in my application for ethics approval to Oxford and to the NBC, I had committed to obtaining written consents. Two local IRBs also wanted written consents. Desiring to fulfill this obligation had compelled me, on one occasion that I did not repeat, to find physical "proof" of my interaction with non-literate interviewees by taking photographs. This was despite the fact that a photograph does not document consent, and despite the cultural resistance to taking photographs of women within a *purdah*-observing (covering the face with a veil) society because this risks their being viewed by unrelated men. This incident illustrates

how ethical (procedural) commitments have implications “for the way one acts in the field. Even though the likelihood of ethical review committees checking up on compliance is remote, the shadow that their formality and quasi-legalism cast is long” (Simpson 2011:382). But, as this incident also shows, following ethical requirements to the letter rather than in spirit may deny some participants’ access to research, and may thus result in skewed findings. It may be appropriate to consider alternative strategies in keeping with local socio-cultural practice and with the spirit rather than the letter of international guidelines. This theme is developed through the empirical presentation of my findings, beginning in the next chapter with an exploration of issues in providing information to patients about a research trial prior to obtaining their consent.

Chapter 3

Information and Understanding

A requirement of research ethics guidelines and of trial sponsors is that physician-researchers obtain patients' consent prior to enrolling them in a trial. For this, as the information component requires that patients must be provided with information about the trial that they can understand and use to reach a decision. For their consent to be regarded as "valid", patients should receive "adequate" information, and should achieve an "adequate" understanding of it, before reaching a decision of their own volition (WMA 2008; CIOMS 2002). No consensus exists about the adequacy of information and understanding. However, at the very least, patients should know their diagnosis and prognosis, the nature of intervention, the purpose and duration of research, alternatives, the risks involved, and anticipated benefits (Belmont 1979).

In this chapter I present my analysis of issues related to this initial phase of the consent process. Written information about particular research trials is available to patients from the consent booklet, which the physician-researchers refer to as the consent form, (as the consent form on which to obtain signatures is at the end of the consent booklet) but the main sources of trial information are the physician-researchers themselves.

I show that the provision and understanding of information at the time of recruitment is influenced by variation in patients' understanding of

research and the time constraints under which physician-researchers work. Physician-researchers attempt to overcome these challenges in ways that raise ethical concerns that I highlight at the end of this chapter. First I present physician-researchers' perspectives, followed by patients' views, and I include my observations as appropriate.

3.1 Physician-researchers' perspectives on information and understanding

3.1.1Variations in understanding

All physician-researchers talked about the challenges of providing information to a patient population with varied levels of understanding. In their views, some patients have a poor level of understanding of their disease and of research, and while patients should decide whether or not to enrol in research, physician-researchers may have considerable influence on this decision:

> You cannot explain everything to everybody; the informed part varies from patient to patient. They may have understood it at their level. It is difficult; you have to adjust [information] accordingly. It is still left to the patient to decide, but it becomes more of a persuasion, but this is because their understanding is so [poor] (Int.P-R1).

To enroll in research, patients must know what their role in research will be. The presumption is that patients may lack the concept of research. For one physician-researcher, to understand research meant appreciating not that the patient will benefit but that the patient *may* benefit:

> Concept of research in this part of world [is lacking], people don't know what research actually means. Research does not necessarily mean gaining things. Research could mean if you take one [medicine] then you can take [an] other, then you

> compare the results and may be help out the people [patient] (Int.P-R30).

3.1.1.i "Education" and "understanding"

If patients are educated and understand English, it is *easy* to talk to them because, as I observed, although consultations take place in Urdu the medical terminology is English. And if patients are familiar with science, their *understanding* is better and the physician-researchers do not have to explain scientific terms. Some physician-researchers consider doctors and engineers to be better at understanding scientific concepts:

> In my opinion, there is a direct relationship [between education and understanding]. [Those] who are less educated require more explanation. The ones who have better education level as - I also have such people, one of my patients was PhD, when I started explaining [to] him, he grasped everything quickly (Int.P-R39).

> There are some patients who would understand the concept - I mean it's always easier to work with patients who have some idea of what research is. Like, if I have a patient who, you know, is possibly teaching in LUMS [Lahore University of Management Sciences], what more could I ask for? I mean, he would know. People, you know who are really enlightened by education are, you know, the kind of people that are easier to talk to (Int.P-R19).

Most physician-researchers believe that patients' understanding of research and their role in it is a function of education. Education in turn makes patients more likely to be active participants in research who will inform the physician-researcher about any side effects, as required by the trial protocol. This frequently influences which patients are recruited into research:

> Comprehension level on the part of the patient is variable, we try and find and get patients who are understanding [understand], they are educated, they can read the consent

> form and then sign. They can really understand these side effects are related to the drug, so active participation [from patient] is required (Int.P-R9).

One requirement of active participation is that patients ask questions about the trial. Educated patients, especially those with some knowledge of science, ask pertinent questions. As this physician-researcher, conducting a diagnostic test using radioactive material, commented:

> I think the only query, and that also is asked by educated patients, is because we inject them with the radioactivity, so sometimes they want to know how hazardous is that to the patient as well as to the attendant (Int.P-R22).

I observed that physician-researchers were more responsive and forthcoming with information, especially scientific information, when talking to patients who were educated and had knowledge of science, or had educated relatives with them. They would discuss the mechanism of action of the trial or the diagnostic intervention, using scientific terminology without hesitation, actively involving the patients during discussion. With Pt. U, for example, a physician-researcher said: "*yeh* medicine *āp kī* body *mein aik* chemical, Phospholipase [A], *hay uss per* act *kartī hay aur usay kum kartī hay* [this medicine acts on a chemical, phospholipase, in your body and lowers its level]. After reading the consent form, some patients asked the meanings of certain terms or seemed worried. Pt.U asked: "what if this one [medicine] reacts with the other medicine that I am taking"; others expressed concerns about the side effects such as what would happen if a particular side effect occurs and they were unable to reach a hospital in time. The physician-researcher would answer such

queries, and explain that evidence from the many patients who have taken this drug in this multicentre trial and from earlier trials (Phase I and II), is that X or Y percentage of patients benefit from this therapy. With non-literate patients, however, physician-researchers discussed trial methodology either briefly or not at all, unless an educated relative accompanied the patient.

I observed that though most patients had their "papers", educated patients were meticulous and organized, keeping records of the disease, its diagnosis and treatment in a chronological order. For example one patient had his file from 1999 and another from 2000. Such patients followed the progress of their disease and attend follow-up appointments.

When patients received information about the intervention, they ask the physician-researcher for time to think, especially if it was a drug trial, some then declined enrolment. But if the intervention was non-invasive involving for example diagnostic equipment or a single (one-off) blood test, I noticed that most patients regardless of their literacy status asked for the physician-researcher's advice and usually complied.

In most physician-researchers' experience, non-literate patients do not indulge in detailed discussion. Their main interest is to get treatment, which, in a research trial, will be free:

> Most of our patients cannot afford the chemotherapy, the price of chemotherapy. And they are happy, one way or the other they are getting at least something, anything. I think what we enrol in Pakistan, 90% are from a lower socio-economic status. Hardly, I guess, 10% to 15% of patients are

> from a higher socio-economic status. This was that other trial I told you about that I spent some six months on and we had screened about 200 patients at least, and I think out of those 200, about 10 patients either declined informed consent or they didn't show up at all (Int.P-R16).

I observed that when giving information to a patient about a trial in which there were four arms (treatment regimens), a physician-researcher (P-R13) stated that patient's data will be sent abroad and fed into a computer, which will choose the regimen, not the physician-researcher, and the patient accepted this explanation:

> We have nothing to do with it. We say that that we will input the data into the computer and whatever the computer tells us regarding the tablet or injection or may be both, we will go for that (Int.P-R13).

A problem physician-researchers highlighted with non-literate patients was that they do not understand the importance of following the required protocol or attending the follow-up visits and this creates problems with the data:

> Illiteracy is an advantage on one side but a disadvantage on the other – the patient stops taking antibiotic two days after his fever has settled. So there are compliance problems. Once the patient has enrolled, we have to follow the protocol of the study. We cannot, like let the patient do whatever he likes (Int.P-R16).

Non-compliance is a problem with non-literate patients in general, so this influences which patients are preferred for enrollment:

> We [take] mostly semiliterate, you see if totally illiterate then reason being you have compliance problem. [Non-compliance] is more common when women are enrolled in trial because either their comprehension [regarding research] is low as most are illiterate and also their inability to come for follow up visits because they are dependent on their men for finances and transport, they are less contactable (Int.P-R9).

Though most physician-researchers recounted problems of understanding with non-literate patients, nine[35] also narrated encountering non-literate patients who understood the research trial they were in, adding that this was because a physician-researcher had set aside sufficient time to achieve that, as well as on the physician-researcher's ability to communicate with them:

> When you have time, perhaps it is easy to make your patient understand – again like I said we need to communicate well. I have seen completely illiterate people really understand the concept of research really well…(Int.P-R19).

In another interviewee's experience, some patients "pick up clues from conversations" (Int.P-R26) between the physician-researcher and the relative accompanying the patient. I observed a similar process in a consultant's (P-R26) office when an elderly, cachectic female patient, in Pushtoon dress, was sitting on the examination bed while her son, standing beside her, was discussing her disease and its prognosis with the physician-researcher. The men conversed in Urdu, which was not the patient's mother tongue but the physician-researcher was convinced that although the patient does not understand Urdu, she realized that she has cancer.

3.1.1.ii Research is an "experiment"

Although understanding is better if a patient is educated and has scientific knowledge, if not, and even if the patient is literate, then to make "them understand is difficult":

> We have this problem [of understanding] with the group [of patients] that is educated to some extent but they do not know

[35] P-Rs.15,18,19,20,23,24,26,29,30.

> about medical terms and they don't have any medical knowledge, so I have more problems with them (Int.P-R13).

Patients' main worry, according to one physician researcher (P-R15), is whether the research being conducted was "experimental work" and that therefore "this *tajarbātī kām* [experimental work]" will affect them adversely and further compromise their health.

Seven physician-researchers (P-Rs 2,11,14,16,19,20,25) reported that whenever preliminary clinical data from ongoing trials were available, they informed potential trial participants that the medicine being tested has already been used and has benefited some patients. They added that even when patients are given a full explanation about the importance of a particular trial they are likely to be sceptical that the physician-researchers are conducting trials for their own benefit and viewing patients as guinea pigs. They might state for example, "You are involved in experimenting on us, we don't need experiments". So while it is easy to talk to literate patients they do tend to focus on the negative aspects of research:

> Q. Why do you think that is?
>
> They take it as *tajarba* (experiment) on them, as if this is something wrong and it will cause them harm. They think about harms more than benefits I mean side effects, that by the way are the effects of almost every drug like nausea, vomiting, diarrhoea and things like that. So they look at the negative aspect (Int.P-R2).

> The uneducated do not ask many questions; sometimes you come up with the situation where you explain everything to the patient and the patient is educated and so is her husband and yet they refuse. You know sometimes, I have dealt with cases where I had explained everything and despite knowing that this trial, this drug is going to give the benefit, they had refused (Int.P-R14).

> Q: Why [did they refuse]?
>
> Probably again, just because that misconception that okay this doctor is going to experiment and we will not gain anything out of it, you know (Int.P-R14).

I observed one physician-researcher (P-R2) attempting to correct this misconception by informing his patient, "This is not experimentation. Experimentation has already been done. Now that this drug has been found to be useful they want to do this research on patients."

In an attempt to clarify the purpose of clinical trials, physician-researchers also at times tell patients that the medicines such as Panadol, which patients take routinely is only available because it was tested on patients; the research process is the same even if the current trial drug is a more complicated one.

> Most of them they do think that okay they are just experimenting. So it is physician's duty to explain to them that okay, you have failed on everything else, okay now this [trial] is the next available treatment and here are the benefits and the risks. Let's say if she [patient] is going to get a medicine which is very expensive, which has shown a benefit in a certain treatment, okay, then, you know obviously if, if an injection costs around one lakh [100,000 Pakistan Rupees] or something, okay, so which is very difficult to manage even for a mediocre, and you explain [to] her, okay you are going to get this treatment free and it will do this benefit…it will increase your life expectancy (Int.P-R14).

According to one physician-researcher there are instances when a patient who "is bent upon being stubborn about not grasping anything told to them then they will just not make the effort to understand; this is not related to their literacy status"(Int.P-R18). Another interviewee was however, of the view that "no matter how good your explanation is, if they do not have the basic understanding, they can never understand" (Int.P-R1).

3.1.2 Patients are overwhelmed

In the physician-researchers' view patients attending these hospitals generally lack knowledge of allopathic medicine. One physician-researcher (P-R26) said that educated patients are more aware of their disease because they have "access to, for example the internet" but account for no more than "five or ten percent [of patients], generally ninety percent are those who do not know" and giving detailed information to uneducated patients "overwhelms" them and creates confusion. Therefore it is better to give "little bit of information to digest" (Int.P-R20).

> The more you talk in detail to people the more actually they get confused about it because they do not have the background knowledge of medicine, necessary to sift through the information. I tell them bit by bit (Int.P-R6).

According to this physician-researcher, each patient's "perception of their disease is variable and intertwined with their social, cultural and economic issues" (Int.P-R6). Non-literate patients especially rely on their physician-researcher to make a decision regarding trial participation, and do not ask many questions.

> At times they say 'we don't even want to know all this'. At times we need to make compromises according to the scenario in which we are, we tell in easy terms, you know. They [patients] need some more time to absorb whatever I have told them (Int.P-R18).

Some physician-researchers aware of the benefits in research may persuade their patients to enrol. One physician-researcher (P-R30) said this might entail telling patients that they will be taking less medicine or that their disease will improve if they enrol in the trial.

> If we tell the patient everything, everything regarding the trial, the medicine, the side effects then patient may get afraid. [The] patient cannot judge benefits versus risks, so in my experience, if a patient comes to know each and everything, they, most of them push themselves to deny and they won't get themselves enrolled in the research (Int.P-R13).

Another physician-researcher was of the opinion that though *all* the details cannot be given in a short span of time, at least the major risks should be communicated:

> Another thing which I have observed that some physicians do not explain the risks, you know, in detail, okay, so I think that is wrong and, especially, you know, even if you are not telling them about all the side effects, you should explain the major risks, hazards to their health, you know, they'll be getting (Int.P-R.14).

Most physician-researchers said that they tailor information about research according to their patient's circumstances:

> We feel if told in very straightforward words that you are in a trial and this is test drug or test something that they may reject it outright. But that does not happen if people take consent in an indirect manner rather than being very direct (Int.P-R17).

I observed that most literate patients, who read the consent form/booklet, were concerned about side effects that may curtail their daily activities. The physician-researchers would explain and allay these fears; but the patients insisted that, although they understood, they should talk to their family or a friend (who is a doctor). Physician-researchers considered this helpful if the relative the patients talk to is familiar with medical research but were concerned that patients seeking advice from people unfamiliar with medical research might not enrol.

3.1.3 Time constraints

Physician-researchers say it takes time to communicate trial information to patients. Sometimes patients do not ask questions at the initial consultation but return later with queries. Having an open door policy for providing information about the risks and benefits, and allaying apprehensions about a trial might be helpful. They thought it would not be necessary to be present in person, and that telephone contact might be sufficient as long as the physician-researcher is accessible.

Physician-researchers reported that their working conditions exert a powerful restraint over the conduct of research. As P-R6 said, there is time, manpower and economic constraints and these affect research; it is necessary to reduce the clinical responsibility to conduct good research. Most stated that accessibility is a major issue in a busy general hospital where, in addition to conducting research, physician-researchers look after “indoor” patients (inpatients) and providing consultation to “outdoor” patients (outpatients), where on average they saw thirty-forty patients daily, and were part of the on-call team too. The system is not streamlined: outpatient clinics are not pre-booked, so doctors must see all patients who attend and are registered on the same day. These physician-researchers reported that they work in conditions of financial and temporal paucity. I observed one physician-researcher gave consultation to four successive patients in a span of twenty minutes. And a direct consequence of lack of time is

the inability to have detailed discussions with patients about research participation:

> There is not enough time, we are not able to give them proper time, it makes [me] feel guilty, and that is because we are overburdened. We call our research patients after 12 [noon] as before that we are busy with ward patients and our ward round. We try to see the research patients quickly (Int.P-R29).

"Shortness of time, increased workload and decreased manpower" (Int.P-R13), leaves physician-researcher with no time to counsel their patients regarding their disease and the "new medicine [trial drug]", and some physician-researchers are cognizant of this:

> Here in the government hospital, there is too much load of patients and I don't have enough time to counsel them. And I think that's a very important phase of our training that we are lacking here, in Pakistan, especially in the government sector, is that we do not counsel the patients the way we should (Int.P-R16).

Two physician-researchers (P-Rs.13,19) described another type of time constraint: the "narrow window" for research enrolment. This leaves insufficient time for patients, especially for patients who have been referred from other physicians, to discuss the trial with their family and then return with a decision. "Once a patient starts treatment they're usually are no longer eligible for clinical trials" (Int.P-R19), so if a patient is to be enrolled in the trial, then consent is imminent. In fact many times it is obtained at the first consultation:

> In case we have time, we have time to enrol them, we give them the form that go and read it and then come up with your decision and if we do not have as much time, we explain [to] them and get their consent right there (Int.P-R13).
>
> Q: Right there?

> Well, every protocol has some limitations, and you know that there is a time like if you have to enter in this study. This much is the time, after this test, after this test within 15 days or within 3 weeks you have to get enrolled and get your first medicine but if patient is coming from far-flung area, or she is staying somewhere in Lahore and her family is in some other city far away, she won't go there. So we will like to get it [consent form] signed right there. She has to depend and she has to trust the doctor for this.
>
> Q: And do they?
>
> Absolutely, these people believe a lot in doctors (Int.P-R13).

Some physician-researchers devised a schedule to assist the "smooth conduct of research and their clinical work". One physician-researcher (P-R2) would book appointments with research patients for his "off duty" days, to allow time to discuss the trial.

> So our attitude is a bit different, I give them [patients] more time, if I spend 5 minutes with each of my outdoor [outpatients clinic] patients then with my research patients I spend at least 30 minutes. Then my telephone contact number is also given which I, or for that matter any doctor does not give to any of the outdoor [outpatient] patient (Int.P-R2).

Three physician-researchers (P-Rs15,18,19) at one institution worked as research officers liaising between patients and physicians with the primary function of counselling patients for research. They were able to have detailed discussion with patients and spent on average "two to three hours with their patient". This, they say, is important so that the "explanation of their research is so clear that the patient herself wants to come into the trial" (Int.P-R15).

Three other physician-researchers (P-Rs13,14,16) addressed this time constraint problem by dividing their day into two parts. In the morning they would do clinical work, in the afternoon they would do research

work and one (P-R37) would ask his trial participants to come in the evening.

> I usually explain by either drawing on paper or using stories. And take 40-45 minutes discussing with the patient [and spouse] so that there is no ambiguity regarding the drug and options available to the patient (Int.P-R14).

A lot of time is "wasted in arranging the logistics in most [government] hospitals…ideally, there should be a department to take care of counseling patients, collecting and compiling case notes and their results" (Int.P-R26). I observed that this physician-researcher found it stressful conducting a trial and an outpatient clinic simultaneously and he complained that he is unable to do justice to either.

3.1.4 Physician-researchers are pragmatic

Some physician-researchers, who said they would not "waste time" explaining everything about the trial to patients also said that when they are convinced that the patient will benefit, they simply tell patients that this trial is good and will benefit the patient. They emphasized that this approach is not based on malafide intentions but is necessary to expedite consent. I observed that one patient being given information about a Phase IV trial was informed that this medicine gave "good" results and is being used "abroad"; the patient was not told that this trial's purpose was to observe the long term effects of the trial medicine.

When confident that an intervention will be effective even when patients have not assimilated the information physician-researchers

"guide" patients towards enrolment. "[I would] definitely guide them that this [intervention] is better for you. We try to guide them as we get [mostly] illiterate patients" (Int.P-R38). The literacy status of patients affects how information is provided:

> We should give the facts especially if patients are educated. But if I feel the patient needs to be convinced because the understanding level is not so much. I think in that scenario, maybe, I would try to convince the patient that it'll be beneficial for the patient, not from my study's point of view let me get that clear (Int.P-R22).

The trial protocol is followed in all cases, but with educated patients the protocol is explained which is not the case with non-literate patients:

> When we come across an educated or literate person, we do what has to be done but we have to explain to that patient [also]; on the contrary when we come across an illiterate person, or very poor guy, at times we do explain to [them] but at times, they are not interested in that [explanation] or they don't understand what we say (Int.P-R16).

I observed that educated patients usually asked questions and wanted, and received, more information. Physician-researchers welcomed such discussion and interaction as they then feel that the patient is not being forced to enrol:

> At times we do enjoy that counseling. Because we have to explain each and everything, they understand almost, if not 50%- sorry 100%, more than 60-70% they understand and then they discuss. And this is a good thing and which probably keeps our conscience clear as well that we have been explaining each and every step of the treatment to the patient and we aren't enforcing treatment on the patient (Int.P-R16).

Another physician-researcher reassured patients by emphasizing the necessity of research:

> Doctors have to work continuously on improving the medicine and although it has shown beneficial results more data is [sic] needed…they have tried it [the trial drug] on 5000 patients in clinical research, we need more patients, and just to, you know, validate the data. So, though it is a study but it's going to give you this benefit, you know. So this is what I tell them that okay they have opened, you know, 52 centres in developing countries and now this is, you know a very expensive [medicine] and is just a gift for you, [you] won't be able to purchase it yourself (Int.P-R14).

The pragmatism is considered "necessary" in this context and is based on physician-researchers' confidence in the trial's claimed benefits, which I explore in Chapter 6.

3.1.5 Communicating information

According to the physician-researchers it is important to consider not only how much and what information they give to the patients but also how they communicate that information. For them, trust is integral to the relationship with their patients. As one physician-researcher said "People still relate to the concept of doctors as their healers and would believe whatever is told to them" (Int.P-R19).

Enhance trust: Effective communication requires that patients feel comfortable and are not apprehensive:

> It is just that they have to feel comfortable with [the fact] that I am not trying to give them something which is going to hurt them it just might help them ,you know. So that concept has to be very clear and it has to be conveyed to the patient that this is not any guinea pig surgery or any guinea pig procedure that we are trying to do (Int.P-R30).

Besides making patients feel comfortable, it is equally important that patients' trust in the physician-researcher is maintained so that, "they know that you're not going to use them as guinea-pigs and the

patient's wellbeing is important" (P-R19). This trust can be enhanced if the physician-researcher talks to patients avoiding "technical terms, in simple layman terminology":

> I'll just make a drawing and I'll explain her that okay this is like, this is a cell, okay, so if this drug is going to act on this receptor, so just imagine that a person is standing half in the cell, half out, this drug is going to act on this outer side on the head and then, you know, is just like a bolus of food that you are taking the food in, it goes, you know, into the cell and, you know, does all the functions. Keeping in mind that most of our patients, you know, I'm dealing with are not well educated, so you have to, you know; bring yourself down at their level (Int.P-R14).

Information in phases: Physician-researchers believe that giving information to their patient over a period of time is better:

> If I am planning to enrol a patient in my trial, like after 3 months, I will talk to them 3 months prior. So by the time the enrolment time, you know, approaches they [are] usually prepared (Int.P-R14).

> The most important thing and I think the gist of this whole thing, is that the patient should get each and every detail of the study, which is not possible in our setup. Even with literate [patients], because at times the scope of the trial is so big that you cannot explain each and every bit… so you have to split it into parts and you have to tell them step by step or when the situation arises you have to guide them accordingly (Int.P-R16).

Patience and physician-researcher: Interviewees consider that patience *(sabar)* is an important virtue. The physician-researcher's attitude to his or her patients impacts on their communication. Most patients seeking medical advice at these hospitals are non-literate and unable to express themselves freely. It is important:

> [To] build a good rapport with patients so that he is comfortable. Whatever we are going to do with him or whatever he is going to experience in the next six months or

> one year he must be knowing and should be comfortable with that (Int.P-R31).

One physician-researcher (P-R5) felt it is particularly important to be patient and empathize with patients: “High ranked doctors” tend to be dismissive and condescending, saying such things as “I am telling you, otherwise go away and consult someone else”. She thought this as “the biggest problem”. Another said, if the “doctor talks to them [patients] nicely, and counsels them, then their disease related problems are reduced by fifty percent” (P-R13). If the information is explained with patience and there is enough time, then most patients understand it, irrespective of their literacy status:

> It is important to be empathic to patients and take time [to explain].If we have fair communication skills, in which you are able to communicate to the patient that what it is that you want to do, whatever level of education, they do grasp and are supportive. People are afraid of interventions, people are afraid of the unknown because of maybe the third world, the fact that there is so much uncertainty around (IntP-R6).

Communication through relatives: I observed that patients who had relatives in the medical profession usually brought this person with them to the hospital to discuss their disease with the physician-researcher, and when trial enrolment was mentioned, would want these relatives to discuss the trial with the physician-researcher.

> If the patient has a relative who is in the medical field, if he comes and meets us then we can explain to him, and if he asks our opinion then we can tell them and they will understand and then they tell their patient (Int.P-R13).

Physician-researchers tended to encourage non-literate patients to bring an educated relative or acquaintance to their consultations, finding this helpful. Although, one physician-researcher (P-R10) noted

this may cause delay initially, she said in the long run it is better as the patient is more compliant.

I observed that ease of conversing with the educated relative invariably resulted in a continuous dialogue between the relative and the physician-researcher that was interrupted only when the physician-researcher wanted specific information about symptoms or medications. In case of most elderly patients or women, the accompanying relative reported these details and the patients did not seem to mind that consultations about them took place between *others.*

Sometimes patients who were eager to start the trial were encouraged to talk to other patients in the trial, before committing:

> [I] try to get them in touch with the patient who is in this [trial].It helps a lot when they share their experiences. When someone who has taken the medicine talks to them then it is understood better by the patients. I think three or four patients I have done like this and I have seen that they are more comfortable than patients who just come and take the medicine and get the details from us. There are so many tiny things which they can share which we can't tell them (Int.P-R31).

On the other hand, in the experience of another physician-researcher (P-R19), if a patient has "decided to enroll" then nothing – no amount of discussion - will change their mind. Affordability of treatment tilts the balance "in favor of research".

I also observed that patients come to these hospitals from different regions of Punjab and from other regions of the country. This meant that sometimes patients spoke a dialect or language different from that spoken by the physician-researcher. In these cases the accompanying

relative, usually the husband or son, facilitated communication by acting as an interpreter and was often involved in the decision making.

> If they [patients] are Punjabi speaking and if you talk in Urdu [even then] they will not understand. The question does not even arise that any of them would understand any English. And if you feel that they are not able to grasp, then you ask the patient that if they have an attendant. Mostly, they do have someone who is educated or at least has some ability in understanding [Urdu] (Int.P-R22).

> There is also some language barrier in our society, right. And there are few cases when like there was a Pathan, Pushto speaking, right, so we have to decide how we should to explain this person, so we bring somebody who knows [Pushto and Urdu], then we explain to him,[the translator] he explains to the patient (Int.P-R36).

I observed some interactions between patients and physician-researchers, where patients could speak neither Urdu nor English. Ten of these patients were Punjabi speakers and two patients – one from Khyber-Pakhtunkhwa accompanied by her son, and one from Baluchistan province accompanied by her husband, spoke Pushto, though the patient from Baluchistan was able to understand and speak some Urdu. Both these accompanying relatives spoke fluent Urdu, and the husband of the Baluchi patient also spoke English. Both the men conversed with the physician-researcher and acted as interpreters. Similarly in case of Punjabi speaking patients, most of the discussion was conducted in Urdu and English with the accompanying relative, who would interpret the concepts that physician-researchers were explaining.

Gender and communication: Six physician-researchers (P-R26,29,34,35,39,40), felt that an important factor influencing communication is the gender of the physician-researcher and the

patient. If both are of the same gender, especially in case of women, then patients are more at ease when discussing their disease.

One remarked that it is important to "be sensitive to the customs and practices" that are prevalent in the society one lives in; "if women do not wish to talk to male doctors then provisions ought to be made for them to talk to lady doctors. Otherwise in my experience women will not talk [to men]" (Int.P-R35). Another said there are instances when "they [women] don't want to be treated by men [doctors]; they prefer that some female should attend them" (Int.P-R26). This applies both in the conduct of research and in clinical practice.

> If for example there is some [research] on gynaecological aspect then in that case we are mindful and have our female colleagues deal with patients and we do not talk directly [to women] (Int.P-R29).

I observed that at three sites (B, C, and E) the gynaecology/obstetrics outpatient departments did not allow men accompanying their wives to enter the clinics. Men were required to wait outside in the main reception; a notice pertaining to this was affixed to the wall next to the entrance to the clinic.

3.2 Patients' perspectives on information and understanding

3.2.1 Understanding of research

The international guidelines state that for patients' consent to be "valid", patients must understand "adequately" the information about that research. Most educated patients are clear that research is to *test* new medicines and that these medicines *might* treat their disease. As

one said: “It is research in which they will be testing a new drug, if it is not me then it can be useful for somebody else (Int.Pt.6).

I observed that educated patients understood English and some understood the scientific terminology. They were knowledgeable about their disease and the treatment they had received to date. For instance, one of these patients discussed his disease with the physician-researcher in detail and was aware of the cause of his condition:

> If my ITP [Immune Thrombocytopenic Purpura] does not improve then he [doctor] will remove the *tilli* [spleen]. You see it [spleen] is eating my platelets. He [doctor] told me of this research. By using this medicine maybe the spleen may not have to be removed and the disease may improve. I have come because my doctor said that it will be beneficial. I am thinking that if this medicine benefits me, I do not have to have the spleen removed (Int.Pt.12).

However, when I interviewed him and another educated patient, Pt. 14 soon after they were given information by the physician-researcher regarding research, both were initially skeptical and hesitant. One said:

> You see they [pharmaceutical companies] from the West come to poor countries; they experiment on us and use people as guinea pigs… But then this research is by the IAEA [International Atomic Energy Agency], so it must be reliable (Int.Pt.14).

When the physician-researcher explained the potential benefits and minimal risks of this trial the patient agreed to enrol:

> I do understand all that you [physician-researcher] are telling me, [the test] is under study, it is not used in any hospital. This [test] will help in the diagnosis of my problem. You [physician–researcher] are the doctor and I think I am in safe hands (Int.Pt.14).

This patient was an engineer with a good grasp of science and its terminology. Although he understood the trial, he was apprehensive and wanted reassurance from the physician-researcher about the safety of the trial's safety. When I talked to him later, and discussed his initial reservations about the trial, he stated:

> I have benefitted [from the trial]. I know that what they were doing was like an investigative report, to collect data, whether that machine is useful or not… I know that all medicines that come into the market do so after being tested and if they find that some medicine is not good for human beings then they withdraw it too. There is constant effort to improve. I think if the test was dangerous then the doctor would have told [me]. No harm was done and I think that it (test) will be beneficial for *khalk-e-Khudā* [mankind] (Int.Pt.14).

The other educated patient (Pt.12) had also read the "brochure" (consent booklet) and was aware that the trial medicine acts on the bone marrow. But, he said, "My marrow is producing platelets, it is the problem with my spleen which is eating them." He did not enrol because in his view the trial drug was not going to help him: "Experiments will go on, my body is tired, I do not want be the *qurbānī kā bakrā* [sacrificial lamb]".

Patients who had previous experience of trials, and had benefitted, considered medical research as a means of finding out whether the new medicine is effective in treating their disease. That is, "*tibbī tehqīq* [medical research]" is a scientific study to see the effects of new medicines and that it will "hopefully treat [the disease]" (Int.Pt.4).

> I was told that this is research (*tehqīq)* on a new drug that may help in decreasing the chances of heart attack …The

> doctors told me that I am eligible for this trial. ... I was then given a consent form to read and after reading it I just signed it there and then and handed the paper to the doctor. Now that it is benefitting me, I am worried that if I leave the medicine then there will be ill effects (Int.Pt.3).

Many other patients, especially the non-literate ones, considered research to be "new medicine that is good," as one patient put it: "My [doctor] said that when some new medicine comes in the market so it is for the good of the people, so in this they experiment on you, and in this no loss will come to you" (Int.Pt.25).

Most non-literate patients did not know that they were in a trial, or else considered they were enrolled as a way of getting new treatment that will cure them of their disease. As one patient said: "No, I have not understood it is [research] (Int. Pt.31), this patient's husband, who was educated and accompanied her on all her visits, added:

> This science, this technology is progress. The problems that we [patients] have cannot be solved without this [medical] research. They [physician-researcher] said that this medicine is for this disease. It is to finish this [disease] so that it does not recur… If you use it then you will benefit though temporarily you will have to bear [the side effects], it will be upsetting, but it is better that you use it, you will benefit (Int.Pt.31's Husband).

There were others who enrolled not only for their own benefit but also that research will benefit other patients too:

> There are two reasons for me to come for this research. I asked the doctor if it will benefit me and for the sake of *insānī humdardī* (sympathy for fellow humans) that was on my mind too (Int.Pt.26).

My observations of consultations between patients and physician-researchers showed that after narrating their symptoms, non-literate female patients accompanied by their husbands, would say very little.

Throughout the consultation, the conversation about the patient's disease, its treatment and investigations took place between the husband and the physician-researcher. Later, when I asked such women about the information they had received, usually the husbands replied. For example:

> The doctor *sāhib* told us that this medicine has been checked at many places [through many steps] and is now here, it is good medicine. And yes, this medicine has benefitted us too (Int.Pt.2's Husband).

When I asked another female patient (Pt.11) if she had understood what had been explained to her about the research, she said she had not, but her husband said he did, adding: "Research is to find causes and treatments for diseases. We want to know if the gene is there, it will be good for her sisters [to know]" (Int.Pt.11's husband).

In one instance, however, I interviewed a non-literate couple (Pts.24,28) and the husband, aware of his disease, had realized that his disease can be transmitted to his wife. When his Hepatitis C was confirmed, he had his wife's test done as well and when the test result showed she was affected, he brought her to the hospital to be enrolled in the trial.

I observed that sometimes patients were eager to start the new medicine. As soon as they had narrated their symptoms they would ask when they could start the medicine. The physician-researcher informed them of the side-effects, the duration of the trial and the importance of following the protocol carefully. Otherwise, P-R31 said if patients do not take the medicine as prescribed in the protocol or do

not attend the follow up clinics to check the progress of their disease, the medicine that the patient has already taken is wasted and this is wrong, given the financial constraints.

> I have been told all about it. It is a new treatment for the disease. [It is a] new medicine that they have discovered and they want to see now on patients. My slides were sent abroad to see if this medicine will work for me. They [doctors] told us [patient and husband] the various stages of the treatment and I am following them (Int.Pt.15).

Patients enrolled in a genetics research understood the research was to discover the cause of their condition. Three of these patients (Pts.7,8,13) had some knowledge of science and were aware that the research is to study the connection between, as one said, “genes and disease”. They were receptive to the information provided and realized that their participation will benefit other patients with their condition. “I know that it will not benefit me but if there is some benefit to anyone, any human being then there is no reason why not do it” (Int.Pt.13).

> This research is to know about why the disease occurred and what it is that caused it. I know what genes means. This research is to find the connection between them and the disease (Int.Pt.8).

Similarly, a woman narrating her family’s experience said that she and her sisters had volunteered for this research because:

> This will benefit others a lot. Obviously when you do this research on us you will come to know something, you will convey to others that do it this way. For this reason, I have said we are always ready, day or night whenever the doctors require (Int.Pt.17).

3.2.2 How much information patients want about research

The amount of information patients wanted was variable. At one end of the spectrum, three patients, (Pts.1,9,22) who wanted to join research, considered detailed information unnecessary saying, "when death has to come none can stop it" (Int.Pt.22).

> What is there to know, I have tried everything and was told that this is good medicine. I am not afraid; I say to them that we will see what happens. What is the use of worrying now? I always say we will see what happens (Int.Pt.1).

> To some extent I want to know but not all the details, what will I do with the [details]? I was given a pamphlet [consent form] to read and I was told that 19% died but I said to doctor *sāhib* that is *kismet* [fate].I know that this is an experiment and I said to him that we are all in an experimental flight, death has to come, I am not afraid of it (Int.Pt.9).

Five others (Pts.7,8,12-14) however, wanted more details. These were patients who had some knowledge of science, knew more about the trial, read up on the trial from the consent booklet/form or, if they were computer-literate, had used the internet.

> I have always liked medicine; I myself did not go into medicine. But I have an interest in it. Ever since I have had this problem then especially I do read up on it. In fact when I had it then I read all on the [inter]net, because the doctors don't have so much time to tell all. So, I read all what it [disease] is, how it occurs, what are the stages, what is the gradation (Int.Pt.13).

I observed this patient's consultation. She wanted more information and had an interactive session. She was a qualified teacher who understood the medical terminology and was familiar with terms like DNA [Deoxyribose nucleic acid], BRCA1 and BRCA2 [Breast Cancer type I and II susceptibility proteins], because, she stated "I read about it, therefore I have some idea". She understood the connection

between genes and her disease and was keen to have tests done for her children. Other educated patients were also aware that participating in their particular trial might make a difference to their disease.

> I know that the medicine has been tested on animals and in the initial phases on some patients. They need to see it on many patients to know how good it is. The doctor said there is no comparable medicine in the market; if there is no benefit there is no loss [to me] too (Int.Pt.6).

> It is important for me to know about this trial as I understand and I know about my disease. The new drug acts on the bone marrow but my marrow is producing platelets it is the problem with my spleen which is eating them. I have read the brochure so I don't think this medicine will benefit me (Int.Pt.12).

In a consultation I observed between a physician-researcher and an educated patient who was an electrical engineer, many technical terms, which were in English, were used with ease within their spoken Urdu sentences. When explaining the procedure, the physician-researcher said; "*āp ko* technetium 99 *kā tīka dein gaye aur kuch* intervals *kay baad* gamma camera *sey* pictures *lein gay* [you will be given an injection of Technetium 99 and at regular intervals the gamma camera will take pictures [record images]".

However, some patients, mostly the non-literate ones, did not know whether they were even in a trial. One patient (Pt.23) said it does not matter whether she is in a trial or not, so long as the medicine cures her, because she could not afford treatment otherwise. Another said:

> No, I don't know [about research]. I understand that I will be cured of this cancer. The treatment is very expensive - I have been told it is one to one and a quarter lakhs [1-125,000 Pakistani Rupees]. The doctor *sāhib* said that your problem [disease] is very advanced. You will need a lot of medicines and you have to tolerate them. Then my husband said '*thīk*

> *hay* [alright] we will do as they [doctors] say' and I also said *thīk hay* (Int.Pt.18).

Another couple (Pt.2 and husband) reiterated that because they could not afford treatment and this medicine seemed promising so they decided for the wife to enrol, and she has benefitted.

I observed that while non-literate patients were aware of their diagnosis, if they had accompanying educated relatives then the relative was more aware of the patient's disease and treatment regimen than the patient, as for example the husband of Pt.15 had his wife's medical file since 2005. Three other husbands (of Pts.5,11,31) had more information about their wives' diagnostic tests and treatment history than the patients themselves. One of these men, Pt.31's husband, knew his wife's biopsy report:

> Her biopsy showed that it was HER-2/neu-3 positive, Agha Khan Hospital [in Karachi] did one of the tests and it was HER-2/neu-3 positive and so the doctor sent us here and said to take these blocks [tissue biopsy] with us. The blocks were also sent abroad so that the test can be performed and confirmed then the medicine will be given (Int.Pt.31's husband).

Some non-literate patients recalled being informed about the trial medicine's side effects and considered that information satisfactory: "We were told all. They [physician-researcher] said that deafness can occur, eyes too can be affected" (Int.Pt.2).

> Enough information was given. We were told to take certain precautions, what you have to refrain from, keep the medicine in a cool place; not in the fridge; not too long in the sun (Pt.2's husband).

> When doctor *sāhib* told me about it, he explained to me what this [disease] is and how this medicine will treat it. I don't know a lot but I know it is new and can affect me but I want

> to start. You see my mother died because of it [breast cancer] (Int.Pt.23).

Another patient stated that although the physician-researcher had informed him that the side effects were anxiety, fever and vomiting, he had benefitted from talking to his brother-in-law who was already taking the medicine. The brother-in-law helped him be "mentally prepared for the side effects and at times be able to pre-empt them and modify his regime accordingly" (Int.Pt.22).

3.2.3 Availability of physician–researcher

Patients stated that whenever they required advice about their disease most physician-researchers were helpful. Patients had the contact telephone numbers of the physician-researchers and knew that when they had to take any medicine other than the trial drug they should contact the physician-researcher. "I have been able to call my doctor *sāhib* whenever I was unwell. He had said that if you get any disease as cold etc. call me before taking any medicine" (Int.Pt.1).

Patients felt confident that the physician-researcher was available, either in person or over the phone. They felt that they will be taken care of and even given priority, in a busy hospital.

> When I would be unwell they had given their telephone number that if you require anything, any advice then contact us. They have all been very nice to us. Before this doctor *sāhib* there was another one, he has looked after me very well, with concern and if ever I need to ask I could call (Int.Pt.2).

Some patients also appreciated that physician-researchers working in these hospitals had restricted amounts of time for consultation and so

they came prepared with questions. One patient (Pt.13) said "I write all my questions on a paper" - a strategy that helps her, and the physician-researcher finds it convenient too.

3.2.4 Gender of physician-researcher

Five female patients (Pts.8,29,31,T and G.) raised the issue of the availability of same gender physician-researchers. These women found discussing their disease with lady-doctors easy and two of them were highly critical when seen by male doctors. One patient (Pt.29) only came to this hospital (site C) because a female surgeon was available and did not want to be operated on by a male doctor. Another patient came to a hospital (site F) thinking the physician-researcher "is a female surgeon"; had she known it was not "I would not have joined it [trial], this should be told to the patient in the beginning" (Int.Pt.8).

3.2.5 Attitude of physician-researcher

Most patients said their physician-researchers' attitude towards them influenced their decision to enrol in the trial. Most recounted that they have come across generally "good doctors". They appreciate a physician-researcher who realizes patient's financial limitations and wants to help, otherwise patients who "do not have that much money. We could not do all this treatment ourselves" (Int.Pt.23), and makes patients "feel cared for, it encourages me to continue with the treatment" (Int.Pt.4).

> Doctor *sāhib* explained about this disease by drawing on a piece of paper. He said that this disease is like a *jarāsīm*

> [germ]. The new medicine hits on the head of this germ. I even asked him questions after reading the pamphlet [consent form]. The patient needs a sympathetic person and she is happy (Int.Pt.9).

> I was explained the disease by the doctor *sāhib* with the help of an example that a *paindu* [villager] can understand so I know what I have. ... Yes they told me that I will have fever, weakness and vomiting and I did have vomiting once or twice but it is the pain…I have talked to him [physician-researcher] and he has told my son the medicine for it (Int.Pt.19).

The empathy and concern shown by the physician-researcher at times seems to oblige patients to continue with the research for this reason, despite certain problems:

> You know how good doctors are at talking; everytime I go with the idea of withdrawing from research he convinces me and so [I continue]… I would not mind coming in frequently but as I told you earlier, I have no one to accompany me to the hospital so I have to request someone from the neighbourhood to take me to the hospital. But you know how the doctor *sāhib* is, in the end he convinces me and I cannot then say no (Int.Pt.26).

Another patient (Pt.4) narrated that after taking the trial medicine for more than a year there was no improvement, and at times she wanted to withdraw but the physician-researcher encouraged her to continue. Now she felt she has benefitted.

Some patients also said that their physician-researcher had advised them about making life-style adjustments in order to cope better with their illness and the side effects of the medicine.

> [I was] counseled that it is important to stay busy, I am doing a job, so that the mind stays occupied and not worry too much about this problem [disease] (Int.Pt.21).

> I do a job on Hall road. They [physician-researchers] had said that keep yourself busy. I have been taking this treatment for

> 5 months now and not taken leave because of this problem. I am regular with my work and in the evening when my children come back from tuition I keep myself busy with them (Int.Pt.20).

A few patients gave details of their experiences with the medical profession. Pt.26 said she had a "soft corner" for those who work for the betterment of humanity, realizing, too, that there is an occasional physician who does not deserve that respect, but that most do.

> I have always met doctors who are good. The doctor in Sialkot was the first one I went to after discovering the nodule who advised me to go straight to the hospital in Lahore. She [doctor] did not do any surgery; [she] could have, to make money…. I think the doctor should help decide, the patient is already under tension and so needs help (Int.Pt.8).

There were however, patients who were critical of certain physicians. Two patients (Pts.1 and 36) said they had "uninspiring" doctors who did not provide satisfactory answers to their questions, so they stopped asking questions and did not follow any of their instructions. As there was no guarantee that this "unfriendly doctor" would not be on duty at the follow up, one patient eventually decided not to return to the hospital. When called repeatedly for her follow up, and upon the insistence of her family, she revisited the hospital and was "pleasantly surprised to find a new and very friendly doctor *sāhib*". She went on to say:

> The first doctor I went to was very *kaurā* (unfriendly). But this doctor *sāhib* is very nice and tries to explain all to me. I cannot speak Urdu but he is still patient with me. I always do what I am told. I can call him anytime and if there is anything wrong with me, he always advises me. I am glad I have come here (Int.Pt.1).

Concluding remarks

My analysis shows that patients have diverse understandings of research in general and of their roles within a specific trial. A number of external factors influence the amount and manner of information provision. The outstanding factors are: patients' education, limited time available to physician-researchers to communicate information about research and physician-researcher's attitude towards the information needs of patients.

Most physician-researchers perceive a correlation between patients' understanding of research and their level of education. I observed that most of the educated patients enrolled in trials understood the research and its implications for their disease. They were more likely to be aware that the outcome of research is uncertain. They hoped that the trial medicine would prove beneficial to them and, at least, would not harm them. Their awareness of their disease made communication with physician-researchers easier and more interactive, as these patients would ask questions and had often also accessed trial information from other sources. Some educated patients tended to be more skeptical of the trial being offered. Patients who declined enrolment were educated patients from the higher socio-economic strata.

Non-literate patients, by contrast, are disadvantaged in being unable to read printed information about the trial. They are almost entirely dependent on the physician-researchers for the amount and quality of information that they receive about a trial prior to enrolling in it. Time

for communicating information about research is, moreover, in very short supply in these hospitals, as I have shown.

Physician-researchers try to overcome the challenges of limited time and patients' low levels of education and understanding by adopting communication strategies that, in their view, suit the local circumstances. When physician-researchers are confident that a particular trial will benefit their patients, they act strategically, knowing that time is in short supply, and will "tailor" the information to what they perceive as the patient's level of understanding. As a result, there is quite a variation in the amount of information that patients receive.

Besides accommodating variation in patients' understandings, this tailoring of information also serves to facilitate a positive attitude in the patient towards the trial and encourage or persuade the patient to enrol, where the physician-researcher considers this to be in the patient's therapeutic interest. I return in Chapter 7 to reflect on the ethical implications of this, but wish to emphasize here the local moral dimensions of this process, as articulated strongly by both physician-researches and by patients. This is that patients trust and rely on their physician-researchers, and the physician-researchers are aware of this trust and respect.

Partly in consequence of receiving "tailored" information, I found it common for non-literate patients to lack a clear understanding that being in a trial is not the same as being prescribed a treatment. Indeed, some non-literate patients enrolled in trials seemed to be unaware that

they were even in a trial, and when informed that they were, they showed no particular concern, for they equated “trial” with “treatment”. This raises an ethical issue of conceiving trial as therapy. They knew the duration of the trial, which for them, was treatment, and were aware of the possible side effects of the drug they were taking. They also seemed satisfied with the amount of information they had received. The physician-researchers also considered this amount of information sufficient for these patients. As I show in Chapter 6, the ethical dimensions of physician-researchers’ practice are dictated by two equally important factors – their duty towards the patient and the context in which research is conducted.

Chapter 4

Decision Making

After the information about a trial has been communicated the consent component of informed consent ensues in which a decision-making process follows before patients consent, or decline, from enrolling in a trial. A criterion for valid consent, in addition to receiving adequate information and achieving an adequate understanding is voluntariness. Although the research ethics guidelines allow for consultations with the family they require that patient's decision to enrol should be determined voluntarily by the patient, him or herself (WMA 2008, [Paragraph 22]; CIOMS 2002, [Guideline 4]). Literature from the developing world shows that there is variance between the requirements of the guidelines and praxis, regarding decision making. Autonomy is usually exercised through the family and /or researcher.

In this chapter I present my analysis of issues related to decision making – the second process of consent - in the local context. I highlight the many "spheres" involved in the decision-making process. There are two types of decision-makers that my analysis of data shows: there are those who rely on others-physician-researchers and family (in this case gender has an influence)-and then there are patients who identify themselves as independent decision-makers. The decision-making process is a complex interplay of physician-researchers, patients and their family, and is influenced by such external factors as patients' dependency on the family and patients'

reliance on the physician-researchers' knowledge and ability. I present physician-researchers' perspectives first, followed by patients' perspectives. Where relevant, I integrate my observations of these processes.

4.1 Physician-researchers' perspectives on decision making

The analysis of the physician-researchers' perspective on the decision-making process shows that at time it creates challenges for physician-researchers.

4.1.1 Reliance on physician-researchers

In physician-researchers' experience most patients ask their physicians for advice or to tell them what they (physician-researchers) would do in similar circumstances. If the relationship between the patient and physician-researcher is good then a trust develops, on the basis of which the patient requests, or may implicitly authorize the physician-researcher to decide for him or her. According to one interviewee, patients who have been treated by the same physician-researcher for 15-20 years would "totally rely on us [the physician-researcher] and trust us to advise them". This, she continued, is not problematic:

> If the relationship between the researcher and subject is strong and the subject [patient] is confident [in the ability of the doctor], then I don't think so there is any problem. You see I know them and they know me. I have treated them and their family for the last 16 years, which is a long time in which they will know what type of person I am (Int.P-R23).

Given their lack of medical knowledge, most patients believe it is the physician, based on their expertise and knowledge, who can guide them best. This reliance is more manifest if patients are not literate.

Many patients accord God-like respect to doctors; as one interviewee said, “Doctor is all in all after God”. From the viewpoint of most physician-researchers, this trust and respect compounds the reliance of patients on doctors. Patients trust not only their physicians but also certain hospitals, because, “patients get such good care at this hospital,” said P-R18. There are times when, “[you] could tell they have not really understood [about the research], and as they are my patients and trust develops and they would then say doctor *sāhib* we will do as you say” (Int.P-R25).

Certain socio-economic factors are key in influencing patients’ reliance on physician-researchers to decide for them or help them decide, chiefly, patient’s literacy and economic status. Whereas non-literate patients want their physician-researchers to decide for them, educated and affluent patients may ask their physician-researcher’s opinion but usually want to know their options before they ask for advice:

> The educated people [patients], [the] majority of them will want to know their options and they want to know what you think. But at the end of the day they will decide or the family. But unfortunately a majority of the uneducated – a majority, not all, - after the discussion say, ‘Doctor *sāhib* what do you think? Whatever you say, we’ll go along with it (Int.P-R20).

Physician-researchers considered non-literate patients to be undemanding, to only want the physician-researcher to do whatever she or he can to *treat* the patient, whereas rich patients, who can afford to pay for medicines, are more demanding. However in government hospitals the patients are mostly poor and, as P-R29 stated: “they are so simple they will do exactly as [they are] told.”

> We have to take [the socio-economic status] into consideration and that is the most important thing. You know, I think if the patient cannot afford any particular treatment and you are left with the only option of enrolment in the study, then I think you should explain [it] to the patient (Int.P-R14).

In the physician-researchers' experience, patients seek advice not only about the disease under investigation but about other medical conditions too – conditions which they (or a relative) may have. Indeed, considering that a physician's role is to treat the sick, they expect the physician-researchers to give general medical advice, and if that is not forthcoming they may distrust the physician-researcher:

> I mean, they know I am a doctor. Now, I have come with a purpose. I need to take some [blood] samples, and I can deal with [other] medical problems; if we do not advise them, patients may think, 'What kind of doctors are they or are they even doctors? Maybe they are not' (Int.P-R25).

4.1.1.i Varied responses by physician-researchers

According to the interviewees, patients believe physician-researchers know what is important for patients' health and so should be able to advise and that to expect patients to explore all their options and decide themselves, as the practice in "foreign countries" is an unnecessary burden. As one physician-researcher said, "Why burden a patient with multiple choices without being forthcoming with suggestions?" She went on:

> Nowadays, in America and *bāhir kay mulkoun mein* [in foreign countries] the trend is to give 10 options and then [patient] is told; 'Now you decide'. I think this is a very wrong approach. I mean, as a physician you should be knowing [know] what is most important for the patient. You should give your input as well, instead of placing the options in front of the patient - this is an option, so is this and so is this, which one do you want to do? Patient does not have any idea; she is already in a miserable condition. Should she go

> home and check on the [inter]net? What should she do? You should of course tell her the options, but what is the best for the patient, you should tell (Int.P-R15).

An inexperienced physician-researcher who has recently graduated is often initially overwhelmed by this sudden responsibility to decide for the patient. However:

> As time goes by, you learn to take that responsibility and you take decisions. You broaden your shoulders a little bit more than they used to be and you say, 'Yes this is right'. Because the patient will many-a-times, more than fifty percent of the time will say, 'Doctor *sāhib* you just do what you want, we rely on you' (Int.P-R6).

Some physician-researchers narrated that the relationship and the confidence between them and the patient deepens as time passes, and the more they discuss the research with them. This expectation of reliance then becomes a matter of routine for physician-researchers. An important concern for them is to avoid making "wrong [medical] decisions", lest irreparable damage to patient's health occurs. Therefore, physician-researchers in effect perform a risk-benefit analysis before advising:

> [This is] a difficult situation because they trust me and rely [on me] so I need to be sure. You are all in all [by yourself] I may place myself in the [patient's] place. I then go back to the drug and read up on the information provided by the company so as not to miss any point regarding the side effects; I do not go blindly into it [trial] (Int.P-R2).

> Definitely if the patient is unable to decide then, I guess, we should consider ourselves in place of that patient and decide and think what should be done… because, if I don't find any problem with the trial - I guess, [in] these trials there is at least minimum 10% benefit which the patient is going to get anyway, minimum lets suppose - so if he is unable to decide or if she is unable to decide then probably we can persuade him in that way (Int.P-R16).

Six physician-researchers (P-Rs11,19,27,28,30,31) however, only provide *information* regarding the trial and let the patient decide about enrolment:

> I only tell them that this is a trial and the benefits and risks. Our job is only to tell them [about the trial] and not what to decide. I say go and discuss with your family and then come and tell me. The decision is theirs… if *I make* them join then it is possible that they will not come again and drop out. I don't want to be in that position, where I decide for them (Int.P-R27).

I observed that some physician-researchers explicitly say to the patients that it is difficult for them to give advice without being partial. They explained the advantages and disadvantages of the research and asked patients to take time to discuss with their families. They gave their contact numbers to the patients. One physician-researcher said that after providing the facts, he usually asks his patients to go home and think about it, discuss with the family. But he acknowledged that there are times when patients would "force you to take decision". Nonetheless he considered that sending a patient home to think is better, for if there is "even 50% of involvement from the patient that helps in patients being more committed to the trial" (Int.P-R31).

4.1.2 Reliance on family

The family exerts an overwhelming influence on decision-making. According to most physician-researchers, it is common practice for patients to follow the advice of the elders of the family. In one research trial about "20-30% participated in research because the

elders of the family were doing so, and this is common in Pakistan" (Int.P-R23):

> In some [instances], I felt, you see our community is not educated especially women, that although I have explained it all to her and she is agreeing, she has not really understood; despite this, she is consenting and giving her blood sample. At that time, I think she [the patient] participates because the rest of the family members were taking part in the research. It was just that personal commitment [from her] was lacking – it was more because 'others are doing it so I will also' (Int.P-R25).

There are many instances, I was told, when patients consult family members and a joint decision is reached. It is typical for patients, especially women or elderly patients, to be accompanied by a member(s) of their family. I observed that the person(s) accompanying the patient usually starts asking questions and remains actively involved throughout the consultation, unless the patient is a young educated man or woman, in which case they were more interactive. It is rare even for a patient who attends these hospitals alone to make a decision alone. Most times, patients insist on telephoning other members of the family who are not present at the consultation and explaining to them what the physician-researcher has said, because:

> The majority of the patients, as I had already told you, they are dependent on their families or they are not that literate. They don't understand their disease very well, so they have to involve, you know, other persons from their family, like their husbands or other family members (Int.P-R14).

4.1.2. i Effects of family influences

Physician-researchers considered that reliance on the family has some advantages in decision making. In circumstances where the patient is under stress, the emotional support from a relative is crucial, and at

that time it is may be easier for the physician-researcher to talk to a caring relative than to the patient. In keeping with this, physician-researchers usually take the family into confidence:

> What I have felt is that [patients'] families are worried. When patients get their medicine and are having problems [i.e. side effects], so sometimes they [relatives] do come and ask us that how the treatment is going. 'Will our patient get better' and stuff like this. They care about [the patient] (Int.P-R31).

Dependence on the family can be crucial, according to the physician-researchers, if a patient has received a diagnosis that can have a devastating effect on the patient such that they give up the will to fight and get better. As one said, cancer is one such disease, that receiving a diagnosis the patient "*hāth pāon chor daytā hay* [gives up]" (Int.P-R13). In these circumstances it is important that the family gives patients the emotional support.

Reliance on the family is also beneficial if patients are undecided about whether or not to enrol in research. There are times when an educated family member can help the patient understand.

> Sometimes patients are double minded whether they should [enroll in a trial] or not. Then they consult their relatives who are close to them…the benefit is that discussion helps clear their mind (Int.P-R27).

Since the prevalent cultural expectation is that the family will be involved in decision making, physician–researchers consider it is necessary to counsel not only the patient but also "[the] two or three persons" who are with the patient:

> You have to know that people who are sitting with the patient are going to be involved in the decision making. So you're usually counselling all of them at a time, not just the patient.

> But you, I mean, I do tend to tell them that the decision is with the patient and that he or she needs to know what is involved. And it's usually – mostly the concern of the family is that, you know, they want to decide what's best for the patient. It's not like they're going to refuse treatment based on their, their liking or disliking. They want what is best for the patient (Int.P-R19).

Indeed, according to most physician-researchers, people in "our" society like to have long consultations and an individual making a decision by him/herself is not the norm:

> Our people in general are very dependent on each other. An individual taking a decision in any frame of life is difficult for them, men or women. They take combined, joint decisions, believe in joint families, so that's the way it's done and you have to accept it (Int.P-R6).

In this "joint family" system it is usually the head of the family who takes decisions, as P-R39 said, "He considers it his right – even after retirement he wants to be in-charge of everything". Mostly it is the decision of the father that prevails. Undoubtedly, in the physician-researchers' view, men have the main decision-making power. I observed that often women accompany patients too, but when patients are asked for their consent, these patients consult their male relatives:

> Exactly this is how it is, ultimately the decision has to be done by the man, females don't decide. Even if for example she is the patient's wife, she will ask his [patient's] father, brother- a male relative will decide (Int.P-R12).

This family-centric consultation not only operates in research but also in clinical practice where although most times beneficial, it can sometimes cause treatment delays. According to one interviewee, "even for routine procedures too patients usually want to discuss with their family" and the chosen option is usually what the family wants, and so:

> Sometimes it gets frustrating because we know what is right for the patient but they come back and say 'my father does not agree'. It is very frustrating. So decision making in our setup, in our culture is a lot different. It's not made by individuals; it's made by families (Int.P-R24).

4.1.3 Gender of the patient

The influence of the family is more prominent in the case of women, who, I observed, were usually accompanied. Of the twenty-eight female patients I interviewed, only five (Pt.7,23,32,34,35) were unaccompanied, although initially three of them had been accompanied until they became accustomed to coming to the hospital alone. Invariably, husbands (occasionally the mother-in-law) accompanied married women to the hospital and unmarried women came with their mothers.

Frequently, the accompanying husbands made decisions regarding married women's enrolment in research, although sometimes only after first talking to their wives. This is attested to by a physician-researcher:

> [A] study I have done in which males were also included – that was a study of hepatitis. So, it's like fifty-fifty. Women are always or 90% of the time they are accompanied. But for men 50% of the time they are not and 50% they're accompanied. Men are usually making the decisions on their own. They don't need a second opinion (Int.P-R18).

4.1.3.i Effect of women's education

Education level, according to the interviewees, influences whether women make their own decisions or allow, or expect, others to decide for them:

> I would again say that [with] those who are educated it's a little bit different. If they're coming from uneducated backgrounds, unfortunately it's usually the family or the husband which is running the show. But see in our culture, there's a male dominance, fortunately or unfortunately, [such] that most of the decisions are made by the male member. We here [in this hospital] make sure that, that we do talk to the patient one-on-one, in person and try to explain. Whether they really understand or comprehend the situation? How much is their will or how much is their family's. So, yes, I mean, that's always a problem (Int.P-R20).

There are however, some exceptions, said a physician-researcher, if the woman is educated, even if her socioeconomic status is low then she will usually determine herself.

On the other hand, while illiteracy may be one reason why a woman does not decide independently, some physician–researchers contend that even educated women are sometimes unable to make their own decision, even though they know that with particular conditions it is important to seek medical treatment early for a successful outcome:

> I have noticed one very interesting fact about, you know, sometimes it doesn't matter if a patient believes in certain norms or practices but she will follow because she, you know, she will be forced to follow those norms. As far as women from higher class are concerned, mostly because they are relatively more educated, they are more aware of the consequences. They have more access to the media, so I mean they usually come early and most of them they understand what is happening with them, okay. But still there is, there is a minor percentage who in spite of being educated will follow similar norms and cultural practices (Int.P-R14).

According to the physician-researchers, most married women involve their husbands (or mothers-in-law) in decision-making. The reasons for this in a few cases, as P-R10 said, maybe social and emotional, because, "the husband will mind":

> [Women] who are educated and they are working class, they understand better and they just want [the treatment] … usually 60-70% are willing to do this [research], but about a quarter or 30% want to ask [because of] things like that, 'My husband will mind these things', so, then they want to ask them [husbands] otherwise most of them they understand, most of them (Int.P-R10).

4.1.3.ii Dimensions of dependency

Age, marital status and financial independence also affect women's decision making. The reluctance to decide without asking the husband is, according to this physician-researcher, not solely attributable to low literacy and finances:

> She will say that let her husband come… it's a male dominant society; it's a straight forward thing…it is also economic, I think to some [extent] it is social and not just economic, social brought up. It's not *against* the women … their decision making is always an issue and [a] problem, they are less decisive, it is rather easier with the man… (Int.P-R34).

Nonetheless, financial dependence is an important factor for women to let men decide. The husband (or father) has to pay for and arrange the medication, the transport and her lodging (if they are from another city).Patients may be helped financially through *Baitulmāl* (*Zakāt*/Islamic charity fund) – however, in most cases, that is insufficient.

> Financial factor is the most important. Even if the [trial] medicine is free, then for their stay, food, travelling, all this, who will pay [for] that woman, who is a housewife. She cannot pay because twenty to twenty-five thousand [rupees] is the cost … she cannot arrange for that money. Now she is looking at them [her father or husband] does he say yes or no, will he bring this medicine for me or not, right, if he says yes then it is [okay]; then she will sign, but if he does not then she will not sign too…We also send patients to *Baitulmāl* [*Zakāt* fund]… Also she depends on them because she has a relation with them, trust on her husband or her parents that you cannot have on anyone else (Int.P-R13).

> Whereas [in] the developed world everybody has their insurance and you know treatment is no problem but here it is different - here it is ultimately the husband who is going to afford … because most of the patients who come to us are from lower or middle social economic class are dependent on their husbands (Int.P-R14).

I observed that when most women patients were called into the consultation room their husbands accompanied them and were more actively involved in discussion with the physician-researcher than the women patients themselves. The husbands not only discussed the treatment options but also were able to discuss the symptoms. At times a husband translated for the physician-researcher, if his wife's mother tongue was different from the physician-researcher's first language. These husbands knew their wives' medical history and knew the treatments they were taking and had previously taken. I observed one where after detailing the history of the patient's illness and writing the advice in the patient's file, the physician-researcher explained the protocol to the husband realizing that the husband had understood his wife's disease better than his wife. Although the husband was keen for his wife to be treated, he explicitly desired that she be "treated by medicine only and not an operation". Appreciating that the husband will make the final decision the physician-researcher therefore entered into discussion of the non-surgical versus surgical options with him rather than the wife.

> Those patients who come [to a government hospital] are middle, lower middle [class] people and mostly they are not that educated. They [women] are the ones who stay in the house, they are not working ladies. Generally the attitude is that they ask because they depend for their finances on their husbands… for everything they are dependent, so they think that this is okay [to ask] (Int.P-R28).

Thus women, mostly want to consent to research only after consulting their husbands and obtaining the husband's permission:

> These patients, most of them are dependent on their husbands; [it] is the husband who is going to afford the treatment, not the patient. Women who are married, they usually take time to think about it and discuss [with their husbands], but women who are unmarried they take less time [in deciding]. But, [yes] they do go home and discuss… (Int.P-R14).

The degree of dependence dictates the extent of involvement in decision making. Elderly female patients, would usually want to ask their sons whether they should take" this *dwāi* [medicine]". In these circumstances, the discussions were again between the sons or occasionally daughters and the physician-researcher. Patients contributed to the extent of narrating their symptoms and listening, at times intently, to the dialogue between their sons and the physician-researchers when the treatment or research protocol was discussed. One physician-researcher (P-R25) stated that "some women are so simple that they will do as [they are] told and never question, even though they do not understand the protocol of the trial." This is, she said, because men have the decision-making power and male dominance pervades society, so usually women delegate decision making to their men-folk.

> Many a times, it happens because this is our culture. Women are unable to take decision. They will rely on the men folk, even if they [the men] are much younger but they will like tell you that 'No, the man will come and decide' and in fact sometimes one feels terrible because of this gender bias because myself being a woman but you forget your own feministic views and end up asking the same questions (Int.P-R6).

The general trend among women, according to the physician-researchers, is to consult the family before they commit to "even giving a blood sample [for the tests]" (Int.P-R10):

> At times women are not accompanied by their [husbands], say because they are alone or they only have their daughter with them, that reluctance [to decide] is there, [and] they say that 'we will ask our husband or father' and if they agree we will come back (Int.P-R18).

I also observed in connection with research enrolment that when physician-researchers told patients that their spouses' tests were also necessary for a particular research project, men, unless elderly, who were mostly unaccompanied, would readily agree in their wives' absence to enroll their wives. But unaccompanied women were non-committal, stating that they would have to ask their husbands first and if the husband agrees only then would their husbands enroll in the project.

All physician-researchers had observed these patterns of women's decision making. There are women who do not make independent decisions, and there are women who will initially want to enroll but want to discuss their enrolment with their husbands before making a final decision:

> There are some women who would, you know, who don't want to make a decision about options of treatment along with research. I mean, for most of women that's too much information…. that is being asked of them. So they want someone else to take on the decision-making role - I mean, they just feel overwhelmed and they want other people to be involved in the decision as well. You know, they do not want the responsibility to rest completely on them….. But then there are women who actually do feel that, they would want to discuss with their [husband] before they take a final decision but they do have an opinion. They do give you their

> initial approval and say 'I do agree to this but I want to discuss this with my husband as well.' And, you know, this may be accompanied by the sentence that, 'If he agrees, I'll give you my consent' (Int.P-R19).

Although it is more common for men to make decisions for women, physician-researchers also emphasized that this was based on men's concern for women's wellbeing. A decision is reached after mutual consultation, in which, "women usually have roughly 40% say and the man would have 60%", but in keeping with social norms, the man conveys the decision to the physician-researcher (where the latter is a man).

> You see, although I've said that the men have a dominant role in making a decision, but generally their decision is in favour of their women rather than for any lucrative purposes or any other advantages risking their women. The other thing is that in our culture, generally, conversation is between the two males. So they may have a say but that say is communicated through [husbands] (Int.P-R17).

4.1.3 iii Implications for health and trial participation

Some physician-researchers talked about the disadvantages of women's dependency on others. One of which is that it reduces women's chances of being approached for enrolment into trials that are not gender specific. It involves extra work and time when physician–researchers have to explain everything to the husband or father before asking them to allow the woman to enrol. In such cases, the husband may assent to his wife being enrolled but physician-researchers would rather avoid the extra work:

> I think mostly men [are enrolled] than women. Men are mostly forthcoming, partly [because] they are mobile, and they can get to hospital on time, and probably women tend to have somebody available to [bring] them. Transportation is a cost, at times drug companies do fund their visits but even

> then it is matter of [a] fair distance, it is matter of [a] full one day. Men try and find things to do while they are in the city if they are not from here [Lahore]. Women have different requirements too and they are less contactable. They have difficulty in complying, partly because you see, because the literacy rate of women is less, the ability to convince and explain to them is, is more difficult, and here [at this hospital] they would want to have signed consent form, after consulting the husband, that adds another dimension - to have the husband come to the hospital. Or [for] the doctor to say [to the husband], 'This [the name of the medicine] is what your wife is having', and then to explain. All this makes the researcher uncomfortable (Int.P-R9).

Physician-researchers were of the opinion that women should pay attention to their medical needs. In their experience women, especially in the rural areas are either ignorant or, as one interviewee stated "they don't even care for their illness or treatment by a doctor". There is a social element to this and that is that "females should not go out of the house; she should stay at home and just do their own thing, home therapies" (Int.P-R10). This, staying at home or using traditional "home" remedies *(desī ilāj)* results in patients seeking medical advice very late.

Many times patients seek alternative types of health advice – such as consulting traditional healers like *hakīms* (practitioners of *unānī* (Greek) medicine) or solely going for *dum darūd* (spiritual healing) and when these remedies fail then these patients (women) come for medical treatment, but sometimes "it is too late." There are instances in physician-researchers' experience when female patients ignore their disease:

> In our practice, we come across these, sort of, norms or practices- self proclaimed cultural values, okay, or norms like women going to *hakīms* and, you know, or women not telling their husbands or their families about, you know, their

> [disease] .So, it is a very sort of complicated issue…they come too late, yes, when it's too late… they are forced to, you know, do these practices [of resorting to alternative forms of therapy]. Sometimes women do understand that they should come to a doctor but their family members put them under a lot of stress. The pressure comes from family and especially from the husbands that she should first see *hakīm or dum darūd* (Int.P-R14).

Many times women are deterred by family circumstances to seek treatment. Ten[36] physician-researchers said it seemed as though women feel guilty about being ill and do not want to bother their husbands, who are already trying to make ends meet. These women feel that the burden of their treatment will add to the husband's financial stress. As one interviewee said, "in our culture, somehow females are more docile [and] passive and do not want to create unnecessary anxiety for their husbands" (Int.P-R17).

Some women also fear being abandoned by their husband or fear the negative reaction of in-laws if they learn of women's illness. One physician-researcher (P-R15) narrated the story of a young woman married for six months and recently diagnosed with breast cancer. The patient requested the physician-researcher not to discuss anything with her husband as she felt it would have a negative impact on her marriage, especially if he was expected to finance her treatment.

I observed a similar circumstance when a patient who had undergone treatment said that she herself had financed her treatment (she was a teacher) because her husband, himself not very well, could not afford her treatment. In view of such experiences, physician-researchers believe:

[36] P-Rs:10,12,14,15,16,17,25,26,29,28.

> [It] is necessary to change these norms or these practices – and it can be done by raising awareness, by mass education, otherwise I don't think so… But you see the economic reasons are there too. Husband would go for the cheaper treatments and alternatives and by the time they come to us it [the disease] is really advanced. We ask them why did you delay it and the husbands just look confused…and say we have been showing them to this person or that (Int.P-R14).

There are also times, the physician-researchers said, when the decision made on her behalf is not the one that patient would have made, but she will not overturn her husband's decision:

> Many times I can tell that this is her husband's decision and not the patient's. Ultimately, you see, it is the written consent and she goes for that [what the husband wants]. There is not much we can do. Even if we ask them that if you do not want the husband [around] we will counsel you [alone] and then you can give us the consent. They feel that by not agreeing with the husband will 'cause problems for us, our family life will be disrupted'. And so they go for that decision (Int.P-R28).

Similarly another physician-researcher reported:

> Well, you know, like I have told you, that I had come across a couple of times…. a situation where the patient wanted to take part, but the husband did not, just because he thought that we are experimenting on her. That's the end**,** unfortunately**.** You know, [you] cannot actually force them. You know your duty is to explain to the patient, okay this is right and this is wrong, and now it is entirely up to her and it does not matter if she is dependent on her husband. Well, unfortunately it is just like that, you know (Int.P-R14).

4.1.4 Independent decision making

Although the general social practice in Pakistan encourages family decisions with mutual consultations, physician-researchers did report occasions when patients took independent decisions. These patients were usually educated patients, mostly men, but some educated

professional women, realizing the benefits of a particular research, decided independently:

> Men are usually making the decisions on their own. They don't need a second opinion. They [men] don't have such fears. They are making their decisions. We are having one-to-one discussion and they don't have any fear, there is a difference…they are more in a position of making decisions. Also with women I knew certain women who were educated and, sort of, independent. They made their decisions (Int.P-R18).

Most physician-researchers hope that after they have provided patients with information about the trial and discussed relevant concerns with them, the patients will understand the benefits of the trial and enrol. However:

> They [patients] have their own cultural, social, economic problems and feel restricted. Quite lot of the time they will go by what you want, many-a-times they will refuse that – that is their prerogative (Int.P-R6).

> I gave this [patient] a lot of my time and explained all the benefits that he will get and I was sure that the trial will benefit him but then after two days he calls me and says he does not wish to enrol. What can I do… it's his decision (Int.P-R2).

According to other physician-researchers, patients in general and women in particular need to reach their own understanding of the significance of early treatment for their disease, without relying on others to decide. Sometimes, in clinical trials there is "a narrow window" for research enrollment as a result of which it is necessary to obtain a patient's consent "there and then", lest the opportunity for research enrollment is lost.[37]

[37] See Chapter 3, section 3.1.3.

Educated, professional/working women do make their own decisions but compose a minority of all women:

> Approximately 10% women are very open in front of their husbands as well, and they take a decision right in front of their husbands. I ask 'would you like to ask your husband', so she said 'why should I, you know, it's my problem, it is for my benefit not his' I mean there in their presence they [women] say this. So these are those women who a bit liberal (Int.P-R15).

However, physician-researchers vary in their views about how many women are able to decide independently:

> Well, I think again if the patient is literate, if she can understand, you know, the nature of her disease then, I think, and I have seen these patients, you know, making the decision without involving anyone else, even their husbands for a particular treatment. Yeah, it's like between 30-40% [of] women (Int.P-R14).

In another physician-researcher's experience, an educated 30% of all women decide themselves:

> Mostly it depends upon the social setup and the education of the patient. If the patient is educated and if even the socioeconomic status is not good then people [women] are there who can [decide]. But in majority of the cases where women and people from low socioeconomic status come, I guess, yes it [independent decision-making] is [affected], I guess very safe guess would be 70% do not [decide themselves] (Int.P-R16).

In contrast, another physician-researcher conducting, a trial on a diagnostic intervention thinks that all her female participants make decisions without requiring their husband's consent:

> You see, patients, even if they're from the lower educated class, they do realize that cardiac chest pain is something not to be taken lightly. You see? So I don't think this issue has ever arisen. As far as I have come across women do decide themselves; they do not need to, you know, get sort of a formal permission from the husband (Int.P-R22).

4.2 Patients' perspectives on decision making

This section on patients' views about how decisions are reached adds an extra dimension to the understanding of the contextual and relational nature of the decision-making process. It shows that, with rare exceptions, patients consider it important to consult their physician-researcher, other physicians known to them and sometimes their primary physician. It is also usual for them to consult members of their family especially for women to consult their husbands or, less often, other close relatives.

4.2.1 Reliance on physician-researcher

Most patients were of the opinion that although it should be the patient's decision to enrol, patients need their physician-researcher's help with decision-making. They said that their physicians know more about medicine and the disease then they do and shared the physician-researchers' opinion that patients cannot decide alone. They added that they trust the physician-researcher to do what is in patient's interest. There is an implicit assumption that, as one patient put it, "Whatever the doctors do will be good for us." Another patient who was accompanied by her niece, said:

> It [should] be [the patient's decision] but I do not know [about medicine], I cannot read, so I have to rely on what they all [doctor and siblings] tell me. If the patient is not clear then she cannot decide. I think that we all need help when [one is] not educated, it becomes difficult to decide alone (Int.Pt.1).

When relatives accompanied patients I noted that they too tended to rely on the physician-researcher to decide about research enrolment. In these cases, the conversation was mostly between the husband and the physician-researcher. The husband (or other relative) usually agreed with the physician-researcher and then, as one (non-literate) husband said to his wife, "*thīk hay* [alright] we will do as *doctor sāhib* says". In another instance, the physician-researcher informed a couple that "there is more than seventy percent chance of you [patient] being saved. The disease has not spread at this point". They were then informed of an oncology trial; the husband (who was educated) felt encouraged and he said to the physician-researcher, "We will come back [after discussing it]." Another patient accompanied by her father said:

> You see I had to discuss it with the doctor [physician-researcher] as he knows what is good [for me] and this medicine but I also discussed it with my husband. I wanted to take part but there was family planning to be considered, because I was told that when I am taking this medicine I cannot get pregnant, so I had to discuss this with him [the husband] (Int.Pt.4).

The father stated that they come from Gujarat for this drug, and that he did not mind bringing her, for "she is my only child you see and I will do anything for her health".

This reliance on the physician-researcher conducting the trial is also reliance that extends to others. Patients often turn to their primary physician, who is different from the physician-researcher conducting the trial. One patient who had just been given information about a trial drug for his condition informed me that he would discuss the trial with

his primary physician who knows his medical history and so can advise whether the trial drug will work or not. Other patients also relied on "their doctor", meaning their primary physician:

> I discussed it with my *doctor sāhiba* [primary physician] because this *doctor sāhib* [the physician-researcher conducting the trial] said if you want to, then talk to her [primary physician]. You see I trust her advice – she is lady doctor who treated me when I had my first heart attack. I was in a very bad state; I did not think I will make it. All through the night she and the nurse were in the ICU [Intensive Care Unit] and I felt as though it was an angel who was there, she was very sympathetic. I have great respect for her. You see how can I not trust someone like that? She talked to this doctor *sāhib* [physician-researcher] and then told me it [participation in the trial] is okay. So I decided [to enrol] (Int.Pt.6).

There were also patients who wanted to discuss research enrolment with other doctors whom they knew and trusted. For example, this patient who was a dispenser, stated:

> I asked others too, because I am a dispenser so I know some doctors and I trust the doctor *sāhib* at my BHU [basic health unit]. I discussed with him. He said why not try it, if it is being done at Mayo Hospital, then it must be good (Int.Pt.3).

Patients reported that they have confidence in the decisions of their physician-researchers or another physician, because such physicians (or physician-researchers) have more medical knowledge than their patients:

> No, it should be the doctor's decision: she has more knowledge about the disease and medicine, the doctor advises and of course it was my personal decision too but I needed to be told what it is that I should do (Int.Pt.6).

In addition, patients consider physician–researchers to be instruments of healing and respect them for this:

> In the whole society few people have been chosen by Allah and given the knowledge to be able to help the pains and troubles of humanity. I know not all doctors are, but mostly they are good and those are really the people who are worthy of respect (Int.Pt.26).

> In addition [to my family], I always do as the doctor asks because I think that they have worked so hard to become doctors so they have so much knowledge that they can cure diseases and treat patients like me (Int.Pt.1).

4.2.2 Reliance on family

All interviewed patients remarked that they discussed their disease, its treatment and trial options with their families. Whereas a few stated that they determined research enrolment for themselves and then discussed it with others, such as their husband, parents and sometimes siblings, most decided after discussing with the family, which for married women usually meant the husband.

When an educated literate relative accompanied non-literate patients, invariably the physician-researcher would communicate with the patient through them. In my observation the physician-researcher wrote details in the patient's file, and then explained the trial protocol to the accompanying relative. The physician-researcher also wrote the names of tests and medicines, in English on a hospital prescription slip and handed it to the accompanying relative, who then relayed this information to the patient. In this way educated accompanying relatives acted as interpreters of medical information and the technical language in which it was described. Most non-literate patients felt comfortable with this arrangement, because otherwise they would be unable to answer the many questions they were asked or to follow the protocol instructions. As one patient from a nearby village said:

> I ask the doctor to explain to [accompanying brother], he is *parhā likhā* [literate]. I can't understand everything. They then tell me in Punjabi. I never come alone to the hospital. My brother and, at times, my husband accompany me. But because he [husband] is a labourer and if he comes then he misses a *dīhārī* [the day's wages] and we can't afford that so today my niece who works at INMOL [Institute of Nuclear Medicine and Oncology, Lahore] has come with me (Int.Pt.1).

Most trial enrolment decisions are made by *bāhmī mushāwarrat* (mutual consultation) between spouses and also with other family members, though this observation was applicable more in case of women than of men. When Pt.2 was asked if she had discussed about trial participation with somebody before deciding, her husband, who appeared worried and concerned, replied instead:

> Yes, we discussed it with the elders. I discussed it with my mother and father-in-law and my elder brother. We were worried about her [patient's] life, that this cancer should be cured, because at that time it was the only thing on *our* minds that *we* should get better no matter what the medicine is. All of them said if it is good then you should go for it. Hopefully the medicine will cure (Pt.2's husband].
>
> Q: Your wife?
>
> Husband: Yes yes, my wife.

Patients stated that it is always helpful to discuss their options with family, especially those close to them. If a relative comes with the patient all the way from the village to the city to the hospital, then this shows that they are concerned about the patient's welfare. In these circumstances the advice given by the relative is considered important and is valued:

> *Bohat ziāda fāida hotā hay* [it is very useful], you should consult. The patient does not know so much. There is an uncle of my husband with whom he [husband] discussed and

> he [uncle] really understood how serious it was and advised that treatment has to be taken, so I came (Int.Pt.31).

According to a few patients it is indeed very difficult to decide because the patient knows so little about the disease, but when someone explains what can be done this helps "one to choose which way to go". This was similar to the experience reported by physician-researchers, that when patients hear they have cancer they need help and support from their families. Patients, who wanted to enrol but were tentative about the decision, found that family support gave them the confidence that they are making the right decision by choosing to enrol. A patient, accompanied by her sister, explained her sister's role in her recent decision to enrol:

> The patient should be told all the details…but it is important to discuss with the family as they will be concerned. I always discuss everything with my elder sister. She has been there ever since our mother passed away. It was her decision and I followed it. I knew it was for the best. I decided to go for the operation because she [sister] encouraged me and I think now that if I had not come for the operation my cancer would have been worse (Int.Pt.8).

This patient, like other patients had tried alternate therapies, seeking spiritual healing (*dum darūd)* and consulting *hakīms* mainly to avoid surgery.[38]

Sometimes decisions are made by the "head of the family". As this patient explained:

> In Pakistan the head of the family is the husband – a wife must follow the husband. But sometime for big issues like decisions about marriage or some other family issues like in joint-family system we follow our elders. Like, I have an elder brother, whom I consult. Not only consult, we will

[38] See also section 4.1.3.iii.

> follow what he says about children's education and marriage issues. But it's not that it is by force – it is the way it is, like I was told to bring my sister for research, she had to ask her husband. If he allows her then she will come otherwise it's up to them (Int.Pt.37).

A week later, this patient's (Pt.37) sister came for her tests and, following up on the comment made by her brother earlier, I asked and she affirmed that she had obtained permission from her husband. She added that sometimes "he sticks to his decision and it is very difficult to make him understand but I have learnt how to deal with it. If I want to do something then I talk about it and sort of prepare him and finally bring him around to doing what I want". Other women reported similar forms of negotiations with their husbands, saying that although their husbands are the main decision-makers many times they are not unreasonable.

4.2.3 Gender and decision making

Most of the female patients I interviewed were of the opinion that it is important for them to consult their husband, or their parents, if they are unmarried. Although one reason, as stated above, why female patients consider it is essential to talk to their husbands or family is the emotional support[39] they get, another reason is that one can get a broader perspective. If the husband decides or helps decide then the decision-making process is easier for wives, even though there may not be many options to choose from:

> A person does nothing and goes into depression, waiting for death to come. That [death] will come either way. The better option is that you go for the treatment, as I was advised. You

[39] See section 4.1.2.i.

> see then there is hope [for a cure]. I think it is better and necessary for family to help the patient. Like I said the patient is very disturbed, so this [advice] from them [the family] is very useful, otherwise they may not go [for treatment] (Int.Pt.31).

Patients, especially female patients, like the physician-researchers earlier[40], also consider that financial dependency is a significant factor: "you see the husband has to be consulted too after all he is the one who bears the cost of everything; I do not earn" (Int.Pt.1).

One of the patients (Pt. 4) with a disorder for which the trial medicine is a treatment told me that a woman in her neighbourhood in Gujarat suffers from the same disorder, but is unable to enrol in the trial as her husband cannot "afford to bring her to Lahore, so she is taking whatever medicine is available from the local doctor… *woh kīā karey* [what can she do]?"

Most patients were of the view that for all women, regardless of their education level it is important to have a husband's agreement to enrolment. If a woman wants to act independent of her husband's wishes, he may withdraw economic support. For example:

> I discussed it with my husband, he had to support me, I cannot do all this alone. I did make decisions but he supported me. When it was time for operation I said I do not want the breast to be removed completely, only the tumour. Doctor *sāhib* said it will be a long process but he [the husband] supported me. He looks after all my medical things. You see, even if you are educated it is better to discuss with your husband – they can see things in different light. After all he is your life partner. He has to look after you, bring you and take you, money has to be spent. If you don't discuss and say *I want* to do this, then he'll say 'then *go* and do it [yourself]' (Int.Pt.15).

[40] See section 4.1.3.ii.

It is not only the financial support that is essential as these women lack independent means, but also emotional support:

> It is necessary to consult the husband. If she [patient] is married then you should ask the husband; involve the husband too. It is important as it gives you the confidence [to deal with the disease]. I needed to consult with my husband for I needed the support and it is also that he has to pay also. I am not much use now and I am completely dependent on him (Int.Pt.9).

During my observation of Pt.15, the husband was encouraging of her decision to enrol and take this medicine. He had maintained a meticulous file of his wife's medical records and treatment schedule, since 2005, the year of her diagnosis.

In my observation of another consultation I asked a wife, whose husband was also present: "Who usually makes decisions in the house? She replied, "He [does] and then informs me of the decision." To this her husband replied, "This is the *riwāj* [tradition] in our village". Another patient was of the view that if her husband had not given the permission "*tay fair nahī karnā* [then I would not do it]" (Int.Pt.23), but adding that her husband encouraged her to do what the physician advises.

Non-literate women and those from other provinces relied more on their husbands. These patients are not fluent in the Urdu and the accompanying relative interprets from their provincial language. One patient (Pt.11) said that she relies on her husband completely. Earlier, this patient had cancer of the colon for which she was operated in Quetta, and her husband was with her throughout.

The viewpoint of the physician-researchers, reported above,[41] was that local gender norms are such that it is not a priority for women to attend to their ailments as soon as possible, particularly in the villages, although women living in cities too delay seeking medical advice. These interviewed patients too stated the same and gave a number of reasons that these such as there is no time, they are busy with looking after the house, kids and husband. *When* they get a chance or feel really sick then they come to the hospital-as one patient said: "this is what we [Pakistani] women do:"

> I did not pay much attention to it. First I did not talk about it to anyone…. then I talked to my husband and he said I'll take you to the doctor. He took me to a lady doctor who is here in *Choubūrjī* [a locality in Lahore], and she said this is not something she can treat. At that time it [nodule] was a bit big and hard [in consistency] also. She said you should go to INMOL. Then my husband took me to INMOL and they made my [registration] card and the check-up then started (Int.Pt.31).

There were patients who considered that the final decision about enrolment and treatment should be made by patients, but as one said; someone needs to advise as sometimes patients do not realize that delay in seeking treatment can have serious consequences. So they need that support; patients cannot be left on their own:

> I needed some support and help. Help in the sense that what I am doing is right. It should be the patient's decision, but they need help, as I could not come to terms with it that I had this cancer and always asked, 'why me'. My husband has been very supportive. You see, sometimes we make mistakes – I was initially reluctant to accept that I have cancer. I went to *hakīms* [traditional healers] and also for homeopathy. This was because I wanted to avoid operation. Then my husband said we have to be serious and he brought me here. But it was late when I came here [site F] (Int.Pt.5).

[41] See section 4.1.3 iii.

This patient then narrated how she could not gather enough courage to enter the outpatient clinic. This, she said was based on the fear that it would turn out that she did indeed have cancer. This fear was compounded by the fact that her mother died of cancer, and she had been advised not to go for surgery as "then the cancer will spread faster". But her husband insisted and brought her to the hospital.

During one of my observations of an interaction between a female patient (Pt.T) and a physician-researcher, the accompanying husband invariably provided the answers to the physician-researcher's questions about the disease or about whether the wife would like to know about the options for treatment including trial participation and affording "good treatment". When I asked the patient why she did not answer the physician's questions, she replied, "He [husband] knows about my disease, so he can tell." Later, this patient (Pt.T) told me that her husband does not always make all the decisions, but sometimes she does not want to be burdened by having to make decisions as "once when I had an ectopic pregnancy, I was in severe pain when I came to the hospital the doctor *sāhib* wanted to remove the "*tubein*" [fallopian tubes]. My husband asked me and I said, 'Do as you feel right.'".

4.2.4 Apparently independent decisions

Most patients were of the opinion that ultimately the decision to enrol must be made by the person who is ill. Although the decision is rarely reached independently, the patient's willingness to take the trial medicine and follow the trial protocol is a necessary prerequisite to a

successful trial. If the patient is not convinced about the benefit of the trial they will not adhere to the protocol:

> Because, see if I were not in it because of my own accord then as in the early days I felt terribly ill. [I had] vomiting and fever. I would have left the treatment then. I am in it because it is my *zarūrat* [need] (Int.Pt.22).

Though a few patients said that they determined to enroll by themselves, I observed that they needed reassurance for this from either the physician-researcher or the family. For example, one patient (Pt.14) said that it was his decision to enrol for a trial to investigate a diagnostic test to rule out acute coronary syndrome, because he understood the importance of undergoing this test when the physician-researcher explained it to him. However, I observed that when the physician-researcher was explaining the details of the diagnostic test, Pt.14 was initially unsure and said to the physician-researcher, "You are the doctor and I think I am in safe hands". The physician-researcher reassured him and then he consented.

Although educated patients wanted to know the details of their disease and possible treatments so that they could determine what to do, they relied on their family for support to reinforce their decision. As this patient, who was a teacher with an interest in science, said:

> No, definitely it will be my decision; I am very independent in this. But it is also important that I discuss and I think my parents will be 100% willing for me to go for this research. They have a very positive thinking. I am also very close with my brother so I will talk to him too (Int.Pt.13).

Another patient said that it was her decision to enroll; she was the one who was ill, so the decision was hers too, though confident in the

knowledge that her husband will support her. It was her nature, she said, to be independent:

> I do not want to be dependent on any one, even in normal life. Others may ask me for help, but I try not to ask for help from, or as little as possible, others. It is just my nature. You won't believe me that when I was to have the surgery, I came myself, stayed in the hospital the night. I had all the tests done myself. There was no one with me. The next day I came in at, I think, 9:00 am. I was admitted and at 12 noon I was at home. No one believed it that I had surgery done. Why make a big issue of it… I am the one who is ill so it is I who has to decide whether I want to do it or not. He has only to spend the money and so he should.
>
> Q: What was his reaction?
>
> A: He was willing – hundred percent (Int.Pt.17).

She (Pt.17) however, relied on her brother, who was an oncologist abroad, for advice. In fact she said her treatment is "remote control treatment":

> When I came to know everything then I discussed everything with my brothers; you see they are doctors too. I depend on them a lot, to get some moral support and they can advise us [she and her sisters] better. Obviously they can tell us [beforehand] that now you have to do this and this medicine is better. We [all the sisters] send all our reports to them (Int.Pt.17).

Concluding remarks

The decision-making process is complex and influenced by socio-cultural factors. The many "spheres of consent" in the local context include the family or husband and physician-researchers. All patients rely on both their family and physician-researchers for decision making, albeit for different reasons. Patients rely on the physician-researchers because of their knowledge of medicine and trust that the physician-researcher will act in their best interest. Patients rely on the

relatives for emotional, financial and logistical support. This is based on trust between the patient and their family. In a Muslim society, the role of the husband (and family) is fundamental to the process. Permission from them, prior to enrolment, especially is case of women is recommended, as I discuss in Chapter 7.

Regarding physician-researchers being asked to decide for patients, I have identified two responses. In one, the physician-researchers consider they should decide or help decide for their patients, keeping patient's best interest in mind. They consider burdening patients with information without advising them to be a "wrong approach" which is an excessively detached attitude that may undermine patient's trust in them. There is then a conflict between these physician-researchers' views and the ethical guidance that requires that participants to determine themselves.

In the other response, physician-researchers provide information without advising patients, in their view participants should decide themselves. This view fails to appreciate that all patients needed help and advice. There is then a conflict between patients' expectations and these physician-researchers' values.

A joint decision reached after mutual consultation is a common mode of decision making. Patients' reliance on the family for emotional support and, mainly in case of women, financial support is widespread and appreciated by both the physician-researchers and patients. Even the patients who claimed to be independent in making decisions discussed with their siblings, whom they relied upon.

There are other dimensions of this dependency - there are instances when patients defer decision-making to the family, usually the husband, or decisions may be made by the husband and patients accept them, either because they consider the decision is in their health interest or they are obviating other risks such as for example the social harms that would ensue from not consulting others (husband). There are ethical implications of this dependency; at times patients' (women's) health may be compromised. Another implication is that women may not be preferred for trial enrolment because they are "less contactable" and have "difficulty in complying" and then physician-researchers have to explain to the husband, and this adds another dimension.

Delegating decision making to others or accepting decisions made by others (husband) raises an ethical issue: whether this heteronomous decision making is an exercise of women's second-order autonomy, or is it because that is the norm. I discuss this in Chapter 7. Sometimes these practices create a tension between physician-researchers values and local norms. If the decision is in the health interest of the patient then physician-researchers accept it. If the decision compromises patient's health then physician-researchers find that their duty towards the patient is impeded by a norm that, in their view, needs changing.

Chapter 5

Documenting Consent

Once a decision to enrol in research is made and patients consent to research, this has to be communicated to physician-researchers so that they can proceed with the intervention. The decision reached is based on the premise that it is an informed decision and following from that, the consent given is an "informed consent". There are two senses in which informed consent exists. First, it is an authorization by a patient, who has reached a decision voluntarily, to a physician-researcher; a concept I analysed in the preceding chapter (Chapter 4). In the second sense, where informed consent exists as a consequence of the institutional or procedural rules, its documentation is required (Beauchamp and Childress 2001). In order to meet this socio-legal requirement of consent, guidelines such as CIOMS (2002, [Guideline 4 and 6]) and Helsinki Declaration (WMA 2008, [Paragraph 24]) require that consent is formally documented, preferably in writing. Similarly PMDC (2001, [20.2]) mandates a written (signed/thumb impression) consent. The requirement of a written consent may be culturally insensitive (Emanuel et al. 2004) and can present challenges for enrolling participants who cannot read and write, as noted in Chapter 1.

In this chapter I present my analysis of how consent is reached and indicated in the interactions between physician-researchers and patients. I demonstrate that reaching consent is in most cases done

orally, or mainly through discussion, but is supported by written, signed, consent. I also explore the practical challenges for the physician-researchers especially of the procedural requirement that consent is formally documented in some way. I should note that the consent form to which physician-researchers refer, is not simply the form that patients must sign to indicate consent, but a booklet of about 15-20 pages, titled “patient informed consent form”, containing both information about the research and the consent form at the end which requires signatures of both, the participant and physician-researcher. The physician-researchers refer to this booklet as the consent form and in my analysis I too refer to this booklet as the consent form. In international trials, this consent form has two sections, one in Urdu and the other in English. The medical terminology in the translated portion is in English, or at times transliterated. For local research, however, the consent form is a single sheet of paper with the information and requires signatures.

I begin by presenting physician-researchers’ views followed by the patients’ perspective on reaching and documenting consent and where relevant I incorporate my observations.

5.1 Physician-researchers’ perspectives on documenting consent

According to the physician-researchers, trust is integral to the interaction between them and their patients, and this would mean that an oral consent is acceptable and culturally appropriate, in addition to being easy to obtain, especially from non-literate patients. However, physician-researchers are also aware of the responsibilities and risks

attached to relying on oral consent, including the difficulties of its documentation. They therefore prefer a written (signed) consent although this too presents challenges.

5.1.1 Oral consent

5.1.1.i Oral consent, trust and responsibility

One physician-research observed that throughout medical history an oral consent has been the norm: "a verbal [oral] consent has always been registered in history" (Int.P-R40). In this view, the inherent trust between physician-researcher and the patient is enhanced when physician-researchers talk to their patients. Moreover, an oral consent may be more appropriate when patients are unable to read or write, which is true of most patients attending these hospitals. As P-R19 said, the means of obtaining consent should match the environment in which research is conducted. Obtaining an oral consent is more appropriate, even though it increases a physician-researcher's responsibilities:

> You do come across situations where the patient cannot read, cannot write, you will have to explain everything and that is where, you know, a great responsibility lies on physician's shoulder that he or she should explain, you know, the consent form….or, as I said, at least the major risks to their health (Int.P-R14).

According to some physician-researchers, it is "no problem" in these hospitals to get a written form signed by most patients, especially non-literate patients (who affix their thumb impression), or their relatives. Such patients do not ask many questions, as I observed too, and they

sign the form (or affix thumb impression) simply because the physician-researcher has asked them to sign:

> Illiterate patients will believe what we tell them and they will sign [affix thumb impression]; they [patients] will sign anything written on the paper, because of blind trust. Then the importance of the written form diminishes, as they [patients] do not know what is written (Int.P-R29).

Similarly, another physician-researcher said that although an oral consent is more convenient to administer, getting a patient to sign (or thumb impression) on a form is relatively easy too, who went on to contrast this situation with the situation in the West:

> So on a feasibility basis, I think the verbal [oral] consent is more [feasible] for us …I guess the main reason why research is flourishing in underdeveloped countries is that getting a signed informed consent in America, in States, in Canada, or anywhere in the developed countries, would be far more difficult than here in Pakistan, or countries like Pakistan (Int.P-R16).

This places the responsibility of getting an "informed" consent on the physician-researcher. He or she must provide "enough" information to the patient. In reality, this does not always happen: "sometimes maybe I would tell them, and sometimes I don't, it all depends upon me" (Int.P-R39).

> I ask if they [have] understood it. It is my responsibility, *thīk hai* [alright]. So I mean this is I think what I can do. Otherwise, if I were to take the copy to him and say, 'Do this [signature], this is important,' then he will, definitely, [do it]. Ninety-eight, ninety-nine percent will do as the doctor says (Int.P-R26).

Trial sponsors and hospitals require a written, signed consent from participants. Some physician-researchers said that they hand over the consent form, which has the Urdu translation, to the patients and ask

patients to read it, or have someone read it to them. While educated patients then return the signed consent form, non-literate patients place their thumb impression instead of a signature, and a relative signs as a witness to the thumbprint. In physician-researchers' experience, sometimes patients who are desperate for treatment, being unable to afford medicine[42]-this tilts the decision in favour of trial enrolment- they sign the form without reading:

> Even putting the consent form in front of him just does not make the difference. He will not read it, he will not go through it, he will just sign it. Even if the patient is not willing his colleagues, his brothers, his sisters, his siblings, they are ready to sign it. So in the third world I think giving a consent form to someone is just [for them] to sign it. It does not mean anything. It does not mean anything to them because they are so eager for the treatment (Int.P-R.31).

5.1.1.ii Requesting a signature can cause suspicion

Four physician-researchers (P-Rs.15,21,26,35) stated that in their experience, getting a signature, at times, raises suspicion. One said that it creates hurdles for them because sometimes people do not want to sign papers, and sometimes asking patients to sign papers sends out a negative message that perhaps the trial is not safe and physician-researchers do not want to take the responsibility for it. So, according to this physician-researcher, conducting local research, what would be easy to administer in the form of an oral consent becomes difficult:

> People say to us, 'Why do you want me to sign?' 'You have told me about the research. Is there something else written on this paper'? So something that can be done easily becomes difficult and explanations have to be given (Int.P-R35).

[42] See Chapter 3, section 3.1.1.

Another physician-researcher, conducting research on pregnant women also realized that many of the women were anxious about the "confidentiality" phrase in her consent form:

> They're usually confused, [about] two things: one is choosing patients *randomly* frightens them since they are primigravidas, they are very sensitive to anything that is different from the routine and the other is signing a form that says '*seeghā-e-rāz'* [confidential]. They say, 'why is this [phrase] in it 'that the result will be confidential', are there legalities involved in this'? (Int.P-R21).

5.1.1.iii Oral consent is difficult to record

According to all physician-researchers an oral consent cannot be documented. So, one alternative, as noted above, is that after the physician-research provides the information, patient's surrogate acts as a "witness" to having received this information, by either signing or affixing a thumb impression on the consent form.

However, I also observed one alternative strategy when physician-researchers from H (at site C) were conducting a local research in school children. The physician-researchers arranged to visit a local government school from where children were to be enrolled, on a day when the children's parents, mostly mothers, would be present to collect their child's examination results, so that the physician-researchers could explain the research and distribute consent forms. While one physician-researcher was explaining the research, another physician-researcher started taking photographs. After a couple of pictures, one woman from the audience got up and asked, "Why are pictures being taken? I do not want my picture taken". A few other women joined her. At this the physician-researcher apologized for not

seeking permission to take photographs, and said she would only photograph women who agreed to be photographed. She said she thought this would not have been a cause for concern, as she was a woman, and she only wanted the photographs as "proof" that information was being provided to these women.

5.1.2 Written consent

Although physician-researchers considered an oral consent more practicable and "good enough", they also considered a written consent to be essential, for reasons I discuss below. Written consent in this context, however, often refers to rather more than the signing of a consent form. It is the information also. In the international trials, as stated above, the booklet has the information and the form for patient-participant's signature and the signature of the physician-researcher providing the information, at the end of this booklet. In local research the consent form is one page of information in Urdu, the national language, with the medical terms usually in English or transliterated. At the bottom of this consent form are required the signatures of both the patient-participant and the physician-researcher.

5.1.2 i Written consent is necessary.

Most physician-researchers considered that there are shortcomings to obtaining *only* an oral consent. One is that there is insufficient time to provide all the information. In a written form all risks are given in detail, while in a verbal discussion there is usually only time to discuss statistically significant risks:

> Definitely in a verbal [oral] consent you cannot explain each and everything; in a written form everything is there - that is, even like vomiting in 1% – the patient would think that, '1% have vomiting'. We do explain but I think that mostly it is the major side effects that patients are mostly told about. This is important because sometimes in the case of a serious adverse event [side effect] we have to admit the patients out of the normal routine. So at the time the event happens and we haven't disclosed it, it's very difficult for the patient. We have to keep that in mind as well (Int.P-R.16).

Some physician-researchers thought that an advantage of having written information is that because a written document will be handed over to the patient, the physician-researchers are more likely to explain everything orally too, and not cut back on information. Also giving written details assures patients that what has been told is backed by the written word.

> I've seen that it's easier to cut back on a lot of information if you just have to fulfil the requirement of a verbal [oral] consent. But if it's a paper that you also have to hand over to a patient, you are automatically involved more you know - it's an automatic quality audit of your consent. Because then you make sure that you tell them of all the information that is available on those papers. A patient might read something that you've not told him and get distressed (Int.P-R19).

Another physician-researcher put it this way, saying that some physician-researcher might "short-circuit" the patient by providing such information as may be conducive to enrolment in the trial:

> Basically, one of the main things is the informed consent form and unfortunately, the majority of our patients are not educated and they don't understand exactly what they're getting into. So we need to tell them in very simplistic manner and …I think, this is the main issue that here, sometimes, we just short-circuit them.
>
> Q: What does 'short-circuit' mean?
>
> I mean, that's what happens- sometimes it can happen that we don't explain [to] them…and we just tell very briefly about

> the study. So that's unethical – that's what I'm trying to say, that we should not be doing that (Int.P-R20).

In other words written information is helpful in providing details of the trial by the physician-researchers to patients, and patients can read it too. It can also be considered later, which may be especially important for patients whose trial enrolment was discussed before patient had time to absorb their diagnosis:

> There's the diagnosis of cancer and then there is the stage and the implications of having that particular stage and the prognosis, chemotherapy, the side effects of chemotherapy – the logistics of it all. And they really feel overwhelmed and I think it often helps if you take consent in more than one sitting (Int.P-R19).

In these circumstances the patient may not want too much information or may not be in a receptive frame of mind. So it may be better to ask them to take the form home and read it. This was the practice I observed, of some physician-researchers, especially those who had divided their time between the two the enterprises – clinical work and research work.[43] They would ask patients to read the information in the consent form. One physician–researcher, who, realizing that his patient may benefit from enrolment in a trial would discuss about the trial in the initial consultations and also provide them the consent form to read and discuss:

> What [I] usually do is give them [patients] the consent forms in the very initial stages of the treatment you know. [I] tell them, okay take your time and read it and then, you know, don't sign it, just come back to me and if you have any questions, any concerns, I'll be here to answer you (Int.P-R14).

[43] See chapter 3, section 3.1.3.

Others are unable to find enough time in a busy hospital, where physician-researchers are already stretched and under stress:

> Manpower shortage and time shortage both create stressful situation. The patients who are enrolled require all the "workup" to be done the same day and there are only two doctors who have to look after that, along with [looking after] the patients in the ward (Int.P-R28).

Therefore this interviewee considered that, in these circumstances, providing a written form would give patients all the information, which they can read, or have someone read to them, before signing.

Obtaining a written (signed) consent is also important, according to some physician-researchers, because people tend to forget and so for your own record it is important to have everything written:

> I think we should take written consent because there are lots of other issues; memories are short. Personally in a research project I go for very clear cut proforma in Urdu, with explanation and everything and get it signed, for the record (Int.P-R34).

Many times, according to the physician-researchers, patients are informed that it is important for them to read the information in the consent form, for it details the reason for conducting the trial and guides the patient through the course of the trial and what is required of them.

According to the physician-researchers a written (signed) consent from patients is a requirement of almost all research protocols- local and international research. These consent forms are given to patients, however:

> What happens is that we have a consent form .We give that consent form to those who are educated and tell them to read it. If they want it in Urdu or if they want it in English, whatever they can read (Int.P-R26).

The physician-researchers said that most patients, especially the non-literate patients do not understand the information in the consent form, which is very long and contains medical terminology in English. They need help to understand it and relied on the physician-researcher to explain it. Despite this physician-researchers still considered that a written consent is important:

> It should be written, not verbal [oral]. For one thing it is a proof, and then in your own research you can say that you did get written consent. This is now a requirement for your dissertation. Written, yes written informed consent, this is because some doctors may not take consent and say that they have (Int.P-R11).

In physician-researchers' experience, patients are sometimes suspicious about why they need to sign the form[44]. One physician-researcher said that in these cases she explains that a written consent is necessary so that patients know that the physician-researcher will not proceed with the intervention unless the patient *wants* them to. It conveys to patients that their signatures are not just for the physician-researcher's safety:

> Then there is the signature on the form, they think 'why are they asking for our signatures?' So now here we are getting them to sign, in a way we tell them the worth of their consent – that we will only proceed if *you* agree (Int.P-R15).

Although patients are given the consent form to read, some patients do not read it. Some only read if an adverse side effect occurs, and then

[44] See section 5.1.1.ii

realize for the first time that the particular side effect is mentioned in the consent form:

> Not all of them [read], because the ones who do read always come back with some questions. Because, I mean, who wouldn't have any questions after, you know - that [technical] language. I usually ask them, 'Did you read?' And they – some of them – tell me the truth that, 'No, I didn't. I believed whatever you told me'. But this [reading] is not something that I can force and I mean, they probably wouldn't [read]. There are some who wouldn't read it unless something goes wrong. And then they would read it and then they would come back to me and say: '*Iss mein to yeh bhī likhā huā hai*!'[It has *this written* in it!] And I'd tell them that, 'If you remember, I told you this… (Int.P-R19).

While some literate patients read the information, as P-R19 also said, another physician-researcher said it is unusual for patients to read all the details, because "in our country people are not in the habit of reading [forms] whatever we tell them it is sufficient for them. But we ensure that they read it, take it with them and come next day and discuss" (Int.P-R15).

5.1.2.ii Oral and written consents are complementary

Most physician-researchers said that patients prefer physician-researchers to talk to them about their disease, the trial and its intended benefits, rather than to hand over the consent form to read and sign. "Although it has to be a written consent, there has to be some explanation to be done. You can't just put a paper in front of a patient and ask him to sign" (Int.P-R17).

Since physician-researchers felt it is important to explain the trial first and give patients the consent form afterwards, this way both consent processes are seen as complementing each other:

> I think both are equally important. They're kind of, what do you say they complement each other. My experience is that they [patients] do not read all that is written on the paper. They say 'what is this tediously [detailed] long paper?' They want the doctor to interact with them and tell verbally; sort of assure the patient (Int.P-R22).

Another physician-researcher emphasized that the longer the duration of the trial, the greater the necessity of a written consent form with information not only about the risks and benefits but also about the follow-up schedule that patients are required to follow:

> I think first verbal [oral] and then written… No, no, it has to be written, because you see, you have to document the description you have given, the patient has to sign that he has been told about the relative risks and benefits, the duration, the [follow-up] visits, particularly for an extensive project, and then he or she signs [it] (Int.P-R9).

5.1.2.iii Written consent is for "legal safety"

A written (signed) form is also viewed as documentary evidence that information was provided to patients:

> I think written consent is better. Written consent for one it will be evidence that patient has gone through the whole information, he has an idea. In verbal [oral] there may be confusion as to what have you told and what he has conceive[d], what was the outcome? [And] you come to that level and talk in Punjabi, tell them to take the paper [consent] and whoever is educated in your house, talk to them … (Int.P-R15).

As such a written and signed consent form provides "legal safety" for the physician-researcher and/or the pharmaceutical company. A consent form that is signed by the patient is "proof" that the contents of the form were discussed with the patient. This is because there is an acute fear of "being dragged" into court:

> It [written consent] is so that the doctor can protect himself, so that tomorrow if the patient says 'such and such a thing

> was not told to me' he cannot then deny that it was. We tell everything verbally but it [written] is only for doctor's safety, so that *kal ko court may na ghaseetā jāye* [they may not be dragged into the court in future] (Int.P-R29).

> I think consent can be either verbal [oral] or written, as you know, but I think it should be written. I think it has not been given as much importance in our part of the world as it has in the developed countries because, I think, there the patients are more educated, okay, and then obviously there is a fear of law suits and so …. I think trends are changing, most of the physicians, they take signed consent form (Int.P-R14).

Another physician-researcher considered a written consent to be essential even if a surrogate signs it. I observed this in the clinical setting, especially for women patients undergoing gynecological/obstetrics surgery. For example if a woman has to undergo an operation she will receive a verbal explanation and a written consent for the operation will be obtained from her husband. This is because, as one physician-researcher said, "If there is any complication, any problem, patient's signatures are not valid [in this case]" (Int.P-R38). Other physician-researchers reiterate the legal implications of written consent: "I think you see legality is always there everywhere, so it has to be a written consent but as I said it has to be explained (Int.P-R17).

Although a written (signed) consent is problematic and is difficult to administer, nowadays in all research , local and international, in which patients are enrolled , evidence is required that patients have received all the information and joined the trial voluntarily. In addition, as P-R15 said that signed consent form serves the purpose of an auditable trail for trial sponsors and researchers.

Physician-researchers said that though patients agree to trial participation when this is discussed, then if an untoward side effect occurs, some patients may claim that the risks were not discussed. "Patients have short memories", and "the way things are nowadays, [there is] a lot more awareness and with the media jumping in, it is better to write everything down" (Int.P-R31), and hand it over to the patient or the accompanying relative:

> The international trials always want it written, yeah definitely, because of the legal issues, so it's a vital part of the thing [trial], taking an informed consent, how to take it; they don't go into details. If you get a consent form signed then it is not a problem. If anything happens then at least the form is there (Int.P-R16).

Another physician-researcher conducting local research was of the same view:

> I think it [consent] should be documented. Suppose the patient has got some other problem and supposing she says, 'No it was that injection that has caused [the problem]' .... So to keep my side safe, I must write all the findings down and inform the patient and get the written permission. I will be safe if I have already taken that permission (Int.P-R10).

P-R26 mentioned that sometimes a trial protocol requires that consent is obtained in stages. For example I observed that, according to the protocol for an International Atomic Energy Agency (IAEA) trial, a patient, was given an initial dose of radiation, and was then kept under observation as an inpatient for three days, because of the danger of serious adverse effects after the initial dose. The protocol requires the physician-researcher to wait and observe after giving the initial dose, which is standard treatment for all patients. The patient is given a couple of days in which to reach a decision about trial enrolment. If

the patient tolerates the initial dose they will be invited to have a second, incremental, dose on a trial basis. Since it is the patient who will undergo the procedure, their willingness is essential for this second step to be taken. If the side effect has deterred the patient then they do not continue. Consent is taken only when patients come for the second dose, which may be 2-7 days later. Only then, when the patient comes for the second dose is the enrolment request sent to the data management centre. As the physician-researcher told his patient:

> We will ask again whether you are ready that we should repeat the second procedure this is where the consent of the patient is required, that 'okay, I tolerated it well. And so you should just continue with the second [dose]'. Here we have to see whether she has got any big problem [adverse effect] due to the first dose or not (Int.P-R26).

5.1.2.iv Written consent is tedious

Consent is a long tedious process. Four physician-researchers (P-Rs 6, 9, 18, and 23) said that as there is so much to be explained, they, and others in their opinion, prefer to enrol patients who are educated. Educated patients are not only easy to communicate with; they can read the consent form, though not always without help, before signing it. According to these physician-researchers, there are however some patients who cannot or do not give consent in writing, and so not enrolled in research. Although the consent form for local research is in Urdu, even so:

> Some people are like, sometimes, because of their educational level, they would not like to sign the paper, because some of them can't even read Urdu, which is the only language available to us for the written consent form, [so] whenever we make consent forms they are always in Urdu so that they can read. But some of them they are unable to read and they don't put their signature or put thumb

> impression [on the form]. So, you see, you cannot include them in the research (Int.P-R23).

Sponsors of international trials also require written signed consent form with the result that again patients, who are unable to sign would not be enrolled in those trial:

> There were certain trials in which it was a requirement for the consent form to be signed and if the patient could not sign then he's not eligible. We have done certain trials in which this [requirement] was there. It becomes very difficult indeed. Of course, that's a tight inclusion criterion (Int.P-R18).

I observed that some physician-researchers had enrolled non-literate patients in a collaborative trial, five (Pt.1,2,18,23 and 31) of whom I interviewed.

Another physician-researcher also said that because the trial sponsors want a written signed consent, in his view enrolling a literate or "semi-literate" is better, because asking someone who is unable to read what is written on the form to sign it or, more appropriately to put their thumb impression on it, is unethical:

> It is a difficulty that is why we select people who are literate, able to understand and read. It is difficult because if you have an illiterate person, even if you have time it is hard to explain, as the level of comprehension is lower. And then having them sign it [consent form] when they can't read the papers, obviously you start being unethical (Int.P-R9).

5.1.2 v Thumb impression and proxy signature

Physician-researchers said that relying solely on oral consent is no longer very common. If a patient is non-literate then one alternative to obtaining signatures on a consent form, is to obtain a thumb impression from the patient that is witnessed by a literate person who may be the patient's relative. Another alternative is for a literate

relative to sign as proxy, on behalf of the patient. I observed this in the clinical practice for gynecology/obstetrics patients. Non-literate patients cannot sign, so according to some physician-researchers their representatives' signatures are obtained:

> Verbal [oral] is not very common, up to now I have not taken verbal [oral] consents. Usually we have been doing written. So verbal [oral], – I don't know why we have not done verbal [oral]. Although we have been enrolling patients with low-literacy, then patients put their thumb impression and it is signed by the relative accompanying the patient (Int.P-R18).

> We explain verbally to those [patients] who are not educated. We tell them about the trial. They do understand alright, but then some of them *sign bhī nahī kar saktaye* [cannot even sign] then we ask the person accompanying them, their *numāinda* [representative], like their son or whoever, to sign on the [patient's] behalf and [we] take the patient's thumb impression [on the form] (Int.P-R27).

5.1.2.vi Language of the consent form

The language of the consent form is another matter that, according to the interviewees, raises concerns. It is necessary that it should be not only in the local language but also simple and easy to read and understand, preferably without the scientific words, which are always in English. A good consent form should explain simply and concisely about the trial.

> I think again that make it very simplistic, number one and consent should be taken in the same language as the local language – the patient's language which he or she understands (Int.P-R20).

This is not only in research; physicians face similar problems in their clinical practice:

> You see, there are so many spoken English words as part of our daily, language patients usually understand them. But you

> have technical words, yes, technical words are difficult, then you have to explain them in another way (Int.P-R9).

Even though the consent form has a translated portion in the national language, Urdu, many technical terms are in English or transliterated. The technical terms are incomprehensible to the patient therefore "the language needs to be simplified for sometimes even I do not understand what is written" (Int.P-R19). Not surprisingly, it is difficult for a patient too:

> We have to explain the patients the informed consent – we do, and we give a copy of that informed consent to the patient, but I think very few of the patients read those forms. And if some do read those forms, I don't think they would be able to extract much out of that consent form (Int.P-R16).

One physician-researcher thought the institutional review board should rectify this situation in which even physician-researchers, let alone patients, find consent forms difficult to read and understand:

> In fact at times the words in Urdu are more difficult to understand and I have seen them. They are very difficult indeed and I agree that the institutional review board (IRB) should be very vigilant about it. The forms that come from abroad [collaborative research], we advise them [IRB], but hardly anything has happened so far. This is very interesting but we do inform them that the language is difficult. IRB should be at least this much vigilant that they should see the informed consent to ascertain whether it can be comprehended or not. I mean that level of even Urdu, can we comprehended it before we expect the patient to do so! I think it can be done, we just need people and time to work on this --- to make it simple according to the literacy level of the people [patients](Int.P-R18).

Another problem said a physician-researcher is that even if the form is translated into Urdu (national language) there are patients who cannot read or understand Urdu because they speak other regional languages.

This according to the physician-researcher is “as bad as having an English consent form” (Int.P-R19).

5.2 Patients’ perspectives on documenting consent

Most patients considered it was essential to talk to the physician-researcher about a trial before being asked for or giving a written consent. For these patients, reaching an oral consent based on their trust in physician-researchers was a necessary step towards consent documentation. Nonetheless, most patients considered a documented, written consent necessary as a supplement to oral consent and to protect physician-researchers. Patients also raised the issue of the language of the consent form.

5.2.1 Oral consent and trust

The interviewed patients preferred that physician-researchers spend time with them discussing and explaining the trial. This, they said, gives patients confidence that their health will not be compromised further, although it does require careful explanation:

> It is very important that the doctor explain all to the patient as my doctor *sāhib* did. He explained by drawing and then when I took the papers home, when I had the time I read and understood some of it…I could not understand all (Int.Pt.9).

Non-literate patients considered a written consent giving printed details of the trial to be of limited and at times, negligible value. These patients said they rely on the physician-researcher or an educated relative to explain the trial to them. Although all patients were of the view that trust is the basis of the interaction between them and physician-researchers, literate patients considered a written consent to

be important nonetheless, while non-literate patients said that, since they cannot read or write, a written consent does not matter, in any case said one patient "it is a question of trust. A person's word is important".

> I cannot read or write, so it does not matter. They [physician-researchers] gave us some papers and my husband signed them I think or my brother, I think it was my husband (Int.Pt.1).

Most non-literate patients did not remember the contents of the written form, although some remembered having had them read by someone else. The wife, in one couple, stated:

> They [physician-researchers] did give us some papers to take and read which he [husband] did. But now I do not remember what it was. It was explained to us at that time…. We do not have any [papers] now (Int.Pt.2).

This patient's husband added that, since his wife "cannot read or write", he read and signed the consent form on her behalf, acting as a surrogate. Three other non-literate patients (Pts.18,23,38) could not recall being given any papers to sign. For example, Pt.38 said that no form was given to her, to sign or put her thumb impression on, although she recalled that the physician-researcher had explained about the medicine. Another patient could not recall being given any form:

> No, I don't think so … I don't remember. All that was said was that on this date you will get a drip [medicine]. I have been coming and getting the drips, today was the last [drip] (Int.Pt.18).

One patient recalled that a registration card was made for her, but that she was given no "form" to sign, "No, I was not given any form. I did

not sign; they just give me the injections. I was given a card" (Int.Pt.23).

Whereas another non-literate couple said that they were provided with forms that they took them home, "Yes they gave us the forms and explained, then our daughters who are educated read and explained what was on the forms" (Int.Pt.24).

I observed that in cases where both the patient and the accompanying relative are non-literate, they depend entirely on the physician-researcher to explain everything written in the consent form. Considering the time constraints, this means that only the information considered necessary by the physician-researcher is provided.

Two patients reiterated that though a written consent is obtained, a trustworthy physician-researcher is more important than having everything written down, because not all patients can read and in these cases written forms are unsuitable:

> But you see it is only if you educated then you can read, otherwise if the person is illiterate then all depends on the doctor… You [physician-researcher] can tell and make them join by just telling very little (Int.Pt.14).

Pt.6 also raised the issue of trust:

> But you see it is a question of trust also. It may be written but what if the doctor does not do what is [written] on the paper (Int.Pt.6).

One non-literate patient (Pt.22) stated that because he wanted to enrol in the trial he put his thumb impression on the consent form even before discussing the trial with anyone.

5.2.2. Written consent

5.2.2.i Written consent is a necessary supplement

Most patients considered that it is best to follow-up a verbal conversation with their physician-researcher by having a written form of consent. Literate patients emphasized that "some form of paper work", detailing the research protocol in simple language, is useful because then the patient is aware of what is going to happen. Some literate patients who understood their disease read the consent form for all its information (and visited the internet).

Patients also felt that a written consent is necessary because physician-researchers are invariably in a hurry and many times are unable to answer patients' queries in a satisfactory manner. This was particularly the concern of literate patients:

> You see the doctors are very busy and sometimes I feel they cannot tell all. In fact, they give the form and say, 'Go and read it too. There will be questions you want to ask so come back and we will talk' (Int.Pt.7).

Most literate patients considered that although physician-researchers should explain the trial protocol orally, a written consent is important as a reminder of what was discussed, because patients may forget some of the details of what was discussed in the verbal exchange:

> First he should explain and then it [written] is important because if I want to know something and even if the doctor told me but I have forgotten then it is better – you can read it. Until the patient is not satisfied, they will not come (Int.Pt.15).

The husband of Pt.15 accompanied her on all her visits to the hospital, carrying a file containing all her medically related papers since 2005[45]. After consultation with the physician-researcher, he wanted to take the consent booklet home to read and then discuss with his wife. On their next visit they brought the signed consent booklet with them. Likewise another patient said, "It should be written. But the doctor should explain too as my doctor did and I could also come back and ask questions after reading the pamphlet [consent form] and signing it" (Int.Pt.9).

I observed variation in the practice of handing over the consent form. At site F, patients kept their own copy of the consent form. At sites A B, D and E, patients were given the consent form to take home but after signing it they were required to return it to the hospital for the hospitals' record.

Pt. 31 and her husband said they were given the consent form that they took home. The husband read it and discussed it with an uncle of his (upon whom both the husband and wife relied). The husband then narrated:

> Then he [doctor] explained to me that this is how it [trial] will be. This is what the problem [disease] is and her disease can be finished by this [medicine]…. Take this *kītābcha* [booklet] and read it thoroughly and understand it, and if there is any question then we will handle it. So then I read the papers [booklet] and was then able to explain all to her [wife] (Int. Pt. 31's husband).

I observed that P-R2 gave the consent form to one patient saying "*isko acchī tarha parh lein,* [read this carefully], if you want to read it now

[45] See above section 4.2.3 and Chapter 3 section 3.2.2.

then fine, or you can take it home." The patient read through it, pausing at points to ask what the medical terms meant. Sometimes, however, physician-researchers do not hand over the consent form to the patient; this tends to occur with patient referred to them by others,[46] where there are time constrains, and when there is a "narrow window" for enrolment.

5.2.2.ii Written consent is for the safety of physician-researcher

Most patients also stated that physician-researchers prefer a written consent:

> I want my doctor to tell me and explain and actually to talk to me. But I think it is important for them [doctor] to have it written. Because then they can say that all was told to the patient, especially nowadays, doctors like to have it all written down and signed (Int.Pt.6).

> Both are okay. You see if it is written the doctor has a proof. Verbal [oral] is also okay, you see, it is a question of trust. I did sign the form [consent] at the hospital; I did not take any [papers] home. Once I signed it [consent form], I was given the medicine (Int.Pt.4).

At site D, I observed that when Pt.14 was handed the consent form, he immediately inquired what it was for. When the physician-researcher explained that the International Atomic Energy Agency requires it, the patient asked, "Why is this necessary?" Later, when I interviewed this patient, I asked about this episode and whether he considers consent should be written Pt.14 said:

> It should be written if the patient is educated, I would prefer that. But I remember when doctor *sāhiba* gave me the paper, the language on it did frighten me a little, you see it had something like 'you are coming into this research voluntarily' and I felt that they [physician-researchers] are not taking any

[46] See Chapter 3, section 3.1.3

> responsibility. Then I did ask the doctor *sāhiba* what is this for? It looks something very legal. I felt that by making me sign this paper [consent form], if anything goes wrong [during the trial] then *I* am responsible (Int.Pt.14).

5.2.2.iii Thumb impression and proxy signature

A few patients recalled being given consent forms to take home, to have read by a literate relative and to affix their thumb impressions before returning it to the hospital. These included the non-literate couple mentioned earlier[47]:

> We took them [consent forms] home and *sādī bachīān nay parh kay dussayā sī* [our daughters read them and then explained to us]. *Hān jī, angoothay lagā'i see*. [Yes, we put thumb impressions]. We both did, *Hān jī* [yes] (Int.Pt.24 and 28).

Another non-literate patient from a nearby village had it read by his son and then he put his thumb impression:

> No, no, I did not sign, *angoothā lāyā sī* [I put my thumb impression]. My son explained it [consent form] to me. He is educated. He studies at the university here (Int.Pt.19).

5.2.2.iv Language of the consent form

Most patients were of the opinion that the language of the consent forms should be Urdu because that is the language most people can read. However, some literate patients thought that whether the language used in the consent forms is English or Urdu was irrelevant; what mattered most was that it should be easy to understand, " I can read and write in English so it does not matter [to me] if it is Urdu or English, but it should be simple (Int.Pt.13).

[47] See above section 5.2.1.

> People who can read English it is okay but how many [people] can read it [English]? So it would be better in Urdu (Int.Pt.14).

Concluding remarks

Both physician-researchers and patients consider that for the patient to achieve an understanding of the research protocol and reach an informed decision about research participation it is better to talk, it is through talking about what is involved that patients will indicate their consent to participate. Physician-researchers and patients also consider, however, that a written consent serves several purposes, and so may be preferable. For example, it enhances trust, indicating the physician-researcher's respect for the patient's decision and signalling that the intervention will only be used if the patient so chooses – although this respect for the patient's authorization can also be conveyed orally. It may also assist in the provision of verbal information by serving as a "script" for physician-researchers to follow during their conversations with patients. As the sponsors require a written, signed consent, physician-researchers adhere to this form of obtaining consent. Similarly in case of local research the requirement by ethics committees of a written consent urges physician-researchers to obtain a written consent. Hence all interviewed physician-researchers irrespective of whether they were conducting local or international research obtained a written consent. The outstanding purpose that a written consent serves, in the view of most interviewees is the "legal safety" it offers to physician-researchers and sponsors (and the hospital).

The mandatory requirement of a written signed form is ethically problematic in two ways. Most of the patients attending these hospitals are non-literate. Moreover, most non-literate patients are ready to sign a consent form because a physician-researcher, whom they trust, has asked them to. There is a risk here of compromising voluntariness where non-literate patients are asked to affix their thumb impression on a form, which is at the end of this booklet, the contents of which they do not know. The pragmatic alternative step, in local practice, is to ask a surrogate to read and sign on patients' behalf, but this too risks compromising informed consent because obtaining a signature from a surrogate or relatives is usually as easy as obtaining a thumb print from the patient. A patient's desire for treatment, in the form of a medicine they need, when there is no affordable non-trial alternative medication available, tilts the balance in favour of research enrolment so that patients will "sign anything".

The second way that the mandatory requirement of a signed consent is ethically problematic is that is can create a situation in which patients who may benefit from research and may be willing to enrol are excluded from research if they cannot or do not want to sign their names on a form (or affix thumb impressions). Apart from affecting their self-determination, their social vulnerability, especially in case of non-literate patients, may exclude this segment of the population from potentially beneficial research. The ethical issue here concerns the requirement of fair selection of research participants, and the acceptability of excluding communities with low or no literacy from

research because of their inability to conform to the requirement of a written consent, the contents of which the patient cannot read.

Physician-researchers' recommendations regarding the consent process and design of consent forms are useful provided they are taken on board in the spirit of collaboration, which is also an ethical requirement.

Chapter 6

Researcher as Physician

As data analysis progressed it became evident that the processes of information provision, decision making and documenting consent raised major concerns for physician-researchers, as I have shown across Chapters 3, 4 and 5. In addition, my data analysis revealed two further sets of issues of ethical concern related to the conduct of research trials in Pakistan. One arises from the fact that physician-researchers regard their primary role to be that of physicians; the other arises from the diverse forms in which patient autonomy exists.

The fact that physician-researchers view themselves as physicians first and foremost, directs their engagement with, and interest in, research. This is not incompatible with international guidelines, which require research to be responsive to the needs of the patient population, especially in case of disadvantaged populations (WMA 2008, [Paragraph 17]), and entitles patients at the conclusion of the study to have access to the proven intervention or to other benefits resulting from the study (WMA 2008, [Paragraph 33]; CIOMS 2002, [Guideline 10]).

The diverse forms in which patient autonomy exists contrasts starkly with the concept of autonomy within international ethics guidance that is unequivocal in patients' right to self-determination (CIOMS 2002,[Guideline 4 and 16]; WMA 2008, [Paragraph 11 and 22]), and with the concept of autonomy that physician-researchers themselves would

advocate or like to encourage in their patients. This, I shall show, raises dilemmas about patients' ability to determine for themselves, and the physician's ability to protect patient confidentiality by not sharing information about that patient with other people.

I present the physician-patient relationship and follow it by exploring the matter of research that physician-researchers consider responsive to the local health needs, in it I also present patients' perspective on the provision of proven intervention. I then examine the concept of patient autonomy and within it, issues concerning withdrawal from research and confidentiality.

6.1 Physician – patient relationship.

All physician-researchers considered their role as a physician has primacy and the researcher-participant relationship is eclipsed by it. Even in cases where the relationship begins as one between physician-researcher and research participant, it metamorphoses into a physician-patient relationship:

> Initially it starts [as] your doctor-research participant [relationship], then when patients come and tell you about their worries; tell you about their problems and side effects, then that relationship builds up. The care level goes up because you start feeling that okay this is my patient now when you have this feeling then you start owning that patient and definitely I think every follow-up increases your [concern] (Int.P-R31).

> Both go hand in hand. I think even as a researcher still the patient's benefit should come first. It has to come first. Otherwise you should not be doing medical research. That's how I feel (Int.P-R24).

According to these physician-researchers, their training as physicians instils a sense of duty towards patients. For them, a researcher is

someone who is aloof and not in touch with patients, P-R29 thought, "The researcher–participant is not a substantial relationship; it has to be a doctor-patient relationship". If a patient, who is enrolled in a trial, has problems unrelated to the trial, even then the physician-researcher should attend to that patient's problems:

> Patients call in the middle of the night, 'doctor *sāhib* I am having this problem [symptom], what should I do?' This happens many times during a trial, and then I have to as a doctor, help him out and tell him what treatment to take (Int.P-R27).

Patients want to enrol in a trial because they believe that by doing so they will benefit and have regular contact with the physician. This is not to say that enrolment in a trial is necessary for access to physicians but that the frequency of consultations increases.

The physician-researchers viewed their role in research as a "temporary phase" in their career, as P-R2 put it, and the doctor-patient relationship as a permanent relationship. For this reason they felt it was necessary for them to be convinced of the value of the trial before enrolling patients, in case the trial drug may worsen patient's illness. Physician-researchers were also aware of the potential damage to the reputation of a physician-researcher that can be done by conducting "bad" research. That is, research that is harmful to a patient's health.

> Doctor-patient relationship is important. That is [a] sort of goodwill of a doctor. That is the main reason that you are a doctor, it affects your reputation as well. The research, the research is more important for [the] doctor and the future patients. So if I do something that will endanger the patient then my reputation is also affected and your [a person's] reputation is important (Int.P-R26).

Physician-researchers also felt it was their responsibility to guide their patient in following the research protocol to ensure the patient obtains the maximum benefit from participating in the trial, otherwise:

> Patients may realize that these doctors are only interested in their research and not our [patient's] health. They will not show up for follow-up. So it is important to educate the patient…. At the end of the day, [the] doctor-patient relationship [is] going to be longer-lasting, these researches come and go. Patients usually come and tell you, [that] two years ago, they participated in my research (Int.P-R9).

6.1.1 Physicians' confidence in the trial

Although physician-researchers realize that research trials are intended to benefit future patients and "yes at times it may be that the patient may not benefit directly" (Int.P-R1), the physician-patient relationship directs physicians to conduct research that they feel confident will also benefit their patients.

> Definitely, the doctor-patient role is much more important and that's what my point was that, initially, what I was telling you that, probably, in Phase III trials, we are more comfortable. Because we know one way or the other the efficacy of the drug has been tested before; in Phase II trials it's too early to say that whether this drug is going to [benefit] or not. So, yes definitely, the doctor-patient relationship is much more important than a researcher-patient relationship (Int.P-R16).

At the time of my interviews with them the physician-researchers were conducting Phase III and Phase IV trials. All physician-researchers considered it is essential that they understood the benefits and more importantly, the side effects, of the new drug because patients rely on them and trust them to know what they are doing. Therefore:

> If the knowledge is sufficient that this medicine is good for the patient, then we like to convince them that you should get this medicine. We will then be partial that you should go for this medicine, it is good for you, but if we do not have sufficient information, then it can be a problem (Int.P-R13).

One physician-researcher reiterated the importance of knowing everything about the new intervention for otherwise incomplete information will be given to patients:

> If you do not know yourself [about the trial], then you are delivering incomplete information to the patient. Now if the patient consents then he is consenting on the basis of incomplete information. If all information regarding all the side effects were given then he may have not consented or may withdraw his consent (Int.P-R15).

Physician-researchers felt they should be sure about two aspects of a trial, before confidently recruiting patients. First, the physician-researchers need to be well informed, as stated above, about the benefits of the trial, indeed, they should have statistical evidence.

> If you are confident of a drug, of a new intervention that is being tested, that it will benefit the patient does affect my convincing capability. It would get compromised if I found myself not sure of the drug efficacy—so I need to be convinced first (Int.P-R15).

Second is the phase of the trial. These physician-researchers are more confident about Phase III and Phase IV trials, when some data about the efficacy of the intervention are available[48]. A physician-researcher, talking about a Phase III trial that he had conducted earlier, said:

[48] Phase I in which healthy volunteers (20-80) are used, or if for use in patients with a particular disease (as cancer) then patients with that particular disease are enrolled, to assess the safety, tolerability and pharmacokinetics. This is followed by Phase II, in which therapeutic efficacy and dose determination is assessed on patients (20-300), this phase is well-controlled and closely monitored. After preliminary evidence of efficacy has been obtained then the drug enters Phase III in which patients in different clinical settings are enrolled to further evaluate its effectiveness and safety. The number of patients in Phase III trials goes up to several thousand.

> That study was good, just after six months we came to know that this is the standard therapy now being practiced all over the world, not in the trials but in the clinical practice. So that was a good study, patients benefitted and we were very happy to enrol patients in that study (Int.P-R16).

Similarly, another reiterated that the "confidence" depends on the phase of the trial:

> Like, this is Phase IV trial; it's easier for me to say that it's an already marketed product – people are using it all over the world. I think it's the hardest for Phase II because with Phase II all we really have is the safety data. So you have to tell them that, 'This is what we know so far, there are new things coming up all the time, I'll let you know if there's something that serious or if there is something that we need to modify'. But then it becomes a little too much for them (Int.P-R19).

Furthermore, these physician–researchers were comfortable with an "open-label" trial (unblended trials), one in which the physician-researcher and patients know which drug is being used. Interviewees also preferred "add-on" trials where the standard therapy is provided to both arms of the trial with the test drug added on in the intervention arm and placebo to the control group:

> See whenever an investigator is doing a trial or any study; first thing that should come to me is that I should be confident that whatever I'm offering to the patient is ethical – even if it is a randomized trial. The patient is going to be randomized to arm A or arm B, the first thing [is that] I cannot go with a trial if I'm not convinced that having a patient in both the arms is okay; we're not depriving them of anything. Without that no investigator can, you know, go with a trial, they cannot recruit patients (Int.P-R18).

Physician-researchers mentioned that the reputation of the hospital where the trial is being conducted is another important factor they

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This is followed by Phase IV (which involves the post-launch safety surveillance of the drug) (see also Friedman, Furberg, and DeMets 1998).

believe affects patients' confidence in the trial. An established hospital that people trust to deliver good care would not jeopardize its reputation by conducting trials that are harmful to their patients.

> We tell them that you have come to such a big [established] setup. Do you think that we will do something to harm our patients' health? Here (at this hospital) Phase 1 or II trials are not conducted. We conduct [Phase] III or [Phase] IV trials in which we have only to compare the efficacy. The [drug's] safety has been established, so then they [patients] understand (Int.P-R15).

6.1.2 Responsive research

Physician-researchers, considering themselves primarily as physicians, expressed clear views about what type of research is relevant to the health needs of their patients. The trials conducted at the time of my interviews of the physician-researchers in these tertiary-care hospitals were both international collaborative and local trials.

The topics that physician-researchers elaborated upon were: relevance of research, care of research participants and post-trial access to proven interventions. As access to proven intervention affects patients enrolled in these trials directly I present patients' perspective too.

6.1.2 i Relevant research

Some physician-researchers felt that not enough trials are being conducted to meet the therapeutic needs of their patients. They observed that data on disease manifestations and on the disease-modifying effects of drugs are from Western populations. These physician-researchers questioned whether such findings are applicable

to their patient population, and recognized that "indigenous" data are required.

Some also considered it important to participate in international research, because, as P-R18 put it, "generalizability" will only be possible if the trial on varied patient populations for the same disease has been conducted at maximum number of sites in different settings.

Medicines being used in Pakistan usually have been tested in the West and not on Pakistani population. In P-R17's view, while the pharmacological effects may be similar; it would still be necessary to ascertain whether the dose is of optimal benefit to local patients: "this is something that would only go in our benefit". In general, new medicines become available in Pakistan a few years later than the West and knowing this gives physician-researchers a general sense of confidence about these drugs. It is still necessary to ascertain the optimal dose for local patients because:

> We feel that dosages in the West because of so many reasons, they're slightly higher than those [needed] over here. But generally I must say in the trials that we do over here, we do start with European doses, and then depending how - the results or the side effect profile or adverse events are behaving [we adjust the dose]. Generally, the dose- the European dose is not such that [it is] toxic for us; but there may be a little- we might be going a little overboard or let's say that, we may be getting the same results with lower dose (Int.P-R17).

The main issue with most international clinical trials conducted in Pakistan, this physician-researcher said is, the "huge risk benefit ratio issue". It is important then to be aware of those Investigational New Drug (IND) trials:

> This is the gross unfairness of those IND clinical trials that are being done. It's changing; it's not always so but it's largely so. And this is- this is the area that I feel needs to be looked upon. It's something that will not be looked upon by the sponsoring companies. It's something we need to, you know; raise our voice against (Int.P-R19).

Physician-researchers therefore do not consider, as P-R 17 said, running "just any trial". They prefer well-structured trials with strict oversight mechanisms such as, for example, those monitored by the "FDA [Food and Drug Administration] or other world authorities":

> Sparingly, not very frequently, pharmaceutical companies would ask us to hold a trial for them and generally these are type of trials which would be scrutinized and which are being scrutinized by FDA or other world authorities and they're pretty well structured (Int.P-R17).

In addition, P-R17 said, "we scrutinize the research document" when asked to conduct a trial. Discussing a trial invitation for a drug called glitazone, to be used in Type 2 Diabetes Mellitus that a pharmaceutical company brought to this hospital, he added:

> I remember we were asked to do, this was quite a few years ago, I think Phase III trials on one of these glitazones. And the one glitazone which couldn't get through, we were asked to do the trial and we, on preliminary investigations, the documents which were provided to us did show that in rats it causes liver problems. So I think that was the issue and we rejected that research project. And lo and behold, it was rejected all over the world as well because of the same issue (Int.P-R17).

A recent development in Pakistan is Contract Research Organization (CRO), which, according to P-Rs 9 and 19, acts as a middle-man. A pharmaceutical company contacts a CRO that identifies a hospital where the CRO may have previously conducted research and so has liaison with the hospital. This creates a situation where the CRO tries

to “be economical and spend only what is essential to run the trial,” said P-R9.

Not that all types of trials are accepted; trials that do not “fit” into the available biomedical technical environment of the hospital cannot be conducted as there is no infrastructure to facilitate and monitor these trials. This is an issue with some international clinical trials, for example Phase 1 trial:

> I’m not against doing Phase 1- I mean, I actually want Phase 1 trials being done here. But then you have to have the kind of, – we’re currently not doing any Phase I trials because we don’t have that kind of infrastructure. (Int.P-R19).

A “tedious” trial, that is a trial that involves the application of technology, may also be rejected on this ground. For example, P-R9 talked of a trial for a drug to be used in pulmonary hypertension. In this trial the pulmonary artery pressure had to be measured, both invasively and non-invasively. It was rejected on the grounds that “first, patients did not want the catheter and second the technology is either not present in our hospital” (Int.P-R9), or the relevant technology may either be too “scarce”, that is, it is not possible to extend the technology required for regular patients to research patients. Sometimes physician-researchers suggest to pharmaceutical company that they should invest in equipment and that would subsequently become hospital property, but the company responds by saying “that the budget is limited” and so the project is rejected.

Although some physician-researchers considered it important to participate in international collaborative research others consider it

more important to conduct "our own research, on diseases that afflict our people". Aware that research conducted abroad may not necessarily represent infectious disease patterns in Pakistan, P-R23 was of the view that local physicians needlessly follow the recommendations they read in western medical publications. Therefore it is imperative to ascertain whether the antibiotic sensitivity patterns of local infections are similar to what is prevalent in "other countries":

> I do not think so we have things which exist in other countries and they [tell] us well now there is Chlamydia and community acquired pneumonia and so we should put anybody [all patients] on clarithromycin; now there are penicillin resistant pneumococci and [we] should start doing this [other treatment]. I think this is not really true for my country. And I think we have different sensitivity patterns and we have different problems than other countries (Int.P-R23).

Due to the lack of local research on wider scale, physicians are influenced by research results from the West, said this physician-researcher, and so prescribe these antimicrobials that are not only expensive but may result in the development of resistant strains, which, according to her, "would be a big problem".

The physician-researchers conducting local research therefore limit themselves to research that provide answers that are of benefit to local patients. The type of research they conduct is to answer:

> Questions which arise during ward rounds to which we don't have clear-cut answers. For example, we get a lot of post-operative fevers and we get fevers in the wards with apparently no known cause, you know PUO [pyrexia of unknown origin]. And we have this issue, whether these patients have liver-phase of malaria which keeps coming up because of diminished immunity. So this is a hypothesis and I

> would dish out- so I think, I feel that, on the whole, the research results would be fairly beneficial directly to the patients (Int.P-R17).

All physician-researchers expressed the need to address "our national burdens" as most essential. These include infectious diseases, cancers, diabetes mellitus and cardiovascular diseases.

6.1.2 ii Care of patients

Physician-researchers were also concerned about which medicine is provided to patients, both in the control arm and the intervention arm of a trial. If a pharmaceutical company compromises on providing standard treatment to the control arm then:

> We refuse trial on these terms. I mean, we just recently even refused a clinical trial on this ground because it was very obvious that they were going to palliate the symptoms but not offer any treatment [in the control arm], so the oncologist refused (Int.P-R19).

Another physician-researcher (P-R18) was of the opinion that trials will not be rejected out rightly, it would be reviewed to asses the risks and benefits, what are the patients being deprived of, and then decided.

After assessing that the patient will benefit from a trial and that the company can provide the standard treatment, then physician-researchers would negotiate with them to provide the same to the local, trial, patients. One physician-researcher said that she had found that, in her experience, pharmaceutical companies conducting active control trials do provide standard medicine to the control arm even when it is not available in Pakistan, because:

> It's not something that they cannot [do]. It's just a matter of doing tough negotiation. And it's something that they suggest themselves; it's not like they are, you know, evil monsters and not willing to do anything. It's, I mean, they would do something as long as it's in their benefit (Int.P-R19).

If there is an established treatment for a disease then it is imperative that patients who are in the control group are provided the established treatment as an add-on. In some cases denying treatment to a patient can cause serious harm such as for example, denying streptokinase to a patient with acute myocardial infarction:

> You know that it has a mortality benefit; you cannot do another trial on it anymore with a placebo, or for aspirin, you can't say, it will be fifty patients on aspirin and not [give] to fifty patients, it cannot be done (Int.P-R6).

I observed that the trials being conducted were either active-control trials in which one group was given the standard treatment for that disease while patients in the intervention arm were given the test drug, or add-on trials in which a placebo was added to the standard therapy for that particular disease, while patients in the intervention group were given the test drug with standard therapy. This, according to physician-researchers, is acceptable as no patient is being deprived of treatment; "there is no negative aspect that we are withholding any drug. So that part at least satisfies you that you are giving the best possible medications to both groups" (Int.P-R1).

> I have only done a placebo-controlled trial in one study that was on acute diarrhoea. So in acute diarrhoea the standard treatment, as at is, was oral rehydration salts [ORS],right, and assessment and feeding and things like that. So when we did that study and we used anti-secretory factor in some patients and ORS in others so there was no ethical problem with that, because normally if they had come in the hospital, they would have received the same [ORS] treatment (P-R23).

> Q: Was ORS given to patients who were getting the anti-secretory factor?
>
> Yes, so one group was given ORS plus anti-secretory factor and the other only ORS (Int.P-R23).

6.1.2 iii Access to proven intervention

Physician-researchers also felt that it is vital that patients recruited into trials should have access to the proven intervention- as medicine or tests- when the research was completed. However, views varied as to whether it should be free of charge or provided at subsidized rates. Some physician-researchers considered it necessary to negotiate with the pharmaceutical companies to give proven intervention free to the patients, for, said P-R19, it is "not something they are going to do for us, we need to negotiate with them."

Even if the medicines, once proven effective, are available in the market, their price is an important concern. P-R16 had stated earlier that three drugs were being used in a trial he was conducting previously and within six months all three were approved and became standard therapy for breast cancer patients all over the world. This was "a good thing" but the problem was the cost, it was beyond the reach of patients visiting these hospitals:

> Here in Pakistan, [these drugs] were too expensive; one drug cost about 40 lakh [Pakistani Rupees four million] per year and the other drug cost about two and a half lakh [Pakistani Rupees 200,000-250,000] per month, and we have to give the treatment for one year (Int.P-R16).

Another physician-researcher remarked that a trial intervention is brought into the market and sold at the market price:

> It [trial drug] is marketed like any other drug and sold at a price that is, you know, the market price. I have yet to see a pharmaceutical company offering all the trial patients free post-trial access to their treatment (Int.P-R19).

Other physician-researchers reiterated that the pharmaceutical company should provide the medicine but the price remains an unresolved issue:

> Yes, it should be made available and the company has promised that it will be made available. The only question which they are unable to answer at the moment and I think it is unfair to ask what the price would be because the price may be too high for the average user in our country, that dilemma still remains (Int.P-R1).

A pharmaceutical company would have no "hesitation in launching that drug in the country, where the trial has been conducted, if the intervention proves to be effective" (Int.P-R17). The problem, this physician-researcher recognized, is with the ministry in Islamabad, which has a lengthy registration process. Having said this, even if it is available the hospital cannot afford to buy the medicine and the price is beyond the reach of the common man too. P-R17 said the medicine is so expensively priced is because of the cost of the research trials:

> Naturally the drugs on which the company spends a lot during trials, their cost is not going to be handy for each and every individual" The pharmaceutical companies pioneer new molecules, they [pharmaceutical companies] have to spend a lot on R & D [research and development] expense has already taken place. So partly they're justified in making them expensive. And partly because in five or eight year's time, their price will be gone [reduced] and they have to earn as much in those five or eight years (Int.P-R17).

According to one physician-researcher, although the pharmaceutical companies do not usually provide cost-free drugs, they do make exceptions on "humanitarian grounds":

> The thing is that when you're doing a trial [on] metastatic [disease] most of your patients are not there once a drug finally does get approved. So it's less of a concern when you're dealing with metastatic [disease] patients because, you know, practically you don't have that many of the patients that are [there] without treatment in the first place (Int.P-R19).

This physician-researcher added that although a pharmaceutical company may be interested in patients' post-trial survival information, once the drug is in the market, companies may say "we are now not actively intervening in that patient's treatment, so we don't have an obligation to provide for that treatment."

A physician-researcher, who was a principal investigator in a trial that showed a drug to be effective, reflected on his primary role as a physician said he would negotiate with:

> The company [to] subsidize it [the drug] for the patients, who have volunteered to participate in the study, and then it is between the pharmaceutical company and patient. The doctor only comes in when the patient have any specific problem (Int.P-R9).

Narrating his experience concerning the availability of Gleevec,[49] P-R 16 added that initially the company provided the drug to the principal investigator to be given to patients "and this went on for two years":

> That was a very good example, I think; the drug which is found to be very helpful for those patients, they have been [given the drug]. I was really amazed that how [a] multi-national company can afford to give the drug in huge amounts to the patients, which is really very useful, and free. But now they have made the availability of the drug a huge problem for the patient; and it is not free; they have to pay for that [though] on a subsidy basis (Int.P-R.16).

[49] Used in patients with Chronic Myelogenous Leukaemia.

One physician-researcher suggested conducting tougher contract negotiations with pharmaceutical, because if a pharmaceutical company knows that a large number of patients will be recruited from a hospital, they would agree to a lot of things. But, usually "what most investigators do not do are tougher negotiations; they just sign whatever comes to them":

> Because, you know, that is not their domain. So they don't know what they can negotiate. And the pharmaceutical companies tend to present a contract as something carved in stone, whereas it is not; it just takes a lot of effort to redraft the whole thing. And it can be done. It is being done – even in Pakistan and not just at Shaukat Khanum (Int.P-R19).

6.1.2 iv Time of negotiations

All physician-researchers felt it was necessary to make interventions, that have proven effective, available to patients but they had different views about when was the best time to negotiate such provisions. One option was to negotiate at the time the contract is being drawn up between the sponsors of the trial and the hospital:

> But I mean it's very, very hard to negotiate on such matters. I mean, we have had a very hard time even negotiating on-trial patient benefits. I mean, getting trial drug is not benefit. That's something that, you know, they'd like to project as a benefit but that is not. And we, you know, we do emphasize this fact. And that's something that- I mean the difference that I've felt in institutions that are experienced in doing contract negotiations – like this institute and Agha Khan also, they give a really hard time to their sponsors when they are negotiating a contract, for the coverage that they're going to offer the patients (Int.P-R19).

Five physician-researchers (P-Rs 6,9,13,14 and 31) however, considered that it would be better to negotiate upon conclusion of the trial, once the effectiveness of the intervention has been established:

> [When you have] done the trial, and you have come up with, the conclusion, once the conclusion is drawn, [because] this is directly related to the results that we achieve, the patient, the company who did it, are willing to cooperate in post study with the participants of the study, but they are also not sure, we are also not sure, whether the drug is going to be beneficial (Int.P-R9).

As stated earlier, local physician-researchers are not well versed in contract negotiations and so tend to accept whatever the sponsors offer, because:

> If we discuss with them before the trial begins the company may not do the trial and take it elsewhere, [so] when the trial is over then it should be [negotiated], to give them [patients] drugs at subsidized rates. I think it should be discussed with the company (Int.P-R6).

According to one physician-researcher, it might be possible for the principal investigators to coordinate "a pressure group" to negotiate post-trial provision, especially if the PI has significant number of patient-participants:

> Say [to the drug company] that the drug is beneficial, and then [now] give it to patients at a lesser cost. They are not going to give it free. But you see [this] is directly related to size of the study, [and] duration of the study. If the duration say is only six months, then the commitment of the company [to the patients] is probably less, [because] they [patients] put less effort. If it is two years trial study then the commitments on the part of the patients are substantial. There is a relationship with the patient and therefore the rapport is something [that develops]. …the benefits ought to be directly passed on to the patient (Int.P-R9).

6.1.2 v Patients' perspective

All patients, likewise, expressed the desire for a proven intervention to be made available to them and to other patients, once the drug has been found to be effective. And some, unsure if the medicine will be

available through the hospital, were willing to buy it from the market; the price, however was a concern:

> I would want the medicine to be available after the trial. I do not know if they will though. But, if they are then I will buy them [medicine] too, if I have to. It depends on the price also. Let us see what happens (Int.Pt.3).

Pt.4 was not responding to a trial drug and had thought of withdrawing from the trial therefore at that time she did not entertain the thought of whether it should be brought into the market. However, when I spoke to her a year and a half later (in March 2012) she had responded to the test drug and was now expecting that the drug will be made available to her and others like her, because in her opinion:

> [Patients] follow every instruction of the doctor to get good results. So I think it should also come into the market [for patients] in Pakistan. The doctor *sāhib* said he will try and get it for us [patients]. When I was in the other trial, the medicine worked but when the trial finished they said the trial is finished and they do not have it [drug] any more. So, I don't know. Doctor *sāhib* said that he will ask the company to make it available for the patients in research but it did not happen before [in the earlier trial] (Int.Pt.4).

After availability of the drug, affordability was a major concern for patients. All patients wanted the drugs to be "brought into the market at a price that we can afford" (Int.Pt.7). A patient narrating why he enrolled into drug trial rather than undergo an operation:

> You see when I had my angiography in 2008 the main vessel was blocked, and the doctor told me that I can have angioplasty then I was told of this trial. I thought that I have only just had a very bad episode of heart attack so why go for an operation on the heart ---I may not come out. You see the fear is always there. Now [December 2010] they have done an angiography and the main vessel is clear. So, I think that because the medicine works well it should be made available to the people and the cost should be according to the buying power of people (Int.Pt.6).

Similar view was of Pt.4 who had benefitted from the trial drug but now in March 2013, was not taking the medicine as the trial had concluded. According to Pt.4 the physician-researcher says they have "talked to the company, but the company says that since the medicine is in the market, it can be bought". But Pt.4 said "it is available at some medical stores but it is too expensive and I cannot afford it as one month's supply of medicine costs 3 lakhs [Pakistani Rupees 300,000] so what is the use of it coming into the market". Other interviewed patients, enrolled in different trials had similar experiences with regards to expense. One patient (Pt.31) said that her husband took out a loan to purchase her initial treatment. Another patient told me that someone she knew had to mortgage their home in order to be able to pay for out of trial chemotherapy:

> The medicine should be within reach of patients. It should be so cheap, so that all cancer patients can buy it without having to borrow money or sell their property. I know of someone who has mortgaged their homes to buy medicine (Int.Pt.9).

6.2 Patient Autonomy

Most physician-researchers' were of the view that obtaining consent from the patient is important since it is the patient's body that will be affected by a trial drug, so the patient, himself or herself should decide whether to enrol in the trial or not. Most physician-researchers consider that they should act as an advisor, not impose his/her decision on patients. However, these physician-researchers acknowledge a difference between theory and practice, saying that the practice in these government hospitals, where mostly non-literate patients come, was very different because there are very few patients

who, as a matter of right, would ask the physician-researcher for details:

> I have never seen a patient who says that okay 'I need this, I want this or [how is] my treatment going. What are you [physician-researcher] doing?' No one ever asked me any question in these six months. They do ask me about the side effects [and] what should I do to get my treatment. But no patient actually comes up and you know force[s] me to tell the details of [his] results and about the therapy that how it is going (Int.P-R31).

6.2.1 Physician-researchers' concept of patient autonomy

Most physician-researchers consider it is necessary to inform patients about the benefits and risks of the trial and therapy, so that they can decide if somebody should intervene with the intervention- medication or surgery:

> So that I can ensure that the patient feels that he/she is empowered in his/her decision and that they don't feel trapped or forced into a study and do not feel taken advantage of (Int.P-R24).

Physician-researchers felt that giving information to patients represented a new departure in medical consultations commenting that, in the past a physician would rarely, if ever, discuss with patients their treatment. Nowadays there is a change in the attitude:

> When I look back about 25 years ago to today, I think there is a difference. [We] talk to the patients a lot more. It is extremely important to define to a patient that what is wrong with them and then discuss their problems, discuss the treatment and then also discuss what the possible consequences are (Int.P-R6).

> When I was young I used to give them my decisions but now I think we should let them make their own minds up, I was enthusiastic then. Now I tell the patient and even suggest to them but the decision is to come from them. Now I never say 'do this' I only advise (Int.P-R23).

Most of the physician-researchers consider that since they have more knowledge of the research trial and medicine than their patients, then the responsibility is on them to guide their patients and communicate medical information to them in a manner that is appropriate for their (patients') level of understanding.

> She [physician] should not force actually, it is definitely that the physician's knowledge is better than the patients, but it should not be imposed on the patient. Don't say "that I know better than you"; that is understood, the physician definitely knows [more], that is why the patient has come to you [physician] (Int.P-R10).

It is important for patients to understand what enrolling in research entails. Once the patient is given information, it is easier for them to understand what is required of them to follow the protocol. Then again although physician-researchers consider it important for patients to know "what is going to happen to them" (Int.P-R12), this awareness is dictated by the literacy status of the patient.

> If [patient] knows, what the thing is, if he is *parhā likhā* [literate] and can understand, then he should be definitely autonomous to make a decision, right, if he doesn't know what it is, then it may be [difficult],[I] mean, main thing is education, awareness … (Int.P-R37).

The interviewees preferred to discuss the trial with the patient because as P-R16 said, "it is the patient who is actually suffering," and whatever medicine that is given it is "the patient who is going to suffer the side effects".

6.2.2 Autonomy and context

The physician-researchers considered that discussions about treatment and research should take place with the patient but reported that in

many instances the accompanying relatives participate in these discussions rather than the patient an experience that is similar to my observations (as described in Chapters 3 and 4). P-R26 said that sometimes relatives "transfer their patient from one hospital to another if they realize that the policy at this hospital is to tell everything to the patient". Then, at the transferred hospital, they inform the new physician why the patient has been transferred here and so would request minimal disclosure of information to their patient. This is not to say that the accompanying relatives are not concerned for the patient; on the contrary, it may be precisely to protect the patient from mental distress or depression that relatives prefer to withhold medical information. This is more likely to be the case if the patient has a life threatening illness:

> Autonomy here in societies like Pakistan, India and like here family oriented societies. Sometimes family does not let you give autonomy to patients… that is the biggest ethical issue you have. A family comes to you in certain cases, and say, 'leave it and don't tell them [patient]', this is there, and that happens when there are life threatening situations like cancers and where they are not going to live much longer (Int.P-R5).

> In social setup like Pakistan I think no patient is autonomous. Their family matters a lot. Patient autonomy is not there at all and even a patient can't take the treatment unless and until their family is willing (Int.P-R31).

Some physician-researchers understand and accept this. In these circumstances the discussion is between the physician-researcher and the family, who then in their "own particular manner tell the patient" (Int.P-R12).

> We think we should tell [the patient], but [for] certain reasons we don't. You see, we are living here; our roots are here, so

> we don't think that this is a big problem. We can understand our social norms and general things. We are following that, and we feel this is may be good for certain patients (Int.P-R26).

Others too consider that families are supportive and joint decisions are useful:

> I think that if the whole family reaches a decision then the outcome is better. This way the patient is not under stress. It is not that autonomy is compromised but it is an option for others to help their patient [in decision making] (Int.P-R15).

I observed during ward rounds and consultations in the outpatient clinics that physicians did not hesitate to discuss a patient's care with the accompanying relative, sometimes out of the hearing distance of the patient.

However, P-R6 stated that although relatives commonly request that a patient is not informed about a bad prognosis, it is nonetheless important for the patient to know, and therefore "I inform them in my own way, bit by bit, not drop it like a bomb on them".

According to seven physician-researchers, (P-Rs5,6,19,23,24,30,33), especially the female physician-researchers among them, exercising autonomy, as these interviewed physician-researchers understood it, was limited and does not pervade society. These physician-researchers represented a segment of population that is in minority and have to adapt themselves to the prevailing norms:

> You know, I'm a woman who is educated, who is working, [and] who is very independent. So, you know, the background I'm reflecting may not be reflective of the general population of this country. I do believe in self-determination. But this might not be true for most of my patients who might not relate to that sense of personal

> freedom. People are used to having others decide for them and, you know, people are also used to making decisions for other people. So you have to, you know, you often have to work in that cultural context where you cannot just come as a foreign authority and maybe impose something that is a completely foreign concept to them (Int.P-R19).

Although these physician-researchers consider patients have a right to determine for themselves what to do regarding treatment or enrolment, instances recur in practice when the local social norms are such that others, particularly relatives, decide for patients. This is especially true of female and elderly patients. This can have an overpowering effect on the physician-researchers' values:

> It happens all the time, I mean for example I am sitting in this chair, I am looking at you and you are the old woman and that's the son sitting over here… He [son] will tell the story, *ammā* [mother] is quiet, so I will talk to the *ammā*, and [she] will not reply. I will talk to the son, the son will tell me everything, [and] then I will say I want to talk to the mother now, so it's my handling of the situation. I would by and large elicit some conversation from the woman…. But yes, sometimes even I have to forget about my views and give in to what is happening (Int.P-R6).

Similarly, I observed in one instance that when a patient was called in for consultation prior to trial enrollment, her husband accompanied her. The patient complained of how her disease was interfering with her daily chores, especially her inability to say her *namāz* (prayers), but her husband insisted that the condition was manageable. The physician-researcher started to explain a test that was required as a preliminary to trial enrollment; the husband asked for an appointment for the required test and ended the consultation. In this instance the physician-researcher was unable to examine the patient or proceed with the consultation.

Although Pt.13 and 17 determined for themselves, as described earlier,[50] though not without consulting their siblings, a few physician-researchers were also of the view that a small number of women make their own decisions;[51] this is not the norm. Physician-researchers reflected that the socio-cultural environment, in which many of their female patients live and were raised, has effectively reduced these patients' confidence to determine themselves what to do. Such women believe that men know best and defer decisions to them; if a husband agrees then so would his wife:

> They don't feel confident making the decision for themselves alone, that is what I think, because we just paternalize them so much that we don't give them the confidence that they can make their own decisions. End of the day that is the structure of the society that we have. But this is more in the lower middle class, [where] women are usually housewives, they don't work, they don't go out of their houses, homes much, may be shopping only … (Int.P-R5).

Other physician-researchers recounted experiences in which they had realized that their female patients felt that by not agreeing with their husband's decision would cause problems for them.[52] In these circumstances, the onus is on the physician-researcher to ensure that the decision made is in the patient's best interest, "much more than it would be in the developed world, because a patient would know her rights there" (Int.P-R19). Here, the physician-researchers felt they sometimes tread on fragile ground, for the husband might feel threatened that a concept of autonomy is being instilled in his wife or daughter and that his status as a man who decides for the womenfolk

[50] See section 4.2.4.
[51] See section 4.1.4.
[52] I described this in Chapter 4 from the physician-researchers' perspective in section 4.1.3 i and iii, and from the patients' perspective in section 4.2.3.

in his family is being undermined. In these circumstances, physician-researchers learn to handle such situations to avoid creating problems for their patients, at times be conciliatory towards the husband and explain the need for examining the patient in private, because an insistence on autonomy sometimes does not work to a patient's benefit.

Moreover, to try and enhance a female patient's ability to be autonomous is not possible because:

> Your social norms are different from the West, your economic conditions are different, [and] your literacy is different. Your religion is different, everything is different, that is why (Int.P-R34).

In the physician-researchers' view it is necessary, keeping local norms and practices in mind, to make policies that are applicable in the local context:

> Because you know they [patients] come from a certain background of values – should I impose my value of autonomy on to them? I mean, this is something that, you know, I don't really agree with. Morality is not something that is new to us. I mean, we do have our values and morals that we can adhere to. But when something becomes something of a fad, you know, we just blindly import it and promoting their [Western] values and we don't really think for ourselves. And that's usually what leads to dilemmas. I mean, you can always achieve a balance. And that's where I think that we need to- we need to have policies of our own (Int.P-R19).

Four physician-researchers (P-R22,23,25,30), recounted instances when women did take charge of situations, such as for instance, when women bring their children for treatment without waiting for the man of the house to accompany them or to give his permission. Five (Pt.7,23,32,34,35) of the female patients discussed earlier too came to

the hospital alone, though not initially. Three of them explained that in the early days of their treatment they were accompanied; one woman was accompanied by her mother-in-law, and the other two were accompanied by their mothers. As stated earlier, in Chapter 4 it was only when they became familiar with the bus (or van) route and the hospital that they felt confident to travel by themselves.[53]

6.2.3 Confidentiality

An issue directly related to autonomy is that of the physician not giving information about "their" patient to anyone else. However, maintaining confidentiality in the local context is very challenging:

> I think that is the confidentiality area because guidelines they say that it is basically the patient's decision until and unless the patient is mentally, you know, incapacitated, but in our setup even if the patient is, you know, mentally okay, she would again ask her husband (Int.P-R14).

I observed, as discussed earlier, that none of the patients objected to the physician-researcher discussing details of the patient's disease or the proposed trial with the accompanying relative. Some physician–researchers explained that patients themselves may be hesitant to speak to a physician in private. For instance, a woman patient is usually unwilling to come into the consulting office without the husband and is more likely to be comfortable if her husband is present.

Similarly, I observed that when one physician-researcher asked a female patient if she wants her husband to be present during the consultation, the patient replied "it is okay [for the husband to be here] because when I have to come for the test, he will bring me. So I have

[53] I explored this in Chapter 4, section 4.1.3.

to tell him why am I going to the hospital" According to the physician-researchers, this practice of women relying on their husbands to discuss their medical cases with physicians, is not restricted to a particular socioeconomic class of patients, nor is it related to the literacy level of patients.[54] Instances where educated women also ask physician-researchers to discuss their medical condition and treatments with their husbands were narrated by this physician-researcher:

> There a few studies- I have done a study, I won't name that study – but, you know, I wanted to have her alone for the discussion because that was a genetic study. Knowing the cultural norms here I was reluctant to tell in front of her husband. Plus it's my ethical duty that, 'see it's a genetic study. And the disease you have it may have a genetic linkage. And it could be transmitted to your children, your daughters'. So I had to convince her that, 'see I would like to maybe, we can have a one to one session'. So - but that was difficult because they were insisting that, 'Why not ask my husband' (Int.P-R18).

Contrary to this, in this physician-researcher's view, maintaining confidentiality is not a problem for male patients. P-R18 went on to state that men mostly attend their hospital appointments alone, similar to my observations, and do not seem to have any "fear of breach of confidentiality"; when the physician – researchers talk to them it is a "one to one discussion"

Six physician-researchers (P-Rs26,29,34,35,39,40) were of the opinion that patients are more at ease when discussing their medical problems with same gender physicians. This was more evident in case of female patients because, as P-R 26 said. "Ladies, in our setting,

[54] See also Chapter 4, section 4.1.3.i.

they don't want to be treated by men" and this is "understandable, considering our society" (Int.P-R 35). Five female patients (Pt.8,29,31,T and G) also said that they want to be attended to by female physicians.[55]

Maintaining confidentiality is a dilemma experienced by physician-researchers not only in their research but also in clinical practice. P-R36 narrated an incident that occurred when he was working in an out-reach clinic (conducted away from the hospital in a rural area). He was examining a young unmarried woman who was accompanied by her mother, and he saw signs of sexually transmitted disease. He was not sure what to do and felt that the patient was not keen to talk, perhaps because the mother was there and also perhaps because he was a male physician. He could not ask the mother to leave for she would not have done so, because as he said it is "just not done here" and there was no female physician during that rotation who could have spoken to the young woman in private. The history of symptoms was sparse; all he could do was to:

> Put her on treatment for [the disease], which I was suspecting [and] she improved. Although I got the same case like that [similar case], he was a male, it was very easy for me to communicate with him I counselled him about his disease and he improved, but regarding this lady, I was very confused, what to do and how to do that. I just put her on medicine and she improved. I just treated the disease. [The] disease vanished and she [patient] also vanished (Int.P-R36).

Issues related to confidentiality were raised at other hospitals too. Three physician-researchers (P-R23,24,25) conducting research to

[55] I explored this in Chapter 3, sections 3.1.5 and 3.2.4.

establish the effectiveness of NESTROFT,[56] recounted how they had to collect blood samples from the immediate family of the patient with thalassemia. The index patients' families were very actively involved in convincing other family members to participate, for they thought this would benefit their relatives, who otherwise would not have had the screening test done. In addition, the physician-researchers and a genetic counselor would offer them advice. When it came to giving the test results, the physician- researchers faced an ethical challenge:

> And [the] main ethical problem which we started facing was, when patients came back to ask us about the results. 'What was [the] result [of] my *khalā's* [maternal aunt's] son?' They wanted to know [the results] of the other relatives and that became a significant issue. We did not tell them, we were perplexed about how to do [deal] with that. What we did is eventually we called them in as [a] group, in one house… and they chose whom to bring. They were then given the results individually [in private]. The understanding was that what ever will be discussed will be discussed here [in this room], and we left it to them to decide [whether to tell others or not]. We did not tell (Int.P-R24).

In the same research project, P-R25 said, some women from these families, who were recently married and living with in-laws did not consent to this test. They were concerned that the results may become known to their in-laws and worried that if the test result is positive it will have dire implications. It was only when the physician-researchers "guaranteed that the test results will be confidential between us [physician-researcher] and them [participant] and there was no way anyone would tell their in-laws, only then the women consented" (Int.P-R25). This is because:

[56] Naked Eye Single Tube Red Cell Osmotic Fragility Test is a screening test for Beta Thalassemia trait.

> In [a] country like [ours], it could happen very easily that males can control the things – and if the woman, say, if she's interested to have it, like, confidential it should not be told to other members, it's out of her control. Because she's so much dependant in a culture like ours, it is a dilemma [for us] (Int.P-R18).

6.2.4 Withdraw from research

Most physician-researchers consider that patients should know that they can withdraw from research at any stage, if they wish to:

> [The] thing is when you get informed consent from patient you have to you are morally bound, ethically bound to tell the patient he or she is free to withdraw from the study project any time he or she may wish. That it is not a bind, not signing a legal contract with the patient (Int.P-R9).

P-R27 said that when or if patients suffer from a symptom that develops soon after being enrolled in a trial then, the patient must be informed that it may be an effect of the new medicine. It is then up to the patient to continue or not with the trial. It is necessary to inform the patients because "in our society people do not know their rights, there is lack of education. They are not aware" (Int.P-R27).

Most patients, when invited to enrol may "not out rightly deny physicians' request; worried that such a denial may have bad consequences", P-R 26 explained that the patient might think by not agreeing with the physician-researcher they may upset the physician-researcher.

There are varied reasons for attrition and the most common is that patients, especially women cannot come because of the distance or there is no one to accompany them or that the family does not permit them to enrol. Most patients who withdraw from research do not

discuss with or inform physician-researchers but either miss the follow-up appointments or do not respond to telephone calls. P-R27, one of the physician-researchers who were of the view that physician-researchers should only provide the information and let the patient decide,[57] said that in order to minimize "dropouts" it is essential to select those who "fulfill the inclusion criteria" and are likely to benefit, and decide themselves to take the treatment, for:

> If I decide for patients then they feel they have to join-but after the first few follow up visits, if they are not convinced [about the trial] they will just stop coming (Int.P-R27).

According another physician-researcher, the issue of non-compliance or "drop-out" has a negative effect on their research. This is because the finances allocated for research are very meagre and if patients do not continue in the trial, then not only is that "drug wasted, but the patient has not benefitted too" (Int.P-R31). So they usually urge the patients that:

> If you think and plan to start then think properly and stick to [research protocol] because we do not have so many finances to keep enrolling new patients. I think this is important that a patient should not drop-out and what I feel is that I always tell the patient that this is a research project it is not like other out patients' clinic being run. It would be a failure for us …a big loss if you just go…. That also reflects like may be this was a failure on our part that we are unable to give the proper understanding of the trial to patients (Int.P-R31).

I observed that P-R 31 explained the protocol of the trial, the time line and the side effects of the drug, namely, weakness, extreme nausea, depression and inability to bear heat, to a patient. Though the patient was eager to start the medicine, P-R31 asked him to "go home and

[57] This was explored in Chapter 4, section 4.1.1.i.

think about it; once you start the treatment then it is a commitment on your part for six months. It would also be good to discuss with others before deciding; especially if you could talk to someone who is already taking this medicine". Another patient responded by saying "no, I have already done so [that is consulted], I want to start [the treatment]" (Pt.25).

When I was conducting an interview with two other patients in the same trial, they narrated that when they started there were many patients who joined but now according to them it seems:

> For the last five months it is only us two [patients] who come. You see the person who gets these injections knows if his body can afford these injections or not. I mean problems like fever, vomiting and pains are not easy to tolerate and so some may stop taking them [injections] (Int.Pt.21).

I observed that some patients know they can withdraw, yet continued in the trial despite no significant improvement in the hope that, since they have tried all other medicines and their condition has not improved, this medicine will help. They discussed it with the physician-researcher, who encouraged them to continue. For instance Pt.4 was advised by P-R13 that since the trial is for duration of two years "so let us use this [medicine] for two years and then see". Seven months later I talked to her and she said that it has been a year now (July 2011) and there is still no improvement in her condition. She was despondent but stated that the physician-researcher had encouraged her to continue. She herself also wanted to continue in the hope that the drug may work. This hope was based on her experience of a previous trial where the medicine "worked then so I am praying it

will work now too" (Int.Pt.4). Her query at this time was "Do you think the company will make some [medicine] for people like us [non-responders]? It is such a big company, is there no hope for patients like us?" Then, she informed me (in March 2012), that after one and a half year into the trial she has responded to the trial medicine and her condition had improved. She attributes her "success" to the physician-researcher's encouragement. She said that the physician-researcher could have said "okay if you want then leave it [the trial]". Now, the trial is over and when I talked to her (in March 2013), and worried that she is not taking the medicine and though the medicine is available in the market but she cannot afford to buy it.

Concluding remarks

Patients attending these hospitals are not aware of their entitlement to information. Although the educated ask questions and get the information, non-literate patients do not. Physician-researchers are aware of the moral imperative of patients' determining themselves what is it they want regarding trial enrolment (and treatment).

Family-centric decision-making is the norm. Some physician-researchers accept these circumstances while others acknowledging its usefulness, find it conflicts with their own value of self-determination. There is dissonance between most physician-researchers' concept of autonomy and local practice. Physician-researchers are sensitive to their patients' social constraints; they are circumspect and seek to manoeuvre the situation in a way that is both congruent with their own values and sensitive to local norms. Another equally important issue is that though most patients value family involvement, it may undermine

their confidentiality. The prevalent norm of family-centric decision-making creates a dilemma for the physician-researchers and they find it difficult to uphold their duty to maintain the privacy and confidentiality of their patients.

Physicians-researchers primary function stems from their role as physicians and the role of a researcher is eclipsed by it. Their research has to fit in with their primary function. So, physician-researchers prefer research that provides answers to the health problems and from which benefits accrue to patients otherwise conducting clinical research is pointless from their perspective, this view is guided by their duty towards patients. Most physician-researchers prefer conducting add–on Phase III and Phase IV as no patient enrolled in the trial is denied "treatment". This raises an ethical issue – the boundary between research trial and clinical care is unclear. Why do physician-researchers consider the trial as an enterprise that benefits their patient? I recognize that this extrapolates from their clinical role as physicians, where treating patients takes primacy, as I discuss in Chapter 7.

Physician-researchers' viewpoint is that research should answer the health problems of their patients. Though they realize that research benefits future patients, they were keen to conduct research that provides direct or indirect benefits to the enrolled patients, who outside of the trial would not be able to afford treatment.

The relationship between the physician-researchers and patients is based on trust. In trials that last for two to three years this relationship

deepens, and patients regard physician-researchers as their doctor *sāhib*. In some physician-researchers view access to the proven intervention also depends on the duration of the trial as in long-term trials patients' commitment is substantial. In addition, patients stated that they followed the instructions of the physician-researcher to get "good results". This raises an ethical issue: whether and what is owed to the patients.

All patients enroll in research primarily to benefit from the trial either in the form of treatment or at the very least to improve their condition. For a few patients an adjunct reason was to help humanity, as I discuss in Chapter 7. Hence all patients and physician-researchers want the proven intervention to be made available by the pharmaceutical company; though some were skeptical. Affordability of the intervention, even if available, was another prominent concern. Though physician-researchers had varied views about whether the intervention should be free or subsidized, most patients were willing to buy it if priced so they (and others like them) can afford it. The necessity of brokering a deal with the pharmaceutical company for making the intervention available to the patient is considered important.

Chapter 7

Discussion

This thesis set out to examine the challenges of fulfilling the requirements for the ethical conduct of research on human participants in developing countries, with particular reference to trial enrolment in Pakistan. My focus was on the two central requirements of ethics guidelines, as discussed in Chapter 1: that of obtaining an informed, voluntary consent from participants, and that of conducting responsive research. On the basis of data collected from interviews and observations with physicians-researchers and patients involved in research trials in Lahore, I described across Chapters 3-5 the challenges of obtaining an informed, voluntary and documented consent from patients. In Chapter 6, I also presented physician-researchers' reflections on the challenges of meeting the requirement of patient autonomy in decision making, on their primary role as physicians, and the issue of responsive research.

In this chapter, I discuss the ethical challenges identified in my empirical chapters and summarized in the concluding remarks of Chapters 3-6, in the light of findings from elsewhere in the developing world and the research ethics guidelines. I draw on the Declaration of Helsinki, primarily because, as stated in Chapter 1, it forms the cornerstone of most research ethics guidelines and the local guidelines- the PMDC and the PMRC refer to it. I also draw on CIOMS since it provides guidance to research in developing countries,

and on the Belmont principles, as they form the foundation of research ethics guidelines. Occasionally a physician-researcher refereed to the Helsinki Declaration in connection with "add-on" trials but most physician-researchers did not refer to the guidelines. These physician-researchers stated that they obtain consent to fulfill the institutional requirement of obtaining consent and so are "guided" by the sponsors.

In the light of these guidelines and my findings I consider the challenges of obtaining an informed, voluntary, consent from patients under three sections: information and understanding; decision making; and documenting consent, in the local context. The fourth and fifth sections consider the ethical implications of physician-researchers' view that they are primarily physicians, and the matter of responsive research.

7.1 Information and understanding

The context in which information is given affects how it is understood, especially among "illiterate and disenfranchised populations" (Bhutta 2004 a:773). In Chapter 3, I identified patients' educational status, the time available for communicating trial information and the attitudes of physician-researchers towards patients' information needs as important contextual factors that result in variation of information provided and patients' understanding of the research. In this section I discuss the implications of these contextual factors for the ethical requirements that patients receive adequate and relevant trial information.

7.1.1 Education

The fact that my patient-participants were a mix of educated and non-literate patients enrolled in clinical trials suggests that trial participation is not dictated by their literacy status, as is also reported from Bangladesh, India and Malawi.[58] However, numerous studies – from South Africa, India, Bangladesh, Nigeria, Egypt, Sri Lanka, Mexico and Thailand – report that patients' education level, scientific literacy and prior exposure to medical research influences their understanding of research trials.[59] It is generally accepted that educated patients have a better understanding while illiteracy and lack of scientific concepts places patients at a disadvantage (Patra and Sleeboom-Faulkner 2009; Dein and Bhui 2005; Lynoe, Chowdhury, and Ekstrom 2001; Adobor 2011). Lack of education is associated with difficulties in understanding trial protocols, even where they are "fairly simple", as reported in a study from India (Gitanjali et al. 2003).

I found that educated patients were generally easy to communicate with and receptive to trial information. Those patients who had some knowledge of science understood "research" (*tehqīq)* as a scientific endeavour to establish the effectiveness of new medicines or diagnostic interventions; they viewed medical research positively, for its potential benefits. Yet some educated patients viewed the trial as an

[58] Patients' participation in trials is more likely to be dictated by their health, stage of disease and their economic circumstances, which may make trial participation the only treatment option (Gitanjali et al. 2003; Lynoe, Chowdhury, and Ekstrom 2001; Mfutso-Bengo et al. 2008).

[59] Van Loon and Lindegger 2009; Kumar et al. 2012; Lynoe, Chowdhury, and Ekstrom 2001; Ezeome and Marshall 2009; Rashad, Phipps, and Haith-Cooper 2004; Sariola and Simpson 2011; Pace et al. 2005; Vargas-Parada et al. 2006.

experiment (*tajarba)* – as something scientists perform in a laboratory on "guinea pigs".[60] This concept is common amongst patients in such varied contexts as the UK, India, Sri Lanka and many African-American patients in the USA.[61] Educated patients were also deterred from enrolling by anxieties about the side-effects of the trial drug; physician-researchers sought to dispel these apprehensions.[62] In a study from India, more literate than illiterate patients refused trial participation (75% versus 67%) (Gitanjali et al. 2003), whereas in a study from Egypt educated women were easier to enroll than illiterate women, who were suspicious of research (Aboulghar 2011). Awareness and understanding of medical research, in addition to education level, is strongly associated with younger age and social class (Flory, Wendler, and Emanuel 2008).[63]

Lack of education is not necessarily a complete obstacle to understanding (Bhansali et al. 2009) but information may need to be provided differently to be understood (Bhutta 2004 a). Undoubtedly education is not a measure of a person's intelligence (Luna 1993; Newton and Appiah-Poku 2007).[64] Intelligence is a global attribute whereas enrolment in research requires specific understanding of scientific concepts (Frimpong-Mansoh 2008). A person may be unable to make medical decisions yet perfectly capable of making decisions

[60] Pt. 12 used the expression, "sacrificial lamb" (Chapter 3, section 3.2.1).

[61] In the study from Sri Lanka, a senior researcher explained how patients may consider themselves "guinea pigs" used by Western pharmaceutical companies, see Sariola and Simpson 2011. See also Corrigan 2003; Mudur 2001; Corbie-Smith et al 1999.

[62] Chapter 3, section 3.1.1.

[63] Another study from Pune (India) aimed at estimating HIV incidence cited illiteracy as an important correlate of lower comprehension of the consent process (Joglekar et al. 2012). See also Hussain-Gambles et al.2004; Dein and Bhui 2005; Hussain-Gambles, Atkin, and Leese 2006 .

[64] See also Jafarey and Farooqui 2005.

related to other aspects of their life. The ethical and practical challenge for researchers, then, is to enable patients with a limited knowledge of scientific concepts and low levels of literacy to understand information about research, often also across language barriers (Hill et al. 2008; Krosin et al. 2006; Jafarey 2003; Kumar et al. 2012).[65]

In Pakistan, English is the language used in medical training. I found that although consultations with patients take place mostly in Urdu, or a regional language, medical terminology is usually English and, lacking equivalents in Urdu or the regional language, is difficult to comprehend by most patients without a scientific background – a problem not unique to Pakistan.[66] I found that patients' understanding can be improved if information and its communication are tailored to meet patients' requirements. Patients' understanding is better when physician-researchers make use of drawings, (as P-R14 did),[67] analogies from daily life,[68] or non-technical everyday language to communicate information. I found that understanding is also better when information is communicated patiently (as P-R31), through the accompanying educated relatives (as P-R13) and if given by same gender physician-researchers - some female patients preferred women physician-researchers. Cognizant of these sensitivities Islamic ethics

[65] In this regard, Flory and Emanuel write: "lower educational attainment…[is] associated with lower understanding. Indeed, the differences in understanding between well-educated and less well-educated individuals outweigh any improvement in understanding from the various interventions" employed to improve understanding (Flory and Emanuel 2004: 1599). See also Lynoe, Chowdhury, and Ekstrom 2001; Tindana, Kass, and Akweongo 2006; Nienaber 2010; Mystakidou et al 2009.

[66] See Molyneux, Peshu, and Marsh 2004; Marshall 2006; Mystakidou et al 2009; Boga et al 2011.

[67] See Chapter 3, section 3.1.3 and 3.1.5; also narrated by Pt.9 in section 3.2.5.

[68] Also narrated by Pt.19 in Chapter 3, section 3.2.5.

prefers a Muslim patient to be seen by a physician of the same gender (Padela and Pozo 2011). It is better too if information is not conveyed all at once in one sitting but over a period of time (as P-R16,19), an observation supported by other studies (Sánchez et al. 2001)[69] and in the ethics guidance (CIOMS 2002,[Guideline 4]; Emanuel et al. 2004).

7.1.2 Time constraints

Effective communication, however, takes time, and physician-researchers had limited time to provide information to patients because of their heavy clinical commitments.[70] Some managed their time efficiently but others struggled, welcoming the respite provided by educated relatives, or by patients not asking many questions. A few physician-researchers felt guilty about having insufficient time to explain information adequately to non-literate patients.

Fulfilling the CIOMS recommendation of discussing twenty-six items of information with participants poses huge challenges (Bhutta 2004 a). Although adequate time and resources should be set aside for informed consent procedures (CIOMS 2002, [Guideline 4, commentary]), it is difficult to allocate extra resources in these hospitals. This indicates a need for alternative strategies for time management, such as used by a few physician-researchers in my study,[71] or for alternative provisions for communicating information,

[69] See also Bhutta 2004; Dein and Bhui 2005; Hyder and Wali 2006.
[70]On average, the physician-researchers see 30-40 clinical patients daily. Similarly, in India clinicians on average see 20-50 patients daily and physician-researchers are not exempt from their clinical duties. See also Thatte and Bavdekar 2008; Prakash and Muthusami 2011.
[71] See Chapter 3, section 3.1.3.

which might entail trial sponsors providing extra resources, or, if this is not possible, involving other staff in teaching hospitals in talking to patients about research (Patra and Sleeboom-Faulkner 2009; Bhutta 2004 a; Malik 2011). My findings also support the view that patients prefer a phased approach to the consent process – giving information "a little bit at a time"[72] - and with substantive interaction with the patient. Research from Tibet, Chile, Ghana, Peru, Haiti, Brazil and Gambia[73] supports this suggestion, which is congruent with ethics requirements (CIOMS 2002, [Guideline 4]).

7.1.3 How much information?

Guidelines require that adequate and relevant trial information is provided to patients (WMA 2008, [Paragraph 24]).[74] To authorize an intervention, the patient should, at the minimum, know their diagnosis, prognosis, the nature and purpose of the intervention, the alternatives, risks and benefits (Beauchamp and Childress 2001). Patients should be able to ask questions and to withdraw from the trial (Belmont 1979).[75] My interviews with patients suggest that most knew their diagnosis, duration of the trial, side effects of the intervention and its purpose which they usually understood as a treatment for their disease. Patients knew they could leave the trial, but physician-researchers discouraged this, a few patients were, nonetheless, unaware they were in a trial.

[72] As practiced by P-Rs 6,14,15,19,26.
[73] Miller et al 2007; Sánchez et al. 2001 ; Hill et al. 2008; Creed-Kanashiro et al. 2005; Fitzgerald et al. 2002; Bento, Hardy and Osis 2008; Yauba et al 2013 ; See also Woodsong and Karim 2005.
[74] See also guideline 4 and 5 (CIOMS 2002); 20.2 (PMDC 2001).
[75] See also guideline 4 (CIOMS 2002); Emanuel et al. 2004.

This variation in patients' awareness of the trial is associated with patients' educational status, time available for communicating information, and the manner and amount of information conveyed. I identified two approaches to information provision. The predominant approach approximates to the "professional practice standard" and the other approximates to the "reasonable person standard" of information disclosure, as discussed in Chapter 1 (Belmont 1979). According to the first standard, physician-researchers, as "professional practitioners" with the knowledge of the research trial, decide what information a patient needs. At a minimum, participants "usually should understand at least what a …researcher believes a patient or a subject needs to understand in order to authorize an intervention" (Beauchamp and Childress 2001:88-89). According to the second, the patient, as a "reasonable person," determines the amount of information necessary (Belmont 1979). I found that in both approaches to information provision, the amount of information communicated varied.

7.1.3.i Physician-researcher determines information provision

Most often the physician-researchers I observed determined the amount of information provided and they consider giving full or extensive information as unnecessary, especially to non-literate patients, patients who are skeptical of research and lacking an understanding of science, and where there is little time available. The guidelines require paying attention to specific information needs of individual participants (WMA 2008, [Paragraph 24]). Physician-researchers felt that providing full information does not guarantee that

patient will understand it all; in fact too much information may overwhelm patients and create confusion. Assuming that scientific information may be overwhelming (Beauchamp and Childress 2001), some physician-researchers were pragmatic and would not "waste time" explaining everything to patients (especially non-literate patients).[76] Imposing extensive information on some patients may indeed be counterproductive (Lynoe and Hoeyer 2005),[77] as it may "short–circuit" reason (Beauchamp and Childress 2001:95), making it necessary to limit the amount of information provided (Sreenivasan 2003; Helgesson, Ludviggsson, and Stolt 2005; Newton and Appiah-Poku 2007).

On the other hand, there were those physician-researchers who consider that "full disclosure" about the trial enhances trust and prepares patients psychologically, and emotionally, for trial participation. This "psychological autonomy" gives patients "some control over their situation" (Cox 2002:36)[78] and serves a practical purpose too: a well informed participant is able to follow the trial protocol better. Although in each case, the ethical dimensions of information provision are set by the physician-researcher providing information to the patient, a generalization of *a* form of information provision cannot be made.

[76] Similarly, physician-researchers may assume that non-literate patients are less compliant because they do not understand the importance of following the trial protocol. However, patients may be unable to attend their appointments for other reasons, such as having no one to accompany them or having domestic responsibilities (Gul and Ali 2010; Murthy et al. 2012; see Kleinman and Benson 2006). There is evidence that adherence to protocols is unrelated to the literacy status (Naeem et al. 2010).

[77] See also Hussain-Gambles, Atkin, and Leese 2006; Epstein, Korones, and Quill 2010.

[78] See also Manson 2010.

The practices whereby physician-researchers, albeit guided by their duty to patients, are pragmatic, for reasons discussed above and tailor the information they give in order to "convince" or "guide" patients to enroll, raises ethical tensions where the accuracy and adequacy of the information provided may be problematic.

Guidelines require that consent is not sought by "unjustified deception, undue influence, or intimidation", but, as seen in Chapter one, they also acknowledge that "the borderline between justifiable persuasion and undue influence is imprecise" (CIOMS 2002, [Guideline 6]; Belmont 1979).[79] The guidance also acknowledges that lengthy details of every aspect of the trial may overwhelm patients (Emanuel et al. 2004), there is a need to create a balance, between what and how much information is necessary for the patient to make an informed decision without being manipulative or making the patient unduly anxious.

To manipulate information such that it places patients in harmful situations, including "withholding information, and misleading exaggeration of information" is ethically (and morally) objectionable (Beauchamp and Childress 2001:95). However, the physician-researchers' use of persuasion in enrolling patients was based on their knowledge of the trial's benefit to patients [80], and this use of the "merit of reason" (rational persuasion) is not precluded on ethical grounds (Beauchamp and Childress 2001:94). Physician-researchers' moral values have an important bearing on their interactions with

[79] See Chapter 1, section 1.3.1.ii.
[80] I explore this in Chapter 4 section 4.1.1.i and Chapter 6 section 6.1.1.

patients – they do not explicitly decide for their patients, but they do attempt to convince patients and encourage them to enroll, on the premise that the trial will be beneficial. [81, 82]

Sometimes physician-researchers phrase the information positively, as offering direct benefits to patients[83] or using more explicit idioms, for instance, "no comparable medicine" or by referring to the trial medicine as a "gift" to the patient.[84] Their intention is based on beneficence, but it may alter patients' perception of the trial (Beauchamp and Childress 2001), since for patients who are unable to purchase the medicine outside of trial the concept of a gift is very appealing. Instances like these create the suspicion that patients are being exploited as a means of obtaining data about the trial medicine. Sometimes individuals are placed in circumstances that make them vulnerable, because without enrolling in the trial there is a high probability that their disease will progress. In these circumstances, the offer of free treatment, leaves patients with little choice but to accept; physician-researchers are not intentionally manipulative when offering trial participation to these patients (Beauchamp and Childress 2001; Brock 2008).

On the other hand, it is ethically problematic for physician-researchers to emphasize a trial medicine's efficacy as a treatment already in use

[81] Towards which as stated earlier, Jonsen writes: "the essence of research is the integrity and vigilance of the investigator" (1998:136).
[82] This is explored in Chapter 3, section 3.1.4 and Chapter 6, section 6.1.1.
[83] CIOMS details the information to be provided to patients. One of the requirements at number 10 is: 'direct benefits, if any, expected to result to subjects from participating in the research (CIOMS 2002, [Guiedline 5]).
[84] This is explored in Chapter 3, section 3.1.4 and 3.2.2.

"abroad" [85] (without explaining that the trial's purpose is to study the long-term effects of the medicine). Likewise, their promises to negotiate with sponsors for post-trial provision of the trial drug,[86] if it proves effective also seem unwarranted, considering that the vast majority of trials (99% of 312 registered trials) do not provide information about post-trial provision of the proven intervention (Cohen et al. 2009). This then necessitates raising the awareness of physician-researchers to the moral imperative of accurate information (Emanuel, Wendler, and Grady 2000)[87] although cautiously, because "one can easily inflate this threat of control by manipulation beyond its actual significance in health care" (Beauchamp and Childress 2001:95).

7.1.3.ii Patients seeking information

Less often patients played a role in determining the amount of information given, but these were usually literate rather than non-literate patients. The guidance is that patients should be provided the opportunity to ask questions (CIOMS 2002, [Guideline 4, commentary]; Belmont 1979), and there is evidence that this aids understanding (Miller et al. 2007). Literature from Pakistan and South Africa indicates that patients do not question physician-researchers about the purpose and benefits of research (Khan 2008), or do so rarely, despite being provided with opportunities to ask questions (Joubert et al. 2003). However, I found that some patients, mostly educated patients, or educated relatives of patients, who had

85 See Chapter 3, section 3.1.4.
86 See Chapter 6, section 6.1.2.v.
87 See also Jafarey 2002,2003; Jafarey and Farooqui 2005; Khan 2008; Jafarey and Moazzam 2010.

background knowledge of the disease and had consulted internet sources and read the consent booklet/form were not content with, or understood fully, the information provided by physician-researchers and wanted more information. By contrast, non-literate patients did not ask questions and relied on the information provided by the physician-researcher.

I experienced a similar difference between educated and uneducated patients when obtaining their consent for participation in this study: the educated patients consented after a brief discussion of my research, while the non-literate patients agreed to participate without indulging in discussions. I found that younger educated patients are also more involved in discussions, as Aboulghar (2011) similarly reports from Egypt.[88] Rajaraman et al write of research participants in India that asking questions is associated with literacy, perhaps because, like my educated patient-participants, literate people are more aware and confident (Rajaraman et al. 2011).[89] Education and awareness about the disease results in an interactive discussion (Qidwai et al. 2013); and patients willing to ask questions are at less risk of ethical violations (Adobor 2011).

Conversely, as stated earlier, most non-literate patients do not ask questions. This may explain why some non-literate patients were unaware they were in a trial. These patients do not ask questions for reasons that might include fear of irritating the physician by asking questions (Kumar et al. 2012) or accepting that physician-researchers

88 See also Lema 2009; Manafa and Lindegger and Ijsselmuiden 2007..
89 Rajaraman et al's research was an observational study on Tuberculosis in infants in South India and consent was sought from parents.

have unquestioning authority (Moazzam 2006). Also, when patients are keen to get "treatment" they tend to disregard information they consider unnecessary (Hyder et al. 2004; Cox 2002; Jianping et al. 2010; Bergenmar, Johansson, and Wilking 2011). A more plausible reason may be that they consider the information they have received already is sufficient. I found that all my patient-participants were satisfied with the information given to them regarding the trials they were enrolled in. A study from Islamabad, similarly report in connection with clinical practices, that although only 40.5% patients (81 patients out of 200) understood the information regarding their surgery, 93.5% (187) were satisfied with the informed consent process (Amir, Rabbani, and Parvez 2009). Another study reports that in Nigeria 15% of patients could not recall being told about the study purpose and 13% said that they were not told, the authors note that education was a significant predictor of patients reporting or recalling being told the purpose of the study (Marshall et al. 2006).

Although information is provided to enable patients to decide if they want to enrol in a trial , it sometimes happens that patients do not want more information to decide, as they have already decided on the basis of previous knowledge (Beauchamp and Childress 2001). I encountered instances when patients had decided to enrol (or not) before receiving details from the physician-researcher, and no amount of information and persuasion would alter their decision.[90]

[90] Experiences of P-R1 and 18; see Chapter 3, section 3.1.1.ii., also see Chapter 6, section 6.2.4.

Sometimes patients do not want much information, commenting "what is there to know?", or have a fatalistic acceptance of the consequences because "that is *kismet* [fate]"[91]. It has been suggested that socially conservative patients prefer less information (Yousuf et al. 2007) and trust their physician-researchers' decisions. It may also be that people who are ill are less able to understand complex information and may consider it burdensome (O'Neill 2002, 2003; Corrigan 2003). Thus a fully informed consent is difficult to achieve in all instances (Verheggen and Wijmen 1996; Corrigan 2003),[92] but from the "fact that actions are never *fully* informed …. , it does not follow that they are never *adequately* informed ….."(Beauchamp and Childress 2001:89, emphasis in original).

What is optimal information is not a settled issue. The pendulum has swung from providing minimal information towards providing too much information – both strategies result in suboptimal information practices. "More information equals better ethics" is an oversimplification; the "quantity, quality and formatting of information" should vary according to the patient (Lynoe and Hoeyer 2005:737).

The ethical imperative is not to "use" the local population in a trial that is of no or little benefit to them (Benatar 2000, 2001; Benatar and Singer 2010, 2000; Glantz et al. 1998; Macklin 2004); my interviewed patients considered they had benefitted from trial participation.

[91] See Chapter 3, section 3.2.2.

[92] Similarly, Freedman writes: "that "fully informed consent" is a goal which we can never achieve, but toward which we must strive. In order to ensure that fully informed consent has been given, it has seriously been suggested that only medical students or graduate students in the life sciences ought to be accepted as subjects for experimentation" (Freedman 1975:33).

7.2 Decision making

In this section I examine the ethical complexities associated with the requirement of autonomy in decision making, in the light of the patient's gender, literacy status, marital status and financial independence, and other actors such as the physician-researchers and the family. In Chapter 4, I identified a conflict between the ethical requirement of autonomy and the fact that patients rely on the physician-researcher or family to decide, in effect employing second-order autonomy, whereby the decision is delegated, or else it is not the individuals' "own" decision but is made by other agents or determined by other factors. In Chapter 6, I showed that physician-researchers think they should be encouraging "independent" decision making not just for itself, but also because this makes meeting the ethical requirement of patient confidentiality easier, these issues were particularly salient in the case of women.

In what follows, I first discuss reliance on the physician-researcher and suggest that while such reliance potentially undermines autonomy, to withdraw assistance undermines beneficence, and I indicate how a balance between beneficence and autonomy might be achieved. I then discuss reliance on the family. I examine the ethical complexities of the requirement to respect social and cultural contexts in which dependence on the family – especially for women – influences and may even determine trial enrolment or non-enrolment and may undermine patient confidentiality. I then indicate how it may be possible to navigate a route that is in the best interest of the patient while respecting their social embeddedness.

7.2.1 Reliance on physician-researchers

Patients generally rely on the physician-researchers for making decisions, perceiving their own role in decision making to be limited and considering physician-researchers to be better placed to decide as other studies have also observed (Cox 2002; Degner et al. 1997). Patients respect their physicians for their knowledge and because they are considered instruments of healing, a belief reinforced by tradition.[93] The suffix *sāhib*, a term used to show deference, is automatically attached to doctor – "doctor *sāhib";* along with the family, doctors play a pivotal role in making health-related decisions.

Trust is integral to the physician-researcher and patient relationship, as indeed it should be (Manson and O'Neill 2007). Most patients chose to enrol because they considered the physician-researcher would only advise enrolment if it would benefit them.[94] A survey from Karachi shows that 63% of 337 respondents considered the researcher to be a patient's benefactor (Jafarey 2006). Other studies have also reported on patient's trust in the physician's decision.[95]

Physician-researchers reported that it is the non-literate patients who rely on them but my observations and patients' interviews show that

[93] It is commonplace for patients to refer to a physician they consider good by saying there is *shifā* (cure) in their hands. Al- Ruhawi in his *Adāb –Al Tabīb* (Practical ethics of the physician) writes: "The philosophers can only improve the soul but the virtuous physician can improve both body and soul." Thus placing the physician in a privileged position (see Levy 1967:9).

[94] Similarly literature from other developing countries also shows that patients enrol in trials because they consider that researchers would only advise enrolment if it is in patient's interest (Sirinivasan and Loff 2006; Lynoe, Chowdhury, and Ekstrom 2001; DeCosta et al. 2004; Molyneux, Peshu, and Marsh 2005; Falagas et al. 2009). See also Patra and Sleeboom-Faulkner 2009; Masiye et al 2008.

[95] See Jafarey and Farooqui 2005; Molyneux, Peshu and Marsh 2004; Agrawal,Goel and Lal 2012; Atkinson et al 2007; Nabulsi, Khalil and Makhoul 2011.

most patients, irrespective of their literacy status rely on physician-researcher for help in deciding, although non-literate patients were more passive and rely solely on the physician-researcher, and accompanying relatives.[96] Most physician-researchers were sensitive to this unquestioning faith, realizing that patient's lack of medical knowledge and the stress of their illness places them in a predicament where they need help and advice, and a detached attitude is unhelpful (Davies and Elwyn 2008; Entwistle, Cribb, and Watt 2012). Most therefore considered guiding and advising patients to be important and that giving information without offering advice is a "wrong approach" (Tauber 2003).

Yet there is a risk that physician-researchers will take advantage of patient's trust (de Melo-Martín and Ho 2008; Lema 2009) and nudge them into making choices the physician-researchers consider beneficial (Miller and Colloca 2011), or manipulate them to choose the "manipulator's [physician-researcher's] conception of patient's good" (Brock 2008:610). However "the number of such reprobates is small", more noteworthy is the physician-researcher's conception of the trial as treatment for their patient (Appelbaum 2002:23).

A few physician-researchers thought they should only provide information about the trial, and that patients can decide themselves.[97] Such an approach is ethically "correct" in that it removes the danger

[96] There exist three broad roles that patients assume in decision making. At one end is the "active role" and at the extreme a "passive role", with an intermediate role which is the "collaborative role" (Degner and Sloan 1992). For other instances, where patients rely on their attending physician and family to decide on their behalf see Yousaf et al 2007; DelPozo and Fins 2008; Sirinivasan and Loff 2006; Corrigan 2003; Irabor and Omonzejele 2009.

[97] This was explored in Chapter 4, section 4.1.1.i.

that a patient agrees to enrol because of the physician-researcher's influence and not voluntarily. But there is more than one way of doing the right thing in real life (Chattopadhyay and DeVries 2012) and my findings show that most patients need help to decide because they lack confidence or because patients may not want to be burdened by difficult decisions (Entwistle et al. 2010; O'Neill 2003, 2002; Corrigan 2003). The dominant view among physician-researchers was that not advising patients is "unhelpful" and a "wrong approach"; they felt that "compassionate" medical practice entails attending to the medical and emotional needs of individual patients, and they should advise, giving reasoned arguments for their recommendations (Chattopadhyay and DeVries 2012; Beauchamp and Childress 2001). This need not affect voluntariness.

The local preference, therefore, is for shared decision-making in which physician-researchers help patients make a choice, thus "an approach that serves the patient best is probably one that promotes a harmonious marriage of beneficence and autonomy" (Chin 2002:155).[98] Autonomy and beneficence can be viewed as being on a "sliding scale", with autonomy at one end and beneficence at the other.[99] During trial participation, the varying phases of a patient's disease and circumstances require varying degrees of beneficence on the part of the physician-researcher. When the patient is unable, or chooses not to make decisions, physician-researchers provide

[98] Rodriguez-Osorio and Dominguez-Cherit write that physicians should offer to share the decision-making responsibility (Rodriguez-Osorio and Dominguez-Cherit 2008).

[99] I borrow this concept from two sources: 1) from 'Principles of Biomedical Ethics' by Beauchamp and Childress where the sliding-scale strategy is discussed in relation to competence and complexity of information (Beauchamp and Childress 2001:74-77) and 2) from clinical medicine in relation to the control of Diabetes Mellitus.

treatment and care; when the patient can or chooses to take decisions then physician-researchers respect this.[100] If the patient's chosen option is at odds with their best health interest, then the physician-researcher must discuss this with the patient, giving reasons. If, and when, the patient is again unable, or does not wish, to make decisions then the physician-researcher takes charge again. The patient trusts that if she needs help in making decisions she will be provided it.[101] Since physician-researchers have an ongoing obligation towards the research participant not just at the time of obtaining consent (Emanuel et al. 2004), it is imperative that they protect patients' best interest when patients are unable to do so themselves (Belmont 1979).

7.2.2 Reliance on the family

Patients in general and women in particular rely on their family. Women, elderly and non-literate patients were usually accompanied by relatives and on whom they clearly relied. This reflects the reality of social life in which individuals are embedded in complex interpersonal webs, which are a vital resource for making decisions (Turner 2009; Kleinman 1995; Westlund 2009). To limit decision making within person-centric rights denies the matrix of relationships in which most persons are embedded.[102]

[100] Similarly, Manson and O'Neill consider that unnecessary paternalism is unwarranted but that paternalism may be ineliminable in certain situations, however that does not mean that when patients are capable of adequate standard of consent that paternalism need be reverted to (Manson and O'Neill 2007).

[101] For example, when Pt.4 was not responding to the trial drug initially, she was urged by the P-R to continue. Later, when she responded to the drug, she was happy that she had followed the P-R's advice. See Chapter 6, section 6.2.4.

[102] For instance in Indian and Chinese society, an individual is deeply rooted in the family and community and in the philosophical sense to a wider universe (Rao 2011; Renzong 2006). A report about consent procedures in a community in India notes

Pakistan is also a family-centered society and joint families are a norm. Typically, brothers and their wives and children live under one roof with their parents, so a household comprises two or three generations. Persons usually define themselves in relation to other members of the family. Their social connectedness is mediated by the family and the family plays a pivotal role in decision-making processes,[103] including health-related decisions. Decisions are often made through consultations with family members even if they are residentially dispersed (Shaw 2000). Although a patient may take the final decision about trial enrolment, the decision is generally a shared task accomplished in concert and conversation with others (Barclay 2000). Mutual consultation (*bāhmī mushāwarat)* is usual for reaching decisions in the local context. The concept of "discussion and opinions *(slaa mashwara)* captures the consensus-based nature of the decision-making process", that prevails in rural Punjab, in which an individual acts "within the ideology of togetherness" (Mumtaz and Salway 2009:1352). Moreover, when overwhelmed by illness patients have a reduced capacity to assimilate complex information and "when feeling lousy" patients will delegate decision making to others or seek their advice (O'Neill 2003:4; 2002).

Patients usually entrust the family with decision making because family relationships are, in principle, based upon ties of affection and care, and values of trust, interdependence and solidarity (Turoldo

that in these communities, "personhood is often defined by one's family, caste, village, or social group" (DeCosta et al. 2004).

[103] This familial relationality is evident in other communities too (Akabayashi and Slingsby 2006; Lanre-Abass 2012; Shaibu 2007; Frimpong-Mansoh 2008; Gilbar and Gilbar 2009; Ito, Tanida, and Turale 2010; Monshi and Zieglmayer 2004; Xiaomei 2011; Khan 2011).

2010). Xiaomei terms family-centered consent decision as "informed consent with the support and aid of the family" (2011:35).[104] South Asian patients in the UK also rely on educated relatives and consider it important to involve their family in decisions (Hussain-Gambles, Atkin, and Leese 2006; Hussain-Gambles 2004).[105]

Since respect for persons entails respecting an individual's culture and values (Belmont 1979; Emanuel et al. 2004), physician-researchers should respect the value that patients give to familial care and connectedness (Renzong 2006; NCoB 2002).[106] The guidelines allow consultations with the family and negotiating "spheres of consent" provided that an individual participant's freedom to decide is not compromised (WMA 2008, [Paragraph 22]; CIOMS 2002, [Guideline 4,16]; Emanuel et al. 2004:934; PMDC 2001, [20.0]). Autonomous decision-making and voluntary enrolment is considered a fundamental standard of research ethics guidelines (Osamor and Kass 2012). Insofar as a person *wills* an action without being "under the control of another's influence" that person acts voluntarily (Beauchamp and Childress 2001: 93),[107] and a person acts autonomously if they act

[104] See also Gilbar and Gilbar 2009.

105 A review of informed consent literature and the implications for minority populations in the USA, also shows that "many minority patients want to involve different decision makers than most majority patients wish to include, and more than medical providers typically allow" (Matthew 2008:156). Another study shows that many Korean-American and Mexican-American patients relied on their family members to decide for them (Blackhall et al. 2001).

[106] Although most cultures are conducive to a person's well being, there are those who argue that in some cultures the potential for individuals to exercise their rights or achieve full potential/ capabilities is restricted (Fagan 2004; Alvarez-Castillo 2002). See also Nussbaum 2000; Shaheed 1994.

[107] Although there are other influences such as "debilitating disease, psychiatric disorder and drug addiction which can diminish or void voluntariness" (Beauchamp and Childress 2001: 93), I, like Beauchamp and Childress, consider the controlling influence of others for the purpose of this discussion.

"intentionally", with "understanding" and "without controlling influences" (Beauchamp and Childress 2001:59).

The assumption in the guidelines is that all patients need, want and should have autonomous control over decisions. An ideal of autonomy insofar as it is "beyond the reach of normal choosers" is not reasonable; in the "practical world" autonomous decision making requires substantial freedom from influences (and substantial understanding) not a "complete absence of influence" (Beauchamp and Childress 2001: 59). Since patients as "persons are embodied, social, and historical" (Childress 1990:13), most patients, as my findings show want to involve other decision-makers and most physician-researchers accept the family's role as central to the decision-making process. Even those few patients, who said they made their own decisions, reached their decisions after consulting their siblings; the decisions may be theirs, but they needed the support and confidence of relatives that the decisions were correct. Hence I contend medical decision-making is not an individual project for patients in Pakistan, as indeed elsewhere, and reliance on the family is an essential support mechanism (Gilbar and Gilbar 2009; Cox 2002; Falagas et al. 2009; Banning et al. 2009).[108] In this case autonomy is clearly relational as it is exercised through relationship with others.

Thus the family's role in decision-making is important, unavoidable and preferred. While engaging with the family it is, however, essential that physician-researchers encourage patients to express their values

108 Family's role in decision making is seen in other cultures too (Akabayashi and Slingsby 2006; Turoldo 2010; Shaibu 2007; Chen and Fan 2010; Dein and Bhui 2005; Ezeome and Marshall 2009; Renzong 2006; Matthew 2008).

and involve them in decision-making. Patients then become more active, collaborative participants rather than merely passive recipients of decisions made by others (Hill et al. 2008). This will help to "engender equality, enable trust, and foster solidarity: these are normative aspirations" (Emerson, Upshur, and Daar 2009:102).

7.2.2.i Gender and family-based decision-making

Though mutual consultations are a common mode of decision making, deferring to others and accepting others' decision also occurs, and such decisions are usually based on trust and the desire to benefit kin. However, there is a fine line between deferring of decision making to others as a rational act and accepting decisions made by others in passivity, which may wittingly or unknowingly cause harms. Low literacy, poverty and the female gender make patients potentially vulnerable to such harms (Begum 2001; Srinivasan 2011, 2010; Macklin 2003 ; Garrafa et al. 2010).

Here I look more closely at the implications of the female gender on decision making. Gender socialization sometimes restricts choices available to women and in it are decision-making choices (Barclay 2000; McLeod and Sherwin 2000). The women patients I interviewed did not feel forced into research and though most decisions were reached after mutual consultations, some delegated or accepted decisions made by the husband or family. When women socialized in a patriarchal society "willingly" assume a "back-seat" in the decision-making process (Jafarey and Farooqui 2005:95), it is not easy to establish whether in this case decision deferred to others is an autonomous choice or whether a decision made by others, but to

which the patient agrees, are of their own will (Kamuya, Marsh, and Molyneux 2011; Bull and Lindegger 2011)[109]. Instances when deferral is an autonomous choice then, albeit heteronomous, it conforms to second-order autonomy; in the instance of simply following the cultural norm, the decision is heteronomous without conforming to second-order autonomy (Childress 1990). Likewise, women may also defer or accept decisions of the family to obviate social harms, such as tensions in family, disharmony in marriage or fear of abandonment (Ho 2006; Mackenzie 2008). Some physician-researchers reported cases where women experienced such apprehensions.[110] A survey from Karachi reports that in the event of a conflict of opinion about research participation between research participants and their family, 74% of respondents felt that if the research participants are men, then their opinion has primacy, whereas only 53% felt this about women (Jafarey 2006). Although in respecting a person's culture, a physician-researcher should respect the patient's family, it does not follow that "oppressive or coercive" practices of a community should be accepted (Emanuel et al. 2004: 932).[111]

I also found that there exists a gender difference in the practice of obtaining permission from spouses. In a Muslim community it is generally preferred that women should obtain permission from their husband (or family) before consenting to enrol in a research trial (Afifi 2007b; Fadel 2010). This extends to her reproductive matters as well (Arafa 2000) and to research enrollment by a pregnant woman (IOMS

[109] This was explored in Chapter 4, section 4.1.3.and 4.1.3.i.
[110] See Chapter 4, section 4.1.3.iii.
[111] See also Benatar 2004.

2004; Fadel 2010). Although a husband's permission does not replace the woman's consent, it is a "sphere" which needs to be negotiated. The rationale is that it maintains a "stronger marital relationship"(IOMS 2004:233); in fact it may act as a protective mechanism against exploitation (Afifi 2007b). Similar experiences have been reported from other settings too. In the Kenyan context, for example, women require the head of household's permission, and a woman who is willing to enrol will not do so without such permission as this would create family problems (Ngare 2007). Women are more likely to do this than men, although a few physician researchers reported that many women did not obtain a formal permission from their husbands and three female patients said that they were independent in deciding (Pt.13,16,17), secure in the knowledge that their family will support their decisions. Likewise in a breast cancer study from Iran, no woman refused participation "due to the lack of their husband's permission"(Bhan, Majd, and Adejumo 2006:39). These instances support my earlier argument that families are usually supportive. Nearly half of the married women in a survey of Nigerian patients reported asking permission from their husbands before enrolling in a study on hypertension (Marshall et al. 2006).[112] While exceptions exist, obtaining permission from the husband is a norm in many developing countries, and is accepted by CIOMS (2002, [Guideline 16]).

[112] Another study from Nigeria shows that nearly one-half (42%) of married women received permission from their husbands, while only 14% of men obtained permission from their wives. These men would have participated even if their spouses had not permitted and two third of the women said the same (Osamor and Kass 2012).

In general I found that physician-researchers accepted the family's role in decision making *but* their concept of autonomy is that trial enrolment should be the patient's decision, because the patient's body will bear the consequences of the intervention. Most physician-researchers felt that they should inform and empower patients in their right to make an autonomous decision, but varied in their views about which patients are capable of independent decisions, some considering that non-literate patients cannot decide for themselves.

7.2.2.ii Gender, health needs and trial participation

There were instances of ethical tension for physician-researchers when a family's decision was not in the patient's interest, for example, when patients, usually women, could not enrol in a potentially beneficial trial, or underwent ineffective treatment, or sought treatment late, not because it was *their* decision but because their ability (liberty) to determine for themselves was restricted.[113] In circumstances like these, forgetting to ask the women affected by these norms what *they* think of such norms (Nussbaum 2000; Macklin 1999a; Fagan 2004), and where this form of (heteronomous) decision-making disregards patients' health interests (and rights), is unethical. Similar tensions are seen in other cultural contexts too (Chukwuneke et al. 2012; Fagan 2004; Gitanjali et al. 2003; Mullick and Serle 2011; Sánchez et al. 2001). In a study of breast cancer patients in India, "most women following mastectomy felt that, had they been involved in decision making they would have opted for breast conservation"(Agrawal, Goel, and Lal 2012:225). Being sensitive to and respectful of an

[113] See Chapter 4, section 4.1.3.iii and Chapter 6, section 6.2.2.

individual's culture does not require uncritical acceptance of norms that compromise patients' best interest and fundamental rights (Emanuel et al. 2004; NCoB 2002 ; Benatar and Fleischer 2007; Macklin 1999a; Benatar 2000). It is ethically imperative to enhance awareness of and sensitize physician-researchers to the need to protect patients where social marginalization, ignorance, political powerlessness, restricted resources and liberty constrain patients' freedom to consent or decline consent.[114]

Financial constraints, high illiteracy and patriarchal norms have been implicated in the downplaying of women's health concerns (Agrawal, Goel, and Lal 2012). Some physician-researchers conclude that more education and economic independence for women would reduce women's dependency, as is consistent with arguments that education contributes to empowering women in all areas of their life (Bento, Hardy, and Osis 2008). A survey from Karachi shows that respondents with a higher level of education were least likely to involve either the father or husband in decision-making (Jafarey 2006).[115]

The implication of women's dependency for trial participation is that women may not be selected as trial participants, unless the trial relates to a women-specific disease, because their circumstances make non-compliance more likely.[116] They may not be able to attend follow-up

[114] See Emanuel et al 2004:933; Guidelines 13 and 16 (CIOMS 2002) and Paragraph 5 of Helsinki Declaration (WMA 2008) and Belmont Report 1979.
[115] Nevertheless, there are few instances when even educated women from higher socio-economic strata follow the local norms (Chapter 4, section 4.1.3.i). In a patriarchal society certain norms are entrenched in the social fabric and it is difficult to be free of them (Shaheed 1986; Fikree and Pasha 2004; Jejeebhoy and Sathar 2001; Shaheed 1994).
[116] Interview P-R 9 in Chapter 4, section 4.1.3.iii.

appointments, because there is no one to bring or accompany them.[117] A report from Nigeria states that some research-designs deliberately exclude women from participating (Chukwuneke et al. 2012).

Brody, raises two concerns: women may be excluded from trial by trial inclusion criteria and insufficient attention is paid to women's specific health needs (1998). I also found that convenience, not scientific or harm-based reasons, restricts women's enrolment into research. This is unethical, as it denies patients access to direct or indirect potential benefits of research participation (Pace, Miller, and Danis 2003; Emanuel, Wendler, and Grady 2000). It violates justice that underpins the core ethical requirement of fair selection of participants and the stipulation of "*fair access to research*" participation (Beauchamp and Childress 2001:227, emphasis in original; see Sherwin 2005).[118] It also has far reaching effects on the validity of trial results because of gender based differences in drug metabolism and toxicity (Schaefer et al. 2003).[119]

I found that some female physician-researchers, who were themselves independent, and strongly committed to being so, struggle with the contrast between their values and the socio-cultural norms prevalent among their patients. Nonetheless, they are sensitive to the socio-

[117] Of the twenty-eight women I interviewed, only five were unaccompanied, and three of these women said they had been accompanied until they became used to coming to this hospital alone. One female patient (Pt.26) said that as no one from her family was available to accompany her she asks someone in her lane to accompany her. See Chapter 4 section 4.1.3 and Chapter 6, section 6.2.2.

[118] See Paragraph 5, Declaration of Helsinki (WMA 2008); Guideline 16, CIOMS (2002).

[119] Excluding women from trials can affect the generalizability of the results of that intervention in women in the general population. This has led to recommendations of introducing diversity (gender and ethnic) of patients at the trial design stage (Coakley et al. 2012)

cultural environment of the segment of society to which their patient population belongs and not wishing to create social risks and harms for their patients, are circumspect and act ethically within locally acceptable norms. This is consistent with the requirement of Emanuel et al's framework (2004) and the Belmont Report (Belmont 1979).[120.]

7.2.2 iii Confidentiality

Guidelines require that participant's confidentiality is maintained at all times (WMA 2008, [Paragraph 11]; CIOMS 2002, [Guideline 18]). Reiterating this, physician-researchers usually make a conscious effort to protect patient confidentiality, but sometimes find this difficult, especially for female patients.

Women and non-literate patients are usually accompanied by relatives/husbands, who were usually educated and easy for physician-researchers to talk to about the patient and patients accept the accompanying relatives discussing matters with the physician-researcher. Just as autonomy is "shared" so is confidentiality, albeit within the confines of the family (Shaibu 2007).

It is also a cultural norm, in a patriarchal society for women to communicate their intention to a male physician-researcher through their husbands.[121] In a study of breast cancer patients in India, "counseling by the surgeon for the type of surgery is usually to the husband as our society is patriarchal and women infrequently participate in the discussion regarding management of their illness"

[120] The Belmont Report states that respect for persons requires individuals with restricted liberty ought to be helped but in a manner that does not create harms – in it are social harms, (Belmont 1979), this is discussed in Chapter 1, section 1.2.1. See also Nuffield Council on Bioethics (NCoB) (NCoB 2002:50-53).
[121] P-R 17 in Chapter 4, section 4.1.3.ii.

(Agrawal, Goel, and Lal 2012:223). In Bangladesh, 70% of researchers considered it important to consult the husband for consent in case of married women (Hossain et al. 2008).[122]

I found that physician-researchers struggle with their duty to maintain confidentiality while accepting the role of the family in the decision-making process. They are aware of the moral imperative of self-determination and equally aware of and sensitive to local cultural norms.[123]

Ethical tensions surround the disjunction between local norms and the guidelines' requirement of autonomous decision-making. Since the ideal of autonomous decision-making is beyond the reach of normal choosers, most physician-researchers consider that any mechanism to reduce this tension must be indigenous rather than "foreign";[124] since there is more than one way of doing the right thing in the real world, a physician-researcher can act ethically but in different ways depending upon a patient's situation in specific socio-cultural context (Chattopadhyay and DeVries 2012). A route that may help reduce this tension would be one that takes account of local values where the social embeddedness of the patients is accepted while also recognizing their moral significance as individuals (Parker 1999; Musschenga 2005). To avoid the abstraction of the guidelines, it is then useful to follow a middle ground (Benatar 2004), that appreciates patient's reliance, emotional (and otherwise) on the family while being

[122] Similarly Irabor and Omonzejele write that consent procedures for married women in Nigeria are different from European practice (Irabor and Omonzejele 2009).
[123] Explored in Chapter 6, sections 6.2.2 and 6.2.3.
[124] See also Jafarey and Moazzam 2010b.

attentive to patient's interests and so simultaneously accommodates the family and engages the patient in the decision-making process.

There are different types of decision-making processes but the shared decision-making process is preferred by most patients (Müller-Engelmann et al. 2013). Many models of shared decision-making have been proposed by for example Lidz et al (1988),[125] Quill and Brody (1996)[126] and the four models by Emanuel and Emanuel (1992).[127] Employing Emanuel and Emanuel's deliberative process and incorporating the relationship-centered approach of Quill and Brody in which the patient, her family (husband) and the physician-researcher engage in deliberations for an outcome that is in the health interest of the patient. This approach will give the husband the confidence that he

[125] Lidz , Appelbaum and Meisel present two models for implementing informed consent ,first is the "event model" where consent is treated as a single event in the treatment process and contrasting it is the "process model"- in which the patient and the physician enter into a dialogue. The authors recommend the latter as it is not just a ritual disclosure of information but "in which both parties engage in a continual dialogue that we call mutual monitoring. This involves ----understanding of the illness, values----and of course, views of the advantages and the disadvantages of the various treatment options" (Lidz, Appelbaum, and Meisel 1988:1387).

[126] Quill and Brody, reflecting upon the shift of medical care from paternalism to "independent choice" claim that the latter has created new problems that are as serious as the former. They then recommend the "the enhanced autonomy model" in which the physician engages in a dialogue with the patient and this is "relationship centred" in which the family may also be included (Quill and Brody 1996).

127 Emanuel and Emanuel present four models: the "paternalistic model", the "interpretive, model", the "deliberative model" and the "informative model" (Emanuel and Emanuel 1992). The "paternalistic model" and the "informative model" are at extreme ends of the spectrum; in the former patient assents to the physician's determination of what the physician assumes is in the patient's best interest, while in the latter the patient is provided all the information vis a vis her disease, treatment options etc. the patient approximates her values to the treatment options and the one that best meets her values is chosen. In this the patient is in charge. Between these two are the other two models: "the interpretive model" and the "deliberative model". The "interpretative model" requires the physician assists the patients in elucidating their values and in determining which therapy best meets those values allowing the patient to ultimately decide. The "deliberative model", the one that Emanuel and Emanuel consider as an ideal, is closely related to the "interpretative model" however here the physician engages in a process of negotiating and attempts to persuade the patient to adopt the intervention that the physician deems best to meet patient goals, i.e. the physician is not a simple information-provider as in the informative model, nor a bystander trying to be impartial as in the interpretive model, but a friend or teacher trying to educate and persuade the patient based on patient's set of values (Emanuel and Emanuel 1992).

is part of the decision-making process and the patient will be able to voice her preferences; “the ethical imperative here is that the well-being of the patient is not jeopardized by others’ considerations”(Malik 2011:45).

7.3 Documenting consent

Once the decision to enroll is made the patient authorizes the physician-researcher to proceed. This authorization, as discussed in Chapter one, has an ethical aspect and a socio-legal aspect; the socio-legal requirement requires that consent is documented.

Physician-researchers consider that obtaining informed consent is important, because patients should know what they have agreed to and preferred a written consent although an oral consent is feasible. In Chapter 5, I showed that though a written consent is preferred, it raises ethical issues. In this section I discuss the practical value of an oral consent before discussing the ethical challenges posed by obtaining a written, signed, consent. However I discuss some useful aspects of written information and indicate alternative methods of documenting consent.

7.3.1 Oral and written consent are complementary

An oral consent is more feasible in communities where literacy is low. In Pakistan the literacy rate for men is 67% and 42% for women (UNDP 2011). I found that patients also prefer discussing the trial with physician-researchers, similar to the conversational style of consent that other researchers have found in low literacy settings (Dawson and Kass 2005; Tekola et al. 2009).

Nonetheless I found that physician-researchers and literate patients prefer a written consent albeit preceded by an oral consent. Thus an oral and written consent complement each other, the printed word reinforces the spoken word. Women in studies from Brazil (Bento, Hardy, and Osis 2008) and Chile (Sánchez et al. 2001) expressed similar views, and in a study from Bangladesh a majority (61%) of physicians-researchers considered that consent should be obtained both orally and in writing (Hossain et al. 2008).

A survey conducted in Karachi on general public and patients who had no experience of trial participation, reports that 39% of 337 respondents were of the opinion that since the doctor-patient relationship is based on trust, and so consent does not require "proper documentation" (Jafarey 2006:S 54). I found that my interviewees likewise said that trust is important but, like the physician-researchers most patients, especially the literate patients, enrolled in trials, want to have everything in writing. Some non-literate patients however were divided on this matter - to a few it did not matter; one considered written (signed) consent unnecessary.

7.3.2 Obtaining a written consent is felt to be mandatory

Most physician-researchers obtain a written consent for two reasons. First, because the sponsors and institutions mandate it, and second it affords legal safety. The institutional requirement of a written consent is supported by research ethics guidelines (WMA 2008, [Paragraph 24]; CIOMS 2002, [Guideline 4]). In fact, CIOMS states that it is the sponsors' and investigators' duty to "as a general rule, obtain from

each prospective subject a signed form as evidence of informed consent", it acts as surrogate evidence that the patient was given information regarding the trial (CIOMS 2002, [Guideline 6]). The PMDC code too states: "it is essential" to obtain a written consent from patients who are to be involved in clinical trials (PMDC 2001, [20.2]).

Obtaining a written and signed consent form to fulfil the bureaucratic requirement may overshadow the moral imperative of *informed* consent. Merely obtaining a signature may also be equated with ethical practice (Jafarey and Farooqui 2005). On this view the procedural use of written consent forms in non-literate communities may be apparent evidence that "autonomy" is upheld; but these patients may have no idea of what they have signed (or affixed a thumb impression) (Chattopadhyay and DeVries 2012), and so informed consent is frequently seen as mere bureaucracy (Takahashi et al. 2011).

On the other hand, physician-researcher may be aware that an *understood* consent and not merely a signature on paper should be the aim (Cash 2006; Bhutta 2004 a), but often times researchers feel compelled to obtain a signature on a consent form. Then the preoccupation of obtaining a signature as "evidence" looms over the entire consent enterprise (Simpson 2011). My experience in the field echoes this (Chapter 2). Others, too, have struggled with the expectation of "study funders and Western collaborators, who required detailed written information sheets and written confirmation of

consent" and to satisfy this requirement, obtained signed or thumb-printed forms (Tekola et al. 2009:e 482).

The second, and the most frequently stated, reason by the physician-researcher and literate patients for obtaining a written (signed) consent is that it affords "legal safety" to researchers, sponsors and the hospital. The interviewees, except for an occasional physician-researcher, do not view it as an authorization from the patient to the physician-researcher; it is a necessary requirement when one attends a hospital. Though physician-researchers consider obtaining consent "empowers" patients, a written (signed) consent is a "box-ticking exercise focused more on offering legal protection to a trial's organizer than actually protecting patients" (Cressey 2012:16).[128]

An occasional physician-researcher[129] was of the view that a written and signed consent form also signals to the patient the "worth" of their signature and denotes respect. In these instances it is then an "authorization" to the researcher to proceed with the intervention (Beauchamp and Childress 2001), which conforms with the moral imperative of respect for person (Emanuel, Wendler, and Grady 2000).[130]

However, obtaining an oral consent does not preclude respect; to show respect does not require signatures. In fact my findings show that

[128] This shift from the trust-based doctor-patient relationship to a law-based legal model has been criticized (Dolgin 2010).
[129] See Chapter 5, section 5.1.2.i.
[130] Emanuel et al conflate respect for person and respect for autonomy and write that "informed consent embodies the need to respect persons and their autonomous decisions. To enrol individuals in clinical research without their authorization is to treat them merely as means to purposes and ends they may not endorse ……" (Emanuel, Wendler, and Grady 2000:2706).

asking for a thumb impression from non-literate patients on a paper the contents of which they do not know is unethical.[131] If, however, the physician-researcher ascertains that patients understand the trial through discussions preceding the signature, then both the ethical requirement, an authorization from the patient, and the socio-legal requirement, as a safety mechanism for the physician-researcher are met. This way both processes complement each other in letter and spirit.

Patients in other developing countries also realize that a signed consent form serves essentially to protect physician-researchers and sponsors.[132] For instance Nigerian patients consider signed written consent "as a procedure that is only there to protect the hospital and the doctors" (Ezeome and Marshall 2009:146).

The extensive detail given in the consent form is an indication of its legal implications.[133] The fact, as my findings show, that the form on which to sign and the information are bound together as a single booklet, conveys the message that, after reading the information a signature is required to affirm that the patient has read or been told about it, especially where a signed consent form is returned to the physician-researcher for their records. Van Loon and Lindegger write from South Africa that researchers termed the consent document a

[131] P-R9, Chapter 5, section 5.1.2.iv.
[132] See Molyneux, Peshu and Marsh 2005; Dawson and Kass 2005; Newton and Appiah-Poku 2007; Molyneux et al 2005; Irabor and Omonzejele 2009.
[133] According to Muthuswamy the industry sponsored consent document usually runs into 25 pages and the language is technical, beyond the comprehension of even educated patients (2013).

"book", which patients do not want; they prefer a "little thing" written in simple language (Van Loon and Lindegger 2009).[134]

7.3.3 Written consent is useful

My findings show that the written consent booklet serves as information tool also.[135] Because of time constraints detailed discussion of the trial is not possible in many instances. It is ethically valid to give the consent form that provides the information to patients, to read or have read to them. But, apart from the very few patients who are educated and want such details, patients generally do not read consent form, because the consent forms are too long and complex (Sharp 2004; Bento, Hardy, and Osis 2008).[136]

I also found inconsistency in the practice of handing over the consent form to the patient, once it has been signed. In these instances the consent form (booklet) cannot serve as an information tool. A report from Nigeria states, that patients in an antiretroviral trial did not have a copy of the information form and so were not able to read the information or have it read (Manafa, Lindegger, and Ijsselmuiden 2007). The consent form would serve well as an information tool, if it were separated into an information booklet (leaflet) and a single sheet of form for signatures. This way, the patient could keep the

[134] The median length of consent forms used in the European organization for research and treatment of cancer's trials tripled between 1995 and 2009 (see Cressey 2012). According to Muthuswamy the industry sponsored consent document usually runs into 25 pages and the language is technical, beyond the comprehension of even educated patients (2013).

[135] See chapter 5. The consent form and the information are bound together as one booklet.

[136] Long, jargony forms mean that many patients have little idea what they are actually signing up to (see Cressey 2012).

information booklet and return the signed consent form to the physician-researcher for their record.

An important purpose a written consent form serves is that it places the physician-researcher on guard not to "short-circuit" or "cut back"[137] on information. Thus, as researchers in a survey commented, the written consent form acts as a script to be followed (Dawson and Kass 2005).

A written, signed, consent form is also useful in instances when patients suffer a side effect and an irate patient or relative accuses physician-researchers of withholding information. The physician-researcher can say that the patient was aware of the side effect and point to the consent form as evidence. So here the advantage of binding together as one booklet the form for consent and the information regarding the trial is that if a patient claims being denied information about the trial, the physician-researcher can show both the information under contention and patient's signature, in the same consent booklet. Instances like these reinforce the socio-legal function of a written consent (Bhutta 2004 a).

7.3.4 Challenges to written consent

Asking patients who are unable to read what is written on a document to sign or affix their thumb impression is insensitive and unethical. Krogstad et al concur with this (Krogstad et al. 2010) and Emanuel et al also query the appropriateness of written consent in a population where illiteracy is high (Emanuel et al. 2004). Similarly, other

[137] Stated by P-R 20 and 19, see Chapter 5, section 5.1.2.i.

researchers working in developing countries consider obtaining a written consent to be "culturally insensitive" in some contexts (Kass and Hyder 2001).

I found that a signed consent form is not evidence of patients' understanding of the information provided, or of their voluntariness. Researchers working in other developing countries have similar views.[138] Patients, attending these hospitals sign or affix their thumb impression on the consent form, or their relatives will sign when asked by physician-researchers, because patients trust them, or because a signature will get them the medicine. Trustworthiness is an attribute that is encouraged in Islam, and trust is a value that pervades my data. Generally patients in the local context believe doctors are their benefactors and rarely question their motives, as reported by others too (Jafarey 2006). A signed consent form is more a sign of physician–researcher's authority and trustworthiness than a validation of participant's understanding (see Pollock 2012). It follows then that if, obtaining a written signed consent is no evidence of understanding or voluntariness and it is unethical, and even a form of "ethical imperialism" to obtain a written consent from non-literate patients (Bhutta 2001),[139] then the requirement of a written consent should be reviewed.

There is another reason for a review of the procedural requirement of written, signed consent. Patients, especially non-literate patients may

138 Mystakidou et al 2009; Manafa, Lindegger and Ijsselmuiden 2007; Ezeome and Marshall 2009.

139 The Nuffield Council on Bioethics (NCoB) also considers that obtaining written consent from illiterate population is inappropriate, it states: "obtaining a thumb impression/ signature from a non-literate person is not consistent with the duty of respect for persons" (NCoB 2002:82).

be wary of signing documents because it has sinister implications for them (Jafarey 2002; Creed-Kanashiro et al. 2005; Marshall 2006; Ngare 2007; Mystakidou et al. 2009; Upwall and Hashwani 2001), I found that "a tight inclusion criterion" of a "consent form to be signed" precludes patients who could not sign or affix thumb impression from enrolling in research for this reason.[140] This violates beneficence and justice, because these patients miss out on research that could potentially benefit them, and this practice contravenes the ethical requirement of fair subject selection. Similar to some female patients, discussed earlier (section 7.2), these patients are not excluded for scientific reasons but for expediency. If it is unethical to enrol underprivileged patients for expediency rather than scientific reasons, or doing so would harm them (Belmont 1979; Emanuel, Wendler, and Grady 2000), it is also unjust to exclude these patients as this violates "*fair access to research*" (Beauchamp and Childress 2001:227 emphasis in original). In view of this Macklin writes:

> An important reason for waiving the requirement for written consent is that some studies involve non-literate subjects. The fact that some people are not literate may not be grounds for disqualifying them and it is certainly not grounds for abandoning an oral explanation and gaining their permission to serve as subjects (Macklin 1999b:30).

Thus moral reasoning requires that when obtaining consent the context in which research is carried out should be taken into account (Krogstad et al. 2010; Benatar and Singer 2000). In this case Emanuel et al's proposition that researchers should use consent procedures that are acceptable in the local community is useful – so, an oral consent is

140 Stated by P-R18 , Chapter 5 section 5.1.2.iv.

acceptable as long as it is witnessed (Emanuel et al. 2004).[141] The PMDC is however silent when it comes to obtaining consent from non-literate patients or those who do not sign, and although the NBC requires researchers to submit the procedure for obtaining and documenting consent for review with the trial protocol (PMRC 2004) but there is no policy guiding alternative consent procedures .

I found that the language of the consent form is another concern that requires attention.[142] Very few patients, who are educated and understand scientific terms, are able to comprehend some information. What my data show prominently is that the information in these consent forms should be easy to read and understand - conforming to the requirement of the PMDC and the PMRC guidelines which state that "non-technical" language should be used (PMDC 2001, [20.2]; PMRC 2004).

The medical terms not only in the consent forms for international research but also the consent forms for local research are in English or sometime transliterated. Even though the translations may be accurate the language used is not comprehensible to ordinary people - a problem encountered with most scientific translations (Shaw and Ahmed 2004). Therefore, as stated earlier, if the purpose is to provide

[141] Similarly, in the US the requirement under the Common Rule is of written consent (OHRP 2009), and Wendler and Rackoff ague that because research funded by the National Institute of Health must follow the US regulation therefore conflicts between signature requirements and patients' inability to or undesirability to provide signatures on the form would lead to not enrolling these patients. So the necessity is to amend the federal regulations (Wendler and Rackoff 2001). Emanuel et al too term the requirement by US regulations as "culturally insensitive in many cases"(2004:935). A recent article in the American Journal of Bioethics argues that the revocation of informed consent by some researchers in certain types of research violates "the most fundamental rights of research subject" (Rothstein and Shoben 2013:34). However, my argument is not to revoke informed consent but to mould it to the contours of the context.

[142] See Chapter 5, section 5.1.2 vi.

information then the consent forms in their present format do not serve that purpose. I found that this is a matter of concern to the physician-researchers who are at the interface with patients and appreciate the problems faced by patients. These physician-researchers make recommendations to their respective research ethics committees, which are not taken on board. As local physician-researchers are both "sympathetic" and have a "full understanding of the local issues", then in keeping with Bhutta's proposal (2004 a:776), and the requirement of collaborative partnership for conducting an ethical research, the suggestions of these local physician-researchers must be incorporated into the design and process of consent (Emanuel et al. 2004; Marshall 2008). An example of such collaboration is evident from a study from Tibet, where local researchers' knowledge of the culture and collaborators' knowledge of the international guidelines results in a consent form that is culturally acceptable and ethically commendable (Miller et al. 2007).[143]

7.3.5 Alternative consent recording and local context

As a general rule the guidelines require a written consent, and the PMDC considers it essential (PMDC 2001, [20.2]), however, CIOMS and the Helsinki Declaration accept an oral consent so long as it is documented (WMA 2008, [Paragraph 24]; CIOMS 2002, [Guideline 4]). Keeping the local environment in mind there should be flexibility in the consent procedures and collaborators should accept alternative

[143] The study was on a traditional Tibetan medicine that prevented obstetrical haemorrhage (Miller et al. 2007).

forms of consent.[144] The onus is on the physician-researcher to obtain an "understood consent" (Bhutta 2004 a; Cash 2006), however, as the discussion shows in case of written consent the responsibility is still that of the physician-researcher.

Different modalities for documenting consent have been proposed, one is audiovisual documentation of the oral consent (Benitez, Devaux, and Dausset 2002; Krogstad et al. 2010; see Petrini 2011; Jafarey 2002). Although this is a feasible alternative, I found that none of the interviewees experienced audio or visual recording of an oral consent. My experience in the field is that consent to visual recording of consent is not easy to obtain - especially in case of women who observe *purdah* (see Chapter 2)[145]- this constraint must be taken into account when planning to use video-recording.[146] Bhutta also considers audio and video-recording as an alternative to written consent, albeit with strict oversight (Bhutta 2004 a).

Considering the local context, and in line with respect for persons, well-planned guidelines for oral consent are necessary. It is also imperative that the PMDC code is amended with details to include

[144]The Times of India reports that because of the allegations of 'using' illiterate patients, some research organizations have decided not to enrol illiterate patients into trials. Although said one trialist "We do not lure illiterate people. In fact, when these illiterate people sign the consent form it is mandatory that one literate guardian has to accompany the person"(TNN 2011).

[145] Also Chapter 5, section 5.1.1.iii.

[146] These incidences reiterate the views of some physician-researchers (P-R 26,29,34,35,39,40) and patients (Pts.8,29,31,Pt.T and Pt.G) that same gender physician-researchers are preferable in the local context, especially in case of women. A study from the UK also shows that women from South Asian community are concerned about modesty and some prefer female trial staff (Hussain-Gambles, Atkin, and Leese 2006; Hussain-Gambles 2004). Further research is needed to understand the extent to which gender of both the research participant, and study team members, influences participation.

alternative processes for demonstrating consent, as is done in other developing countries such as Uganda[147,] Sudan[148] and India.[149]

7.4 Researcher as physician

In Chapter 3, I identified an ethical concern about physician-researchers' tailoring of information where it encourages patients to enroll and in Chapter 6 I showed physician-researchers view themselves primarily as physicians and consider research as an extension of their clinical duties. In this section I discuss the ethical implications of the dual role of physicians as researchers and patients' motivation to enroll in research trials.

Physician-researchers, guided by a sense of duty towards their patients, assess the risks and benefits of a trial and do not hesitate to offer enrolment if they consider the trial is an enterprise for the good of the patient, which is most likely the case with well-conducted trials (Chiong 2011; Mann 2011).[150] Conversely enrolling patients into trials that would increase risks and not provide some benefit was inconsistent with the physician-researchers' primary duty (Kottow 2009). Guidelines also invoke a vigilant researcher to protect the

[147] UNCST 2007:6.4, 6.5; see also Loue and Okello 2000.
[148] Directorate and Research 2008.
[149] The Indian Council of Medical Research, which states: "When the written consent as signature or thumb impression is not possible due to sensitive nature of the project or the participant is unable to write, then oral consent can be taken after ensuring its documentation by an unrelated witness. In some cases, ombudsman, a third party, can ensure total accountability for the process of obtaining the consent. Audio-visual methods could be adopted with prior consent and adequate precaution (ICMR 2006).
150 Echoing the views of local physician-researchers, Braunholtz et al in an attempt to see the "side effects" of a randomized controlled trial (RCT) conclude: "We may, as scientists, gain a little comfort from the (weak) evidence that well conducted trials tend to benefit the participants and do not seem (on average) to result in harm…the conclusion seems stronger where the experimental treatment turns out to be more effective than control, which is difficult to predict, or where there is pre-existing effective treatment that is included in the trial protocol " (Braunholtz, Edwards, and Lilford 2001:223).

health of the patient and to give the patient's well being precedence over all other interests (WMA 2008, [Paragraph 4 and 6]; CIOMS 2002, [preamble]).[151]

Lidz and colleagues conducted a survey to observe the implications of the dual role of clinician and researcher. Out of 741 respondents, one third agreed or mostly agreed that researchers should participate only in trials that are likely to benefit patients (Lidz et al. 2009).[152] Reflecting this, I found most physician-researchers prefer trials that are in the later phases - Phase III and Phase IV trials, and diagnostic interventions. This is because by the time the trial drug has been through earlier phases (I and II), preliminary data may provide some basis for assessing the potential for benefit (Brock 2008; Emanuel, Wendler, and Grady 2000; King 2000).[153] When physician–researchers had such information about a trial and were confident that patients will accrue benefits, direct and/or indirect (King 2000)[154], these "benefit enthusiasts" (Miller and Joffe 2008)[155] persuasively "convince" patients of the same, especially when patients do not

151 See also Paragraphs 3 and 11 (WMA 2008). In the Islamic code of medical ethics too consent from the participant does not remove the "obligations and duties of traditional- doctor-patient relationship (Afifi 2007a).

152 A third agreed or mostly agreed that patients who are not doing well with standard care should be recruited most actively so as to benefit from trial participation. Larger numbers of respondents endorsed ignoring minor clinical trial entry criteria or deviating from the protocol if doing so would be in the medical interests of patients (Lidz et al. 2009).

153 Friedman et al write that since well-run clinical trials are costly, they should be run only when preliminary evidence of an intervention's efficacy looks promising enough to warrant the effort and expense (Friedman, Furberg, and DeMets 1998).

154 King distinguishes three different types of benefits: i) direct benefits from receiving the trial intervention; ii) collateral (indirect) benefits arising from participating in the trial, even when not receiving the intervention; iii) aspirational benefits, which are benefits to society and future patients (King 2000).

155 Miller and Joffe use this phrase for physician-researchers (oncologists) motivated by therapeutic intent , as opposed to 'benefit skeptics' who are mainly bioethicists (Miller and Joffe 2008).

respond to standard treatment or unable to afford standard treatment.[156]

I also found that physician-researchers preferred add-on trials and the Phase III trials they were conducting were add-on trials where the patient is not being deprived of a treatment. CIOMS also, in an effort to minimize harms to control subjects recommend add-on trials, where the trial treatment and placebo are each added to the standard treatment (CIOMS 2002, [Guideline 11, commentary]).[157] This way whether the patient is in the intervention arm or the control arm he or she will be "getting something" and is less likely to be harmed (Vist et al. 2005; Sackett 2005). The expectation is that a drug that has reached Phase III has shown some efficacy and promise as a treatment option, so will bring some relief to the patient; the medicine is, at the very least, no worse than the present available treatment,[158] conforming to the requirement of CIOMS (2002, [Guideline 8]).

Thus physicians, with the self-image of healers, consider that the trial provides care, including treatment, for their patients (Joffe and Weeks 2002; Bailes 2000; Lidz et al. 2009). This therapeutic misconception where physicians view research as treatment-driven is partly because

[156] Similar practice is observed in other developing countries, Edejar, writes in her article of how a clinic in Guatemala city caring for HIV/AIDS patients who cannot afford treatment are enrolled into trials (Edejer 1999). Cleaton-Jones writing on the post-trial availability of antiretroviral drugs presents his ethics review committee's views that it is necessary that trial participant must continue to receive therapy until they cease to benefit or are enrolled into another trial (Cleaton-Jones 1997).

[157] In this regard CIOMS also recommends that the Data and Safety Monitoring Board performs "interim analyses of the data pertaining to efficacy to ensure that the trial does not continue beyond the point at which an investigational therapy is demonstrated to be effective"(CIOMS 2002, [Guideline 11,commentary]).

[158] An analysis of trial protocols states that the primary purpose of the trial is treatment. This along with words like 'STABILITY' in the trial title, or part of the acronym as 'TREATMENT OPTIMIZATION' reinforces physician-researchers' perception of the trial as a form of treatment. See also Lema (2009).

medical research is often understood as continuous with clinical practice (Miller and Rosenstein 2003; Chiong 2010; Appelbaum 2002), especially in oncology. Though this concept of a trial as treatment is contested (Miller and Brody 2007; Miller and Joffe 2011; Joffe and Miller 2008; Miller and Rosenstein 2003), there are calls for raising awareness of patients, especially in oncology, to enrol in trials for treatment (seeBerman 2011).[159] A survey of paediatric oncologists found that physicians prefer their role as a therapist over a researcher and consequently are convinced that by enrolling patients into research they promote child's best interest (de Vries et al. 2011). Some consider that clinical research would benefit from physician-researchers dissociating themselves from their therapeutic obligation (Jansen 2008), because many researchers are likely to perceive that they are delivering clinical care through research and this may mean that researchers may not be able to provide "accurate" information (Goldberg 2011:309).

On the other hand, when separating the physician-researchers' dual role, two things need to be considered. First, separating the two roles is not practicable in case of Phase IV trials and Kottow recommends that Phase II and III trials may also be managed by the treating physician (Kottow 2009). Second, this divergence between research and medical ethics would move patients from under the protection of clinical ethics "from the ward to the lab" (Kottow 2009:162; see

[159] In an interview Dr. Robert L. Comis, Group Chair of the Eastern Cooperative Oncology Group said: "Awareness of clinical trials as a treatment opportunity is quite low at the time of their [patient's] diagnosis and before treatment decisions are made -- in the range of 10%-15%. So the vast majority of patients are never really aware that they might be able to participate in a clinical trial for their cancer treatment" (Berman 2011).

Kimmelman 2008) and patients may be seen as "clinical material, not sick people" reminiscent of the Tuskegee syphilis study (Jones 2008:93).[160] Although this topic is significant, it is beyond the scope of this thesis.

7.4.1 Why patients enrol in trials

My findings show that the outstanding reasons to consent to research were the benefits accrued from research - both the trial process and trial intervention were considered useful (McCann, Campbell, and Entwistle 2010). For most patients this is a compelling reason to enrol.[161] However, there were a few who viewed sympathy for fellow humans (*insānī humdardī)*[162] as an adjunct reason, that McCann et al term "conditional altruism" (McCann, Campbell, and Entwistle 2010).[163] It could also be that patients motivated by personal benefit also understand that research is serving a wider purpose, that of benefit to society (Kim et al. 2009).[164] A therapeutic misconception arises:

> When individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may

[160] See Chapter 1, section 1.2.1.
[161] Most patients enrol for potential personal (treatment) benefits (Corrigan 2003; McCann, Campbell, and Entwistle 2010; Edwards, Lilford, and Hewison 1998; Townsley, Selby, and Siu 2005; Locock and Smith 2011; Paskett et al. 1996; Madsen et al. 2002; Kass, Maman, and Atkinson 2005; Jones et al. 2006; Kost et al. 2011).
[162] See chapter 3, section 3.2.1.
[163] McCann et al term this outlook as "conditional altruism" in which, although people may be willing to participate in a trial to help others in practice if participating in the trial benefits them then it is more likely that patients will consent (McCann, Campbell, and Entwistle 2010).
[164] Some patients enrol for altruistic reasons and also want to help other patients and/or help advance medical science (Corrigan 2003; Wendler et al. 2008; McCann, Campbell, and Entwistle 2010; Hussain-Gambles 2004; Canvin and Jacoby 2006; Locock and Smith 2011; Hussain-Gambles, Atkin, and Leese 2006; Paskett et al. 1996; Madsen et al. 2002; Jones et al. 2006; Kost et al. 2011).

> potentially benefit from the intervention under study or from other aspects of the clinical trial (Henderson et al. 2007:1736).

This conflation between the goals of research and clinical care (de Melo-Martín and Ho 2008), is similar to that reported from other developing countries. From Malawi, research shows the desire to seek medical treatment and better care was the main incentive for patients enrolling in research (Mfutso-Bengo et al. 2008); in Bangladesh patients participate in medical research to have access to services that are not otherwise available to them (Lynoe, Chowdhury, and Ekstrom 2001); in Nigeria the most outstanding reason to participate was personal benefits - 67% wanted to know more about their disease and 30% to get medical care; none cited altruism as a motivation (Osamor and Kass 2012).[165]

This therapeutic misconception is widely prevalent in developing countries, where literacy rates are low and health-care facilities poor, although it is experienced in developed countries too (Appelbaum, Roth, and Lidz 1982; Appelbaum et al. 1987; Bhutta 2004 a).[166] What appears to be common between the two "worlds" is that the patient "transfers to the research setting the presumption that obtains in ordinary clinical treatment: that the physician will always act only

[165] Similarly in another study from Nigeria the major motivation was to obtain medical treatment (Marshall et al. 2006).

[166] Debate on therapeutic misconception is ongoing ever since Appelbaum and colleagues described it in 1982. In that article they narrated about a patient who despite her clear understanding of the process of randomization was unable to apply the abstract to her concrete situation (Appelbaum, Roth, and Lidz 1982). Some argue that the therapeutic orientation of clinical trials, should be discouraged as both clinical trials and clinical practice have opposite aims (Miller and Brody 2007; Miller and Rosenstein 2003; Joffe and Miller 2008; Peppercorn et al. 2004; Miller and Joffe 2011), while others consider them in apposition (Weijer and Miller 2003; Grunberg and Cefalu 2003; Weijer 2003; Kimmelman 2007).

with the patients' interests in mind" (Appelbaum 2002:22).[167] Patients start a prescribed treatment in the clinical setting in the belief that it will work. It is plausible then, that this belief extends to the research paradigm because when patients, are informed of the option of a clinical/medical trial, in which a new medicine will be given by doctor *sāhib,*[168] they may interpret this as a new treatment for their condition (Cox 2002; Kim et al. 2009). This is reinforced when patients, as I found, benefit from the trial, similar to a survey from Nigeria in which 60% of patients stated participating in research is beneficial and 96% did not consider that participating in research had bad outcomes (Osamor and Kass 2012).[169] When outside of trial, the drug is either unavailable, unaffordable (Meropol et al. 2009), or available treatment in government hospitals is limited, trial enrolment may then be a rational choice (Mfutso-Bengo et al. 2008).

7.5 Responsive research

Responsive research requires that research should be relevant to the needs of the local population and should benefit them. In Chapter 6, I showed that research has to fit in with physician-researchers' primary role of physicians and that in some trials there is substantial commitment on the part of patients. In what follows I first discuss

[167] In a recent article on the physician-patient relationship, in the New England Journal of Medicine (2012), Truog suggests that patients need to be informed that the purpose of research is not to optimize their treatment but to gain knowledge that can be generalized (Truog 2012), with some physicians responding that the term "therapeutic misconception" is itself a misconception (Lawson 2012). This however does not apply to early phase trials (Miller 2000; Cousino et al. 2012).

[168] Dresser writes that in this the role of the researcher is also very important. Physician-researcher is dressed in the white coat and the hospital surrounds conveys to patients that they are here to get therapy (Dresser 2002).

[169] Arguably, physician-researchers could perpetuate this "misconception" in the minds of patients regarding the benefits of the trial, for ensuring adequate number of recruitments, this however tantamounts to unethical behaviour (Glannon 2006), yet the physician-researchers are aware of the duty of care owed to the patient and so the threat of control may be minimal.

relevant research, then the necessity and the reasons underpinning post-trial provision of the proven intervention, and the importance of negotiating the provision.

7.5.1 Relevant research

Physician-researchers view themselves first as physicians and, guided by their primary duty, consider that research should address the medical problems of "their" patients, such as dose-optimization studies to suite local population and disease patterns.[170] Their viewpoint, like that of other physician-researchers from developing countries is that research should be conducted on diseases that most commonly afflict local populations (Sastry, McGoon, and Gibbs 2010; Yadev et al. 2011),[171] as is consistent with the ethics guidelines (WMA 2008, [Paragraph 17]; CIOMS 2002, [Guidelines 3and 10]).

I found that physician-researchers are aware of trials that are being brought into Pakistan and that not all of the trials are accepted for reason that include a high risk to benefit ratio, lack of facilities which limits the type of trials that can be conducted in a government hospital and the fact that pharmaceutical companies are not keen on investing in equipment in these hospitals. A new phenomenon are the clinical research organizations who act as the "middle-man" keen to run an efficient trial (Foster and Malik 2012; Srinivasan 2012).[172] Trials that

[170] Lang et al too consider that drugs in developing countries are prescribed in wrong doses and therefore local data are required (Lang, Cheah, and White 2011).
[171] In a survey by Kass and Hyder 83% of the respondents were of the view that the reason for conducting research is the greater prevalence of the disease (NBAC 2001a).
[172] Khan reports that The Trade Development Authority of Pakistan (TDAP) has plans to increase biomedical research business. Aware that multinational pharmaceutical industry is outsourcing the clinical research business and realizing

are being outsourced carry a higher risk than would be permitted in the sponsor's country (Wilmshurst 1997; Mudur 2001), and so physician-researcher prefer trials that have very strict oversight mechanisms.

Some physician-researchers realized that collaborative trials are important conduits for evidence regarding an intervention's generalized applicability and all types of research should be encouraged, so long as patients are selected fairly - on the basis of their appropriateness to answer the research question and will be among the beneficiaries (Belmont 1979).

7.5.2 Why is post-trial provision of intervention necessary?

Although there is growing consensus that at the end of the trial something is owed to patients and communities, there is disagreement as to what that is (Macklin 2004). The stipulation of the proven intervention being "reasonably available" may guarantee a benefit but it does not guarantee a fair level of benefit (Emanuel 2008; Setouhy et al. 2004; Emanuel et al. 2004).[173] Since "reasonable availability" can be expected in Phase III trials in which a proven intervention may become an established treatment rather than early phase trials (London 2008; Countries 2002), I focus on the provision of proven intervention

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the potential of Pakistan to be an attractive venue for contract biomedical research TDAP aims to develop partnerships with international contract research organizations. TDAP plans to attract international outsourced clinical trials into Pakistan and create a network of "well-regulated, ethical and quality contract research activity" (Khan 2008 a).

[173] There is an ongoing debate regarding "reasonably available" (CIOMS 2002, [Guideline 10]) which concerns what type of benefit and "fair benefits" which concerns what and how much of the benefits (Emanuel 2008; Setouhy et al. 2004; Countries 2002; Millum 2011; Gbadegesin and Wendler 2006).

because my data are based on the viewpoint of patients enrolled in Phase III and IV trials.

That research should be of benefit to the researched population is one aspect of the responsiveness principle. One way that can be done is by making the intervention available to trial participants at the conclusion of the trial. I found that all interviewees wanted the proven intervention to be provided because patients needed it, a concern common with other researchers and reviewers in developing countries (Hyder et al. 2004; Shaffer et al. 2006).

There are two reasons for providing post-trial access to the proven intervention. One is practical and the other ethical. The practical reason is that conducting research that will not benefit the patient, either during or after the trial will result in patients querying physician-researchers' intentions and the purpose of the trial This will add to the scepticism that physician-researchers are doing an experiment (*tajarba)* on patients. Similar apprehensions are stated by researchers from Kenya (Shaffer et al. 2006).

The ethical reason is that ethics guidance entitles trial participants to the proven intervention (WMA 2008, [Paragraph 33]) which should be made "reasonably available" for the benefit of the local community. In fact CIOMS requires that sponsors should continue to provide the proven intervention to participants pending its approval by the drug regulatory authority (CIOMS 2002, [Guideline 10 and 21]). In this regard, CIOMS requires that patients should be informed at the outset whether the proven intervention will be available at the conclusion of

the trial (CIOMS 2002, [Guideline 5])[174]. The NBC guidelines also require researchers to share the research results with the study participants and society (PMRC 2004).[175]

The ethical principles that underpin the above requirements are justice and beneficence. Justice requires fairness in distribution, one formulation of which is that each obtains according to their contribution (Belmont 1979; Beauchamp and Childress 2001). Since patients' commitment in some trials is substantial, denying participants post-trial access to proven interventions in environments where such treatments would not otherwise be affordable or available to participants may be considered exploitative (Glantz et al. 1998; Benatar 2000; Crouch and Arras 1998; Shapiro and Meslin 2001; Wilmshurst 1997; Benatar 2001).[176] Exploitation occurs:

> … when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness or dependency of others by using the latter to serve their own ends (those of the wealthy or powerful) without adequate compensating benefits for the less powerful or disadvantaged individuals or groups (Macklin 2004:101).

Equity, based on distributive justice, then "requires that no one group …receive disproportionate benefits or bear disproportionate burdens" (Macklin 2004:70). That is, distributive justice requires that the

[174] A requirement that the Pharmaceutical Research and Manufacturers of America considers constitutes undue inducement (see Macklin 2004).
[175] See Chapter 1.
[176] As stated in my literature review, Emanuel et al write that as a mark of respect for the participants, plans regarding their care should be made. This may either be ensuring access to proven intervention or referring to primary physician (Emanuel, Wendler, and Grady 2008:131). However, in the context where access to treatment is either unavailable or unaffordable, referring to the primary physician may be of no (or little) benefit to the patient (Schuklenk and Gallagher 2007). See also Kottow 2002; Cleaton-Jones 1997; Annas and Grodin 1998.

burdens and benefits of research are fairly and equitably distributed among all involved (Shapiro and Benatar 2005).

I found that in some trials patients' commitment is considerable and they "follow every instruction of the doctor to get good results".[177] In this case, post-trial access is substantiated by another formulation of justice - "justice as reciprocity", which in the context of a clinical trial would:

> Mean that something is owed to research participants even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researchers are able to generate findings necessary to advance knowledge and develop new medical interventions' (NBAC 2001:54).[178]

Although pharmaceutical companies may develop a medicine, its effectiveness needs to be proven otherwise it is not approved for marketing. The only way to tell how well a medication works is to "feed it to a sick person" (Kahn 2006). The pharmaceutical company then needs this biological model to further the development process and in this way patients contribute to drug development. Pharmaceutical companies falsely portray the trial drug as a benefit that they are providing to patients in the trial; rather it is a necessity for the company.

Beneficence supports the core ethical requirement of maximizing benefits and minimizing harms to participants and requires refraining

[177] See Chapter 6, section 6.1.2.v.

[178] National Bioethics Advisory Commission. In recognition of the contribution of research participants in the generation of research results they should receive proportional benefits hence in this case it is reciprocity based on beneficence, which is an act of "making an appropriate (often proportional) return" (Beauchamp and Childress 2001:174).

from intentionally harming participants (Belmont 1979). In fact it requires efforts to secure participants' wellbeing (Levine 2005; WMA 2008; CIOMS 2002). Trial participation by a patient is a trajectory where a patient moves from the clinical paradigm into research and at the conclusion of research back to clinical settings to continue with the treatment which may be the proven intervention or at least another effective treatment (Joffe and Miller 2008). This may be the case in the West, where the proven intervention is available to all trial participants after the trial is ended for as long as it is not yet available through the healthcare system, and there have been calls for the same provisions in developing countries (EGE 2003; CIOMS 2002, [Guideline 10, commentary]).[179] Otherwise, patients who responded to the intervention may be harmed once the trial is over and they have no recourse to the effective medicine (Zong 2008; Lurie and Greco 2005). I found that patients worried about "ill effects" if they "leave the medicine", or patients may feel at a loss if deprived of the new effective medicine.[180] In view of this, the provision of the medicine to patients who improved on it prevents "harm" to these patients (Cleaton-Jones 1997).[181]

[179] The European Group on Ethics in Science and New Technologies (EGE), in its opinion to the European Commission on the ethical aspects of clinical trials by European research programmes in developing countries writes: "In industrialised countries, free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal healthcare system. In developing countries, the same rule must be applicable even if this implies supplying the drug for a lifetime if necessary" (EGE 2003, 2.13).

[180] As seen from the interviews of Pt.3.in Chapter 3, section 3.2.1. and Pt.4 in Chapter 6, section 6.1.2.v.

[181] Zong writes that taking the Indian Council for Medical Research (ICMR)'s clause 'if need be' as a template for provision of intervention. Patients who need it ,should be given it (Zong 2008). However, in the 2006 ICMR guideline specific to drug trials states: "After the clinical trial is over, if need the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the

7.5.3 Negotiations for post-trial access to intervention

I found that patients rely on their physician-researcher to negotiate access to the proven intervention, because their contact is only with the physician-researchers. While most patients were hopeful, some physician-researchers were unsure as are researchers working in other developing countries (Kass and Hyder 2001; Shaffer et al. 2006). This is because post-trial commitments are often vague (Cohen et al. 2009). Even if physician-researchers, especially the principal investigators, negotiate with the pharmaceutical company to provide the intervention, there are no guarantees of provision and even then the price remains a contentious issue.[182]

If a viable plan for access to intervention is not made at the outset, then an aim of the guidelines that benefits are maximized is redundant (Glantz et al. 1998). For this it is important to do tougher contract negotiations to ensure access to effective and affordable intervention (Pace et al. 2006). I found that except at two institutions, these agreements are not effectively negotiated,[183] perhaps because of lack of skill and experience to negotiate (Lavery 2008).

It is important to ascertain the time to negotiate post-trial access and my findings show that opinions vary on it. Some physician-researchers' view it should be "*a priori"*, others too recommend this (Cash 2006; ICMR 2006). Negotiating in advance may help build confidence in the host community and reduce uncertainty (Shah,

patient till it is marketed in the country and thereafter at a reduced rate for the participants whenever possible" [sic] (ICMR 2006:36).

[182] I explored this in Chapter 6, section 6.1.2.iii and 6.1.2.v.

[183] One is Site F and the other institution is not included as my research site.

Elmer, and Grady 2009). Other physician-researchers think negotiations should be at the conclusion of the trial, once the intervention has proven effective. This may be because a commitment to prior agreement may not be forthcoming (London 2008), and may mean the pharmaceutical company takes the trial elsewhere. A power differential between the local researchers and sponsors exists (Macklin 2004) and the golden rule – "whoever has the gold makes the rule" - is evident in these interactions (Cash 2006:S40).[184]

I also found that negotiating the price of the proven intervention is important to my patient-participants, since most of the health care is borne by patients privately (Aziz et al. 2010).[185] Some physician-researchers think the effective intervention should be free; others think it should be subsidized. Patients, realizing that the medicine will not be available free of cost, were willing to buy the medicine themselves, so long as it is within their purchasing power. Countries where national health-care systems are weak or absent, patients do not think they will receive the trial medicine free of cost, but the medicine should be at an affordable price (Sofaer et al. 2009; Pace et al. 2006).[186] A study from Kenya reports that participants felt that a proven intervention should not be discontinued, and if it has to be then

[184] My experience at two sites bears testimony to this. At site A and C physician-researchers were wary of committing to anything without the approval of the pharmaceutical company running the trial. See Chapter 2, section 2.4.2.

[185] In Pakistan, 82% of the total health budget is out of pocket expenditure (WHO 2008). See also Lorenz (2012).

[186] There have been proposals for setting up of funds to target clinical health research needs of developing countries as the Global Health Research Fund (GHRF) (Garrafa et al. 2010). Borrowing from this I suggest a common pool of funds contributed to by all pharmaceutical companies conducting research wherefrom finances are used for patient treatment /education. Another is to provide shares for that particular medicine to enrolled patients who contributed to its development. This, I realize is a simplified suggestion and needs to be worked out on economic principles.

patients viewpoint was that it should be made available through other means or at subsidized cost (Shaffer et al. 2006).

Availability of intervention is limited because of pricing and supply issues. Either it is too expensive or the supply is intermittent. If the medicine is expensive these patients cannot buy it. Here again the spectre of exploitation raises its head. Although the research question is relevant to these patients' disease, and the proven intervention is available in the "market", it is available at a price that these patients cannot afford.[187] Hence these patients are precluded from being "among the beneficiaries of subsequent applications of the research" (Belmont 1979; CIOMS 2002); only those who can afford the medicine will benefit. Here then, Schuklenk's concern of arbitrary interpretation of the guidelines is valid (Schuklenk 2004). Moazzam appeals to physician-researchers' moral responsibility towards their patients for, she writes, "the crux of the matter is that [pharmaceutical] industry must increase profits for shareholders and physicians must protect the interest and welfare of patients above all else"(Moazzam 2012).

To overcome supply issues a collaborative effort, where collaboration is equal partnership between the researchers, sponsors and local health ministry is important, so that there is a sustainable flow of the intervention (Molyneux et al. 2012; Mulholland 2001; Ashcroft 2005). Ad hoc remedies are unsustainable[188]. Bhutta's recommendation of bringing about a change in the local health-care by the research

[187] See Chapter 6, section 6.1.2.v.
[188] The Declaration of Helsinki, which is undergoing a revision at present (2013) states this point too.

community (and the government) negotiating post-trial provision on behalf of the local population is useful, the case in point is the Hib and Hepatitis vaccine trials (Bhutta 2002).[189]

The consequences of negotiating and providing post-trial access to the proven intervention will have practical implications for research. First, when patients know that the trial intervention, if proven effective will be available to them at the end of the trial they would follow the research protocol diligently. Second, it is necessary to observe the new medicine's effectiveness in the "real world" over a long period of time (Lang et al. 2006). That is, post-registration, Phase IV, surveillance. In this case continuing to give the new medicine for another couple of years to the same patients who as trial participants have already used it for 2-3 years would help to receive results of post-launch surveillance earlier, than starting anew on other patients.

Although it is said that researchers are not responsible to make up for what the government should provide, they can act as "a catalyst for change" (Cash 2006:S40). An example of this is the *Gadchiroli* trial discussed earlier. In that trial, researchers, guided by the Declaration of Helsinki (WMA 2008, [Paragraph 17]) implemented the proven intervention as standard care. The principal investigator of the trial, Abhay Bang, writes:

> As an ethical responsibility, we have continued care in these 39 intervention villages until today, 11 years after the original trial was over in 1998. We considered that the situation in the "control" villages represented the situation in the rural areas of Maharashtra state and in India as a whole and it was our responsibility to change it once the HBNC trial had shown

[189] See Chapter 1, section 1.3.4.

> that the approach was effective. Hence, for the last 11 years, we have strived to influence policy at the state and national levels to incorporate home-based newborn care in rural areas and among other steps one important step is that in the 11th Five Year Plan has introduced the HBNC in 250 districts of India (Bang 2010:13).

Summary

In this chapter I have discussed my findings in the light of ethics guidance and literature from other developing countries. I found variable challenges to the application of some of the ethical requirements that, though common with other developing country settings, play out differently. I showed that these challenges arise when guidelines are interpreted without paying attention to the context in which research is conducted. My research shows that awareness and sensitivity to local norms is important. In this certain practices need to change while others need to be enhanced.

I show that there is variation in the practice of providing information. The physician-researchers struggle between the expectations of patients and the requirements of international informed consent practices. However, it is important that physician-researchers' awareness of obtaining an understood consent from participants is enhanced and one way is, training in ethical reasoning. This ethical reasoning should be informed by, and respectful of, local norms. This training in communicating information and ethical reasoning can be provided either at the undergraduate level through the curriculum or during post -graduate training, through workshops.

I also show that when obtaining consent, sensitivity to the relational spheres of the trial participant is not only important it is an ethical

prerequisite as well. A balance (middle ground) between autonomy and beneficence can be achieved such that patients' trust and reliance on physician-researchers are maintained. Another imperative is to work within the local socio-cultural environment to ascertain the willingness of the participant for trial enrolment. A modus operandi can be to have a shared decision-making process in which the physician-researcher draws the patient into discussions regarding matters pertaining to them, and also the family, so that the family (or husband) does not feel alienated, which may result in social harms for the patient.

In the local context an insistence on a written signed (or thumb impression) consent form from non-literate participants is not only unethical; it precludes patients who do not or cannot sign. The procedural intransigence on the part of the physician-researchers, to meet the sponsors' and ethics committees' requirement is evident in these instances. An approach that takes into account patient's inability or "fear" of signing consent forms is necessary; alternative forms of recording consent can be worked out that are flexible and at the same time, ethical.

Similarly, when and if, at the end of the trial the sponsors make the proven intervention "available" in the market but the price cannot be afforded by the trial participants, who contributed to the intervention's development. Arbitrary interpretation of guidelines reduces their moral force. Hence interpreting these guidelines in a manner that the moral imperative is not undermined is essential. Otherwise, although the guidelines' "requirements" may be fulfilled, the spirit of ethics is

missing. Physician-researchers' suggestions regarding the format for obtaining consent, language of the consent form and post-trial provision of the proven intervention at an affordable price, should be paid attention to as they know the realities on the ground, and is congruent with the ethics of collaboration. Physician-researchers should be able to negotiate these with the research ethics committees and trial sponsors (either directly or through ethics committee members).

On the other hand, I also showed that valuing local norms and culture does not mean uncritical acceptance of these norms and values. There are instances when these norms violate fundamental rights of patients. Though changing these norms is essential, it should be from with in.

Whether the patient-participants are exploited, manipulated, persuaded or convinced about trial enrolment and whether research participants are selected fairly or for expediency, is dependent on the person at the interface with patients - the physician-researcher. Physician-researchers' awareness of the requirements of ethics and the local socio-cultural norms places the onus of ethical research on them and thus I reiterate that it is necessary to enhance their ethical reasoning, which is sensitive to the local culture and respects local norms.

Conclusion

This thesis contributes to contemporary, empirically informed, discussion of the challenges to fulfilling the requirements of ethical guidelines for research on human subjects with particular reference to Pakistan. I have focused on two key requirements; obtaining an informed voluntary consent and ensuring distributive justice. These require that patient-participants consent to research in an informed manner, and that the burdens and benefits of research are distributed justly. These requirements hold true wherever research is conducted. However, there is disagreement over what constitutes the essential requirement of informed consent in different contexts and also what constitutes fair benefits.

In order to inform these debates, my research provides data on "indigenous" practice relevant to meeting these requirements from the viewpoint of those involved in research. I explore the views, experiences and practices of physician-researchers conducting research trials in tertiary-care hospitals in Lahore, Pakistan, and the patients attending these hospitals who are recruited into these trials. For this I used qualitative research methods based on interviews and observations, which are well suited for an exploratory process.

My findings show an understanding of the context in which research is conducted is important and that some aspects of the application of the requirements for informed consent and responsive research raise ethical concerns that are shaped by the local socio-economic and

cultural environment. It also emphasizes sensitivity to local culture and respecting local norms that do not trespass fundamental rights of patients. I found notable variation in how much information is provided to patients and patients' understanding of this information. Education in general, knowledge of science in particular, as well as physician-researchers' communication skills and the time available for consultation influence this process. Education influences understanding by making communication easier and quicker. If time is available and if the information is given in simple everyday language, most patients, including those who are non-literate, understand it better.

Time constraints, patients' skepticism about research and the fact that non-literate patients are especially dependant on physician-researchers, influence the provision of information. The physician-researcher usually determines how much information is provided. In this case, the practice approximates to the "professional practice" standard of information provision, according to which physician-researchers, aware of the moral imperative to respect patients' ability to comprehend the information, make judgments about how much information is necessary. Most physician-researchers adopt a pragmatic approach to information, tailoring it to the circumstances and their own assessment of the patient's information requirements; few provide full disclosure of information. Less often, patients are proactive in seeking information and the practice approximates to the "reasonable person (patient)" standard of information provision. Educated patients and relatives accompanying patients are more

aware, confident and proactive than non-literate patients who are more inhibited and rely on the educated accompanying relative. Patients' understanding of the purpose of research was variable but at a minimum they knew their diagnosis, the duration of "treatment" and side effects of the medicine. Most patients knew they are entitled to withdraw from the trial; the few who considered doing so were encouraged not to.

Research ethics guidance require adequate and accurate information to be given. Although most physician-researchers are aware of the importance of this, and some employ various strategies to communicate the information; in view of their pragmatic tailoring of information it would be appropriate to enhance physician-researchers' awareness of the importance of providing accurate information, which can be done by conducting training programmes for physician-researchers. This is vital for maintaining patients' trust in the research enterprise. Importantly, the commitment of those conducting research and at the interface with patients determines the ethics of research trials.

As time seriously constrains information provision; though a few manage it efficiently, it might be appropriate to involve other members of the staff in these teaching hospitals in the process of discussing trial participation with patients. This would improve patient's understanding and build local capacity. Such a strategy is necessary if providing information is to fulfill its main purpose, which is that patients *understand* the information before they decide whether or not to consent to research.

Meeting the requirement that patients make an autonomous decision about research enrolment raises complex questions about the nature of autonomy where decisions are usually shaped by interactions and views of other actors besides the patient, especially the spouse and also the physician-researcher, and factors such as age, gender, education and financial independence.

Patients rely on physician-researchers for their knowledge and trust them to give advice that will be in the patient's best interest. The physician-researchers are cognizant of the trust placed in them but vary in their responses. Some guided by a sense of moral obligation as medical knowledge bearers, decide or advise patients. Others do not, for fear of acting unethically by offering advice that may influence the patient's decision, but by so doing fail to appreciate that patients generally desire advice and support, and in this case are likely to seek advice from other physicians. There is tension between autonomy and beneficence. The ethical dimensions of these practices are ascertained by the physician-researcher at the interface with the patient.

A balance between beneficence and autonomy would therefore be appropriate here in which decision making is shared between patients and physician-researchers. Beneficence is called upon when necessary and patients decide autonomously when they can.

The family plays a prominent role in patients' decision making in general, and women's decision making in particular. Commonly decisions are made jointly by mutual consultation; decision making is not an individual project. Sometimes husbands decide for their wives

and women accept their decisions and at times women defer decision making to their husbands or family. The family usually plays an important and beneficial role by providing emotional and financial support. In case of non-literate patients reliance on educated relatives is prominent. Thus dependency on the family is common and many times preferred.

Most women attending these hospitals also rely on men – husbands, fathers, and sons for financial support so these men must be willing to pay for medicines, diagnostic tests and travel to the hospital. For this reason, women were usually accompanied by a husband or son, who was usually more involved in the discussions with the physician-researcher than the patient herself. The degree of such dependence influences the degree of patient involvement in enrolment decisions. Men, on the other hand, are more independent economically, and this extends to their decision making.

The vulnerabilities associated with low literacy and poverty compromise patients' access to trial enrolment in ways that are particularly manifest in the case of women. Poor and uneducated patients, especially women, may be unable to access research because they are not approached by physician-researchers for enrolment, or may not be allowed by their families to seek treatment, or seek treatment late or seek alternative treatment. Ethical challenges arise where women's liberty is restricted to the extent of damaging their health. Additionally, some local physician-researchers are reluctant to enrol women into trials because doing so adds the extra burden of having to involve the husband in the decision-making process,

whereas men can be enrolled directly. Women therefore are being denied the potential benefits of research, while the generalizable validity of trial data may be questionable if women are substantially excluded from trial enrolment. My research has highlighted this issue, however further research is needed to know the extent to which women are excluded from trial participation.

Although physician-researchers are aware of the moral imperative of patient's right of self-determination and are sensitive to local values, it is important to enhance the practice of encouraging patients to be active in the decision-making process. Research ethics guidelines consider self-determination has primacy. However, autonomy, voluntariness and confidentiality in the local context acquire particular meanings that reflect the relationality of social life, and may need to be negotiated through the "spheres" enveloping the individual. Although areas of tension exist between ethics guidance and local practice, the mechanisms for reducing these tensions must be "indigenous" in harmony with the local norms, rather than "foreign".

To address these issues an approach is needed that respects and maintains patients' emotional connectedness to their families while enabling them to voice their concerns. This would help realize the spirit of research ethics guidelines while being sensitive to the local culture, since the interpretation of guidelines should be guided by both moral reasoning and sensitivity to the context. This would give the family the confidence that they are a part of the decision-making process and patients a chance to voice their concerns.

The varied practices observed in the processes of information provision and decision making recede into the background when it comes to documenting consent. Although written and oral consent complement each other, and oral consent is both feasible in these hospitals and is ethically adequate, a written (signed) is considered mandatory in the local milieu because the sponsors, guidelines and research ethics committees want it.

While one can understand the apparent necessity of a written “proof”, this proof does not imply that a patient is enrolling voluntarily, or has received the information and understood it. A carefully formulated policy could also regulate an oral consent. Insofar as a written consent serves as an information tool or script to follow for providing adequate and correct information to patients, is a valid reason to prefer a written consent. But the outstanding reason for obtaining a written consent was that it is a formality that affords “legal safety” to physician-researcher and the hospital, and is documentary “evidence” that the trial was discussed with the patient. Consent obtained only for this purpose fails to meet the moral requirement of the guidelines because now it is a “mere formality”.

A prerequisite for ethical research is also that it entails collaboration between local physician-researchers and trial sponsors and is not hierarchical but based on equality. Thus when physician-researchers, recommend modifications to the consent forms and the consent process they should be acknowledged, in the true spirit of collaboration.

An important concern that my research highlights, and needs further exploration, is that the “tight inclusion criterion” of a written and signed consent excludes from research patients who do not or cannot sign or affix a thumb impression. Such patients are excluded from research not on scientific grounds or because of risk of harm but for expediency, as is also true for other reasons in the cases of women mentioned earlier. Although the overarching ethical imperative is that patients are not exploited, nor should they be deprived of the potential benefits of research, and so in keeping with the principle of justice, both should be avoided. Moreover, obtaining a thumb impression of a person who is unable to read what is written on the paper is ethically tenuous.

It is ethically imperative that consent, whether written or oral, is truly informed, so an ethically obtained oral consent is appropriate in many instances. However, this does not preclude obtaining a written consent where feasible. A flexible approach would help mitigate this situation. Nevertheless, whether consent is written or oral, there needs to be more awareness among those responsible for obtaining consent that it is imperative to obtain a truly informed consent - one that is understood.

Physician-researchers working in these tertiary-care hospitals viewed the doctor-patient relationship as primary and most of them considered research an extension of their role as physicians. They preferred research that addresses the health problems of their patients because this is consistent with their primary duty as physicians to care for their patients. Physician-researchers generally recommend trial enrolment

to patients if they are confident that research participation will provide benefits for patients. In this sense, the physician-researchers suffer from a “therapeutic misconception” about research - a phrase widely used in regards to patients who misconceive or mistake trial participation as treatment.

The outstanding reasons to consent to research were the benefits to be accrued during and after the trial. Patients considered both the trial process and the trial intervention to be useful. As stated, a therapeutic misconception amongst patients is widely prevalent. Although it is important to dispel this misconception, it should be understood in the context of local circumstances. Separating the two enterprises - clinical therapy and therapeutic trials – is not easy, especially when patients find they benefit from enrolling in a trial because outside of the trial, treatment is either unavailable or unaffordable.

Local physician-researchers and, more importantly, their patients expect the proven intervention to be provided at the conclusion of the trial, and is consistent with the principles of beneficence and justice, and the ethics guidelines. This, however, is the responsibility of the trial sponsors and the local government who need to collaborate in order to make affordable access to these interventions possible. In these negotiations, physician-researchers, congruent with their primary duty as a physician, can act as a catalyst, if, as mentioned earlier, there exists a partnership between local physician-researchers and sponsors.

There are limitations to this research in that the viewpoint of patients who did not enrol in research was limited. There is also need to do further research to substantiate the views of physician-researchers regarding non-enrolment, particularly in the case of women and of patients who do not sign consent forms. The patient-participants in my study were competent adults; research into the informed consent process with regards to children and incompetent patients is also important and needs to be explored. Since my interviewees were either conducting or enrolled in Phase III and IV trials, their perspectives do not reflect the viewpoints of physician-researchers and participants in early phase trials (I and II).

Although the views and experiences are of physician-researchers from one major city of Pakistan, which limits its generalizability nationally, my participants reflect a wide cross-section of patients and physician-researchers from a significant number of tertiary-care hospitals. To this extent these findings are likely to be applicable to other parts of the country.

My research identifies the challenges that operate at ground level between those who conduct research trials and those who participate in research trials. Future research to explore the views of research ethics committee members on the issues highlighted in my research will be useful before going on to investigate the views of individuals who formulate the local ethics guidelines. This study highlights and informs the need for developing tools of ethical reasoning that are appropriate for the local context – these would be useful both in research and clinical settings. This research thus simultaneously

identifies the challenges pertaining to the application of these requirements and offers some suggestions for overcoming them.

Interpretation of research ethics guidelines needs to be conducted in the contexts in which research is taking place in a way that ensures that the guidelines are relevant to the everyday lives of the local participants. It is necessary that well-intentioned guidelines are matched by observations and knowledge of particular research contexts for ethical research to be conducted. In this regard my findings from Lahore, Pakistan, have important implications for practice and policy. My research highlights the need for enhancing the awareness of physician-researchers to provide accurate information. A shared decision-making process, which involves the family as well as the patient, would be appropriate. This is important since, in my experience and that of a few physician-researchers, excluding the family creates social 'harms' for patients, especially for women, while including the patient in the process engenders equality and trust. This form of decision making does not necessarily dilute autonomy, in fact it gives patients confidence. It is also helpful to have same-gender physician-researchers, especially in case of female patients. Excluding women (and patients who do not give written consent) from trial enrollment for expediency is unethical and a policy to emphasize their enrollment should be encouraged. To these ends physician-researchers' training and capacity building in the use of tools for ethical reasoning that are locally developed so that they cohere with local norms, would be useful.

My analysis also shows that while the research ethics guidelines and sponsors require a written, signed, consent from patients, this signed consent is mainly for the sponsors', physician-researchers' and hospitals' purposes and not for the benefit of patients. Documenting consent is important but there should be flexibility in the process. Audio-recording and video-recording of consent have been recommended as alternatives, but these processes can also raise difficulties, especially in contexts where women observe *purdah*. A well thought-out policy that is appropriate for this particular context should therefore be developed.

In accordance with the research ethics guidelines that require the proven medicine to be made available to patients enrolled in a trial, at the end of the trial, I found that sponsors usually seek to make the medicine available in the market. However, in the Pakistan context, the price of such medicine generally is such that the majority of patients enrolled in the research trial cannot afford the medicine, as is also the case for most patients; only wealthy patients can purchase such medicines. So, although the sponsors have conducted an "ethical trial" insofar as "ethics" refers to the literal application of the guidelines, the trial is not ethical in spirit where there is insistence on obtaining a written consent and where due to economic constraints patients, including enrolled patients, are unable to access the proven intervention at the conclusion of the trial.

The goal should therefore be to uphold the spirit of the ethics guidelines rather than to follow procedural requirements in a dogmatic manner; and at the same time be sensitive to the need to challenge

local practice that ignore fundamental rights and to support change from within, where this is appropriate. It is essential that local guidelines are formulated that are attentive to the concerns highlighted by my findings.

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List of Appendices