

**THE ADEQUACY OF THE ETHICS REVIEW
PROCESS IN MALAYSIA: PROTECTION OF THE
INTERESTS OF MENTALLY INCAPACITATED
ADULTS WHO ENROL IN CLINICAL TRIALS.**

SHARON KAUR

UNIVERSITY COLLEGE LONDON (UCL)

**THESIS SUBMITTED IN FULFILMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY**

I, Sharon Kaur, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

.....

Sharon Kaur

ABSTRACT

The objective of this thesis is to answer the question, “does the ethics committee review process in Malaysia provide meaningful protection to mentally incapacitated adults who enrol in clinical research trials?”

This question is answered by examining three important aspects of the ethics review process. First, the quality of the deliberations of ethics committees is examined by looking at the underlying principles that are meant to guide ethics decision-making. Second, the thesis looks at the current regulatory framework under which ethics committees operate and considers the adequacy of these guidelines in protecting human subjects. Finally, this thesis considers the notion of conflicts of interests in the clinical trials arena and calls into question the independence of the ethics review process and how this impacts on the interests of human subjects in general and mentally incapacitated adults in particular.

The conclusion reached at the end of this thesis is that the ethics review process in Malaysia fails adequately to provide meaningful protection to mentally incapacitated adults. While the reasons for this are many, several factors are particularly significant, namely, the creation of a globalised clinical trials market, the lack of formal and systematic training of ethics committee members and the institutional structures of ethics committees.

Although the main focus of this thesis is the Malaysian ethics review process, many of the comments and discussions put forward in this thesis are highly relevant to the ethics review processes in other jurisdictions given the international regulatory scheme that currently governs the conduct of clinical trials in many parts of the world.

ACKNOWLEDGEMENTS

In thinking about and writing this thesis, I have received advice and assistance from a number of people, all of whom I gratefully thank. I am deeply indebted to my principal supervisor, Professor Michael Freeman, for his invaluable guidance. I have benefited tremendously from his intellectual stimulation, advice and support, especially during periods of self-doubt over the years. I am also very grateful to him for reading through the final draft of this thesis with great care. I am particularly grateful to my secondary supervisor, Professor Dame Hazel Genn, for her critical comments and guidance. I am also grateful to Professor Stephen Guest for providing me with supervision for the first year of my research.

I must acknowledge my profound gratitude to my sister, Karen, who not only provided me with strong support and encouragement, but also contributed her valuable time to read through the entire thesis and provide helpful comments. Thanks are also due to my colleagues, Dr Tay Pek San and Dr Azmi Sharom who proofread some chapters of the thesis as well.

On a personal note, I must thank my father, Dato' Dr Gurmukh Singh, for his support and encouragement. I will also always be grateful for the friendship and the intellectual stimulation provided by my coursemates on the PhD programme at UCL, as well as the unending support of friends at All Souls Church, London.

TABLE OF CONTENTS

ABSTRACT	3
ACKNOWLEDGEMENTS.....	4
1 Chapter One	8
Introduction.....	8
1.1 <i>Clinical Trials</i>	8
1.1.1 Evolution of Clinical Trials	9
1.1.2 Clinical trials – human subject protection	16
1.2 <i>Mentally Incapacitated Patients</i>	17
1.2.1 Vulnerable populations	17
1.2.2 Mentally incapacitated patients and clinical trials	21
1.3 <i>Objective, scope, outline of chapter, terminology and research methodology</i>	23
1.3.1 Objective of the research	23
1.3.2 Scope of the study and outline of the chapters	24
1.3.3 Research Methodology	27
2 Chapter 2	32
The Malaysian Context.....	32
2.1 <i>Medical Research in Malaysia – A Brief History</i>	32
2.1.1 Early days	32
2.1.2 Emergence of the local clinical trial industry	34
2.1.3 Government support of clinical trial industry	38
2.1.4 Globalisation and the impact on human subject protection	
40	
2.2 <i>Regulation of clinical trials in Malaysia</i>	42
2.2.1 Legislation	42
2.2.2 Guidelines	43
2.3 <i>Incapacitated subjects and clinical trials in Malaysia</i>	46
2.3.1 Legislation	46
2.3.2 Guidelines	55
2.4 <i>Ethics committee review</i>	56
2.4.1 History of ethics review.....	57

2.4.2	U.S. Experience	58
2.4.3	Ethics Review in Malaysia.....	63
3	Chapter 3	67
	Ethics committee review and the ethics of clinical research	67
3.1	<i>History of clinical research misconduct</i>	70
3.1.1	World War II Human Experiments and the Nuremberg Code 70	
3.1.2	Henry Beecher’s Article and the Declaration of Helsinki... 77	
3.1.3	The Tuskegee Syphilis Study and the Belmont Report	83
3.2	<i>Basis of research misconduct - Undervaluation of Human Life</i> 88	
3.2.1	Group based undervaluation of human life.....	89
3.2.2	Undervaluation of the individual person	91
3.3	<i>Ethical Basis for Clinical Research Involving Human Subjects</i> 98	
3.3.1	How to value human life?.....	99
3.3.2	Valuing life based on human dignity.....	101
3.3.3	Human Dignity as accorded to all humans	104
4	Chapter 4	118
	Ethics Committee Review and the ICH-GCP Guideline	118
4.1	<i>Ethics committees’ roles and responsibilities and ICH-GCP</i> ...120	
4.1.1	Safeguarding rights safety and well-being of all trial subjects – substantive duties.....	120
4.1.2	Administrative duties	125
5	Chapter 5	157
	Ethics Committee Review and Conflicts of Interest.....	157
5.1	<i>Historical context of independent ethics review</i>	157
5.2	<i>Conflicts of Interest</i>	160
5.2.1	History of Conflicts of Interest in the Research Environment	160
5.2.2	Current Emphasis – financial conflicts of interest	162
5.3	<i>What are Conflicts of Interest?</i>	165
5.4	<i>Conflicts of Interest as the Clash Between Primary and Secondary Interests</i>	166

5.4.1 (1) What sorts of relationships give rise to primary interests? – Erde’s social role	167
5.4.2 Which relationships in the research environment fulfil Erde’s social role?	169
5.4.3 (2) How are primary interests to be discovered?.....	185
5.4.4 (3) When can it be said that interests other than primary interests amount to secondary interests?	204
5.4.5 Secondary Interests and Research Ethics Committees	220
6 Chapter 6	232
Conclusion	232
6.1 <i>Are ethics committees independent?</i>	234
6.2 <i>Do ethics committees engage in meaningful ethical discourse?</i>	235
6.3 <i>Conclusion</i>	239

1 Chapter One

Introduction

The objective of this research is to analyse and evaluate the adequacy of the ethics review process in providing an adequate level of protection to mentally incapacitated adults who participate in clinical trials in Malaysia.

Clinical Trials

Advances in medical science are largely achieved by way of medical research projects. To highlight a few examples, there would be no organ transplants, vaccinations or chemotherapy drugs if it were not for research. Medical research covers a broad range of activities aimed at improving or maintaining human health. Research activities range from basic research in areas such as animal studies, psychology, statistics, economics, physics, chemistry, etc; to clinical research, which involves research on human participants.¹

The clinical research trial is medical research that is carried out on human participants and is the last leg of a long journey. The American National Institutes of Health defines a clinical research trial² as a prospective biomedical or behavioural research study of human subjects that is designed to answer specific questions about biomedical or behavioural interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical research trials can be described in several ways. They may be

¹ See the U.K. Medical Research Council description of clinical trials at <http://www.mrc.ac.uk/Achievementsimpact/Clinicaltrials/Whatareclinicaltrials/index.htm> accessed August 17, 2010

² At <http://clinicaltrials.gov/ct2/info/glossary> accessed on August 17, 2010

described as being therapeutic or non-therapeutic in nature.³ Therapeutic trials are run on subjects with not only a view of proving a particular hypothesis, but also of providing a curative therapy for a particular condition. To this end, all research participants are necessarily patients suffering from the particular illness, condition or disability being studied. A therapeutic clinical trial is carried out at a point at which a drug or therapy has shown enough promise and is deemed sufficiently safe to be tested on human subjects. It is usually the last step before a drug or therapy is introduced to the general population. Non-therapeutic trials on the other hand, are usually run to test the safety profiles of drugs or are bio-equivalency studies and trial subjects are usually healthy volunteers.⁴ Clinical research trials may also be described according to the objects being studied. They may involve testing drugs, diagnostic methods, devices or even treatment methods and may be invasive or non-invasive.

In order fully to appreciate the context in which modern clinical trials are run and the reasons for the development of principles and mechanisms to protect human subjects, it is necessary to first consider how clinical research has evolved over the centuries.

Evolution of Clinical Trials

The modern scientific tradition of medicine⁵ has evolved over centuries of trial and error. Early physicians worked at the bedside and hypothesised causes and effects of diseases and illnesses and tested out their theories on their patients. Treatment modalities were more often

³ The use of the terminology therapeutic trial instead of non therapeutic trial has been the subject of some debate as using the word therapeutic seems to infer that the primary aim of the trial is treatment, which is not the case as the primary aim of any trial is the generation of generalisable knowledge. See J. Menikoff and E. P. Richards, *What the doctor didn't say: the hidden truth about medical research*, (New York ; Oxford 2006) at 22

⁴ The subject population may also include patients who are not suffering from the specific condition that is being researched.

⁵ Hippocrates and his followers are generally recognised as having laid down the foundations for the modern scientific tradition of medicine.

than not based on anecdotal evidence of past successes or failures to cure patients. In this way the breadth and depth of medical knowledge grew slowly and fitfully. The line between medical practice and medical research had yet to be drawn and in truth, almost all medical practice was also clinical research. Bedside medicine⁶ as practised by the Hippocratics, was founded on the idea of humoral medicine, which emphasised the importance of diet, exercise and bathing and believed in the body's ability to heal itself. This form of medicine was typically observational rather than experimental.⁷

Over time, medical practice moved⁸ from the bedside into the hospital and the science of medicine moved from passive observation of patients to active laboratory based medicine. The emergence of hospital medicine transformed the practice of medicine in both terms of location and its content. The hospital became the centre of medical teaching, research and the arbiter of medical knowledge.⁹ This type of medicine was especially associated with the city of Paris between 1794 and 1848.¹⁰

Clinical research began to take on a more systematic and scientific approach during the ascendancy of hospital medicine since it was in the hospitals where the “three pillars of the new medicine – physical

⁶ Bedside medicine is said to have held sway in Western Europe from the Middle Ages to the 18th Century. See Andrew Cunningham and Perry Williams, *The Laboratory Revolution in Medicine* (Cambridge: Cambridge University Press, 1992). at 1

⁷ Few records exist of pure research activities and the most frequently cited cases involve testing the efficacy of poisons on condemned prisoners. (See S Post (ed) *Encyclopaedia of Bioethics* 3rd Ed, Vol 4, Thomson Gale, pg 2316) Some accounts of human vivisectional experiments were also recorded in this age and in each case condemned criminals were also used as subjects. (S. F. Spicker, *The Use of human beings in research: with special reference to clinical trials*, (Dordrecht ; London 1988) at 33)

⁸ The history of Western medicine has been described as involving five types of medicine: bedside: medicine, library medicine, hospital medicine, community medicine and laboratory medicine. See W. Bynum, “Reflections on the History of Human Experimentation” in Spicker, S. F. (1988). *The Use of human beings in research: with special reference to clinical trials*. Dordrecht ; London, Kluwer Academic at 29-46

⁹ Cunningham and Williams, *The Laboratory Revolution in Medicine*. at 2

¹⁰ *Ibid.* at 1

examination, autopsy and statistics could be developed.”¹¹ Hospital medicine also made it possible to run clinical experiments on large numbers of people.¹² This in turn provided physicians with rich data upon which to design treatment modalities. Using hospital patients as research subjects was considered appropriate because for most of the eighteenth century, hospitals were administered to care for the poor and infirm who were considered the most suitable subjects for experiments because of their illnesses, their perceived resulting obligation to society and the power structure within hospitals that created a regulated research environment.¹³ The attitude of practitioners toward test subjects reflected this view of the entrenched social hierarchies of the community. Bernard de Gordon¹⁴ advised that medicines should be tested “first on birds, next on mammals, then [on patients] in hospitals, then on lesser brethren, and then on others in [ascending] order, because if it should be poisonous it would kill.”¹⁵ Notwithstanding the advances in the number of subjects and statistical analysis made possible by hospital medicine, clinical research remained largely observational and the border between practice and research was still indistinguishable.

This changed with the advent of laboratory medicine, that is, the use of laboratory tests in clinical problem solving,¹⁶ which gained prominence in the second half of the nineteenth century¹⁷ and continues to

¹¹ Erwin Heinz Ackerknecht, *Medicine at the Paris Hospital, 1794-1848* (Baltimore: Johns Hopkins Press, 1967). at 15

¹² In the early seventeenth century, a group of French professors revolutionised medicine by using big public hospitals for research. See Roy Porter, *The Cambridge Illustrated History of Medicine* (Cambridge: Cambridge University Press, 1996). at 173

¹³ Stuart F. Spicker, *The Use of Human Beings in Research : With Special Reference to Clinical Trials*, Philosophy and Medicine ; V. 28 (Dordrecht ; London: Kluwer Academic, 1988). at 36

¹⁴ Master of the Faculty of Medicine at Montpellier, who is considered to be possibly the most noteworthy representative of the academic quality and professional standards of that age (1250-1350), see Luke E. Demaitre and Pontifical Institute of Mediaeval Studies., *Doctor Bernard De Gordon, Professor and Practitioner* (Toronto: Pontifical Institute of Mediaeval Studies, 1980).

¹⁵ *Ibid* at 28

¹⁶ D Burke, "Laboratory Medicine in the 21st Century," *American Journal of Clinical Pathology* 114, no. 6 (2000). at 841

¹⁷ Spicker, *The Use of Human Beings in Research : With Special Reference to Clinical Trials*. at 39

dominate the practice of medicine today. Claude Bernard, one of the pioneers of laboratory medicine and among the greatest scientists of his day, maintained that hospital medicine had two limitations. First, it was observational and thus purely passive whereas what was required was the active observation of the subject under controlled conditions. Second, the sickbed involved too many factors that could not be assessed to allow for precise understanding.¹⁸ The solution was laboratory medicine according to his famous statement in 1865:

“...I consider hospitals only as the entrance to scientific medicine; they are the first field of observation which a physician enters; but the true sanctuary of medical science is a laboratory; only there can he seek explanations of life in the normal and pathological states by means of experimental analysis.”¹⁹

Laboratory medicine, which was actively experimental and based on systematic and standardised methodologies, essentially separated the practice of medicine from medical research.²⁰ Clinical research thus developed into formally run scientific trials, setting out to prove or disprove specific hypotheses, while medical practice moved into the age of evidence-based medicine.²¹ In this way, the foci of clinical research and medical practice drifted apart. While medical practice remained concerned with treating the individual patient, clinical research fixed its eyes upon the advancement of scientific knowledge.²² Significantly,

¹⁸ Porter, *The Cambridge Illustrated History of Medicine*. at 182

¹⁹ Claude Bernard, *An Introduction to the Study of Experimental Medicine* (New York: Dover Publications, 1957) at 146

²⁰ This is not to say that the division of medical practice and research is complete; doctors faced with new diseases or difficult cases continue to experiment with new methods of treatment and care. Some prominent physicians continue to regard the task of separating medical practice from medical research as a very important and exceedingly difficult task. See RJ Levine *Ethics and Regulations of Clinical Research* (2nd edn Urban & Schwarzenberg, Baltimore-Munich, 1986) at 3

²¹ According to the Centre for Evidence-Based Medicine, this is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. See <http://www.cebm.net/index.aspx?o=1914> accessed on August 17, 2010

²² In America, World War II is generally considered as the moment when human experiments lost their directly therapeutic character. For a greater discussion of this, see David J. Rothman, *Strangers at the Bedside : A History of How Law and Bioethics Transformed Medical Decision Making* (New York, NY: Basic Books, 1991).

however, this never resulted in a formal and distinct separation of the notions of clinical research and medical practice. This is particularly true of therapeutic clinical trials where physicians enrol their patients into research projects. Because research and practice are ultimately seeking to achieve very different ends, the fact that there remains an indistinct boundary between practice and research, both in terms of institutional arrangements and mindsets of participants, places patients/subjects at risk. This is especially manifested in the discussion in Chapter 4 concerning the informed consent process in clinical trials.

Clinical research has continued to evolve in sophistication and in the past 30 years, the face of clinical research has dramatically changed, resulting in a much larger, more distant and complex enterprise. Modern clinical research projects are to a large extent initiated and funded by governments²³ and multinational pharmaceutical companies,²⁴ which outsource trials to large business enterprises known as contract research organisations/clinical research organisations (CRO). A clinical research project might involve physicians running trials in several different countries, enrolling thousands of subjects and be supported by a host of other professions. The United Kingdom Medical Research Council (MRC)²⁵ notes that:²⁶

‘Well run clinical trials rely on the expertise and commitment of a range of healthcare professionals: the researchers who will pose the research question and plan the trial; the nurses and

²³ This is because states bear the primary responsibility for the health of their citizens and many are also signatories to international commitments on health see Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2006* at <http://www.globalforumhealth.org> accessed August 17, 2010

²⁴ The pharmaceutical industry is responsible for half the global total of research and development investment in health research. See Global Forum for Health Research, *Monitoring Financial Flows for Health Research 2009, Behind the Global Numbers* at <http://www.globalforumhealth.org/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2009-Behind-the-Global-Numbers> at 10 accessed August 17, 2010

²⁵ The United Kingdom Medical Research Council is a national organisation funded by the taxpayer. It promotes research into all areas of medical and related science with the aims of improving the health and quality of life of the public and contributing to the wealth of the nation. See <http://www.mrc.ac.uk> accessed 21 January 2006

²⁶ Medical Research Council, *Clinical Research It's Everyone's Business* Medical Research Council 2004 at 5 at http://www.ct-toolkit.ac.uk/db/documents/MRC_clinical_research_leaflet.pdf accessed August 17, 2010

therapists who administer the treatments being tested; and the trial manager and administrators who are responsible for the efficient day to day running of the trial, including data management and recruitment of participants, and recruiting thousands of subjects.’

The modern clinical research industry is a flourishing activity, largely because it has been very successful in contributing to better health care. Medical research and in particular, drug development has played a significant role in improving health care. Increased global immunisation coverage has resulted in a fifty percent reduction of the infant mortality rate in developed countries over the last 25 years²⁷ and new drug therapies such as antiviral and cardiovascular drugs have substantially decreased mortality rates in developed countries.²⁸ It is estimated that health-related technology improvements led by the introduction of new drugs have reduced human mortality by more than fifty percent between 1960 and 1990.²⁹ As recognised by Daniel Callahan,³⁰ “It has been a wonderful contributor to a reduction in mortality, to improved health, and to the relief of pain and suffering. It has thus by most measures been a glorious enterprise. It works, and we want more of it.”

²⁷ International Federation of Pharmaceutical Manufacturers Associations, *The Pharmaceutical Innovation Platform, Sustaining Better Health for Patients Worldwide* (IFPMA Oct 2004) 11 quoting The World Health Organisation, *World Health Report 2003. Global Health; Today's Challenges* (WHO 2003)

²⁸ *Ibid* at 14

²⁹ *Ibid* at 11, quoting J Wang et al *Measuring country performance on health: Selected indicators for 115 countries.*(The World Bank, Human Development Network, Washington DC, 1999)

³⁰ D Callahan *What Price Better Health? Hazards of the research imperative* (University of California Press, 2003) at 33

We want more of it because we place a very high value on good health. In a global survey³¹ commissioned for the Millennium Summit of the United Nations, good health ranked as the most important desire of men and women around the world.³² Health brings the capacity for personal development and economic security in the future and is the basis for job productivity, the capacity to learn in school, and the capability to grow intellectually, physically, and emotionally.³³

Successful medical research also carries a vast amount of economic value. An economic analysis of the potential gains from improvement in health care estimates that reducing deaths from heart disease by 10% would generate approximately \$5.1 trillion in economic value, while reducing cancer death rates would be worth roughly \$4.4 trillion.³⁴ It is thus not surprising that the medical research industry is one of the most lucrative industries in the world. In 2003, a Reuters Business Insight Healthcare Report noted that the pharmaceutical market was growing at an annual rate of approximately 8% and estimated that it would be worth over \$400 billion by 2005.³⁵

Consequently, spending on medical research is ever increasing. Globally, annual spending on medical research rose by an average of US\$4.6 billion a year during the 1990s to reach US\$84.9 billion in 1998. It then rose much more steeply, by an average of US\$7.0 billion per year, during the next three years, reaching a total of US\$105.9

³¹ In 1999, Gallup International sponsored and conducted a Millennium Survey of 57,000 adults in 60 countries, the world's largest ever public opinion survey.

³² K A Annan, Millennium Report of the Secretary-General of the United Nations, Chapter 2, Globalisation and Governance, at 9 in "We the peoples" *The Role of the United Nations in the 21st Century* United Nations 2000 available at <http://www.un.org/millennium/sg/report/> accessed August 17, 2010

³³ Report of the Commission on Macroeconomics and Health, *Macroeconomics and Health: Investing in Health for Economic Development* Chaired by J D Sachs Presented to Gro Harlem Brundtland, Director-General of the World Health Organisation on 20 December 2001 available at <http://www.emro.who.int/cbi/pdf/CMHReportHQ.pdf> accessed August 17, 2010

³⁴ Kevin M. Murphy and Robert H. Topel, *Measuring the Gains from Medical Research : An Economic Approach* (Chicago, Ill. ; London: University of Chicago Press, 2003) at 42

³⁵ D Jackson "The Pharmaceutical Market Outlook to 2010. – Essential Analysis of Key Drivers and Change" *Reuters Business Insight – Healthcare*, Datamonitor PLC, 2003 at 21

billion in 2001.³⁶ In 2005, global investments in health research amounted to US\$ 160.3 billion.³⁷ The pharmaceutical industry is the biggest non-public health investor in medical research worldwide.³⁸ Total research and development expenditures by pharmaceutical and biotechnology companies in 2002 reached almost US\$50 billion.³⁹

Clinical trials – human subject protection

The evolution of clinical research from intimate interactions between physicians and patients at bedsides, to the activities of multi-national, billion dollar enterprises that involve interactions between thousands of different players the world over, has as discussed above, been to a large extent a great success story. However, at some point during this progression, there was a transformation of the relationship between the physician/researcher and the patient/subject. At some point, the research enterprise, or rather the way in which clinical research was carried out, changed the way in which the public viewed the physician/researcher, which in turn led to a proliferation of guidelines and restrictions and the devising of mechanisms to circumscribe the actions of physicians/researchers. Rothman⁴⁰ places this transforming event as occurring during World War II. He ascribes the transformation to four factors: first, the establishment of co-ordinated and extensive government funded research programmes; second, experiments were no longer being carried out for the benefit of subjects, but for others – specifically the soldiers engaged in war; third,

³⁶ Global Forum for Health Research, *Monitoring Financial Flows for Health Research* 2004 at http://www.globalforumhealth.org/filesupld/monitoring_financial_flows2/MFF04chap0.pdf accessed 20 Jan 2006

³⁷ Global Forum for Health Research, *Monitoring Financial Flows for Health Research* 2009, *Behind the Global Numbers* at <http://www.globalforumhealth.org/Media-Publications/Publications/Monitoring-Financial-Flows-for-Health-Research-2009-Behind-the-Global-Numbers> at 136 accessed August 17, 2010

³⁸ *Ibid* at 10

³⁹ International Federation of Pharmaceutical Manufacturers Associations, *The Pharmaceutical Innovation Platform, Sustaining Better Health for Patients Worldwide* (IFPMA Oct 2004) at 17

⁴⁰ D. J. Rothman, *Strangers at the bedside: a history of how law and bioethics transformed medical decision making*, Second ed., (Hawthorne, NY 2003) at 30

researchers and subjects were more often than not, strangers to each other; and finally, consent was often superseded by a sense of urgency.

In the clinical trial environment, two main mechanisms were put into place to protect human subjects who participate in these trials: ethics review of trial protocols and the informed consent process. This thesis examines whether the first of these mechanisms, the ethics review process, as it is carried out today in Malaysia, provides meaningful protection to mentally incompetent adults who participate in clinical research trials.

This examination will be carried out by looking at three aspects of ethics review: the underlying principles that guide the decision-making process; the administrative and legislative structures under which ethics committees operate; and the independence of these committees. The hypothesis of this study is that the process of ethics review falls short of its purpose to provide meaningful protection to research subjects and even more so in respect of mentally incapacitated patients.

Mentally Incapacitated Patients

Vulnerable populations

Certain populations are considered to be vulnerable and are thus afforded special protections, above and beyond those available to the general public. Even though there is no universally accepted definition of a vulnerable population, there is little doubt that mentally incapacitated persons fall within this category. While a detailed dissection of the notion of vulnerability is beyond the scope of this thesis, it is worth taking some time to consider the idea of what a vulnerable population is, as this provides a valuable starting point for constructing a framework for protecting mentally incapacitated patients.

Vulnerability and vulnerable populations have been described in a number of ways. Vulnerable subjects have been defined as those who are cognitively impaired or subject to intimidation.⁴¹ In a paper commissioned by the American National Bioethics Advisory Commission, Kipnis sets out what he describes as a 'useful taxonomy for the concept of vulnerability'.⁴² Six discrete types of vulnerability are identified: cognitive, juridic, deferential, medical, allocational and infrastructural; and the types of vulnerability are distinguished by asking six specific questions.⁴³ More controversially, according to Levine et al.⁴⁴ the current concept of vulnerability in the research arena is both too broad and too narrow to be of any use. Instruments such as the Declaration of Helsinki⁴⁵ and CIOMS guidelines⁴⁶ describe what it means to be vulnerable in such an all-encompassing way, that it is hard to imagine anyone not being vulnerable at some level. At the same time, the authors note that identifying vulnerability by focusing solely on group characteristics such as gender or age, 'diverts attention from features of the research itself, the institutional environment, or the social and economic context that can put participants in harm's way',⁴⁷ and also stereotypes 'whole categories of individuals, without distinguishing between individuals in the group who indeed might have special characteristics that need to be taken into account and those who do not.'⁴⁸

⁴¹ P Backlar 'Human Subjects Research, Ethics, Research on Vulnerable Populations.' in TH Murray and MJ Mehlman (eds) *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology*, Volume 2, (New York: John Wiley & Sons, 2000) at 641.

⁴² Kenneth Kipnis, "Vulnerability in Research Subjects: A Bioethical Taxonomy," in *Ethical and Policy Issues in Research Involving Human Participants* (Bethesda MD: National Bioethics Advisory Commission, 2001). at G4

⁴³ Ibid. at G6

⁴⁴ Carol Levine et al., "The Limitations Of "Vulnerability" As a Protection for Human Research Participants," *The American Journal of Bioethics* 4, no. 3 (2004).

⁴⁵ World Medical Association, "Declaration of Helsinki: Ethical Principles Of Medical Research Involving Human Subjects," (2004). Principle 8

⁴⁶ (CIOMS) Council for International Organizations of Medical Sciences, "International Ethical Guidelines for Biomedical Research Involving Human Subjects," (2002). Guideline 13

⁴⁷ Levine et al., "The Limitations Of "Vulnerability" As a Protection for Human Research Participants." at 46

⁴⁸ Ibid at 47

It is worth making two observations at this point. First, it seems that when Levine et al. contend that vulnerability is defined in too broad a manner, they have not picked up a flaw in the way vulnerability is understood, they have in fact, discovered a truth about human subject research. All research subjects are in some way vulnerable. They are vulnerable because every research trial carries a certain level of risk. Moreover, recognising the environment in which human subject research is carried out today, it is almost impossible for any person to be able to meaningfully review the foreseeable risks and adequacy of protection or accurately assess the research process itself and its social and economic context. It is for this very reason that the mechanisms of human subject protection have been put into place.

Second, some research participants will be in more vulnerable positions than others because they possess certain physical, psychological or social characteristics that render them particularly susceptible to intimidation or exploitation. It is generally these populations that are referred to as being vulnerable. Examples of such vulnerable populations would include the mentally incompetent, children, prisoners, medical students, armed forces, women and refugees. Although Levine is right to point out that the categorisation of people based on membership of certain groups fails to recognise diversity and individuality within the group, it is nevertheless important to be aware of the fact that people who fall within such a categorisation may be subject to abuse. There is undoubtedly some value in recognising that some group-held characteristics make it more likely that certain people might be treated badly and to require that special attention be paid in such situations.

However, at the end of the day, it is submitted that vulnerability is really about unequal relationships⁴⁹ and has been described most aptly as being about powerlessness⁵⁰ and the attendant loss of control that ensues from it, and the potential for abuse and exploitation by more powerful groups. History has borne witness to many instances where the devalued vulnerable have served as unwitting subjects in research benefiting "privileged members of society".⁵¹ Therefore, a person is vulnerable if he is in a situation where he is potentially subject to abuse and exploitation by more powerful individuals or groups. The roots of his vulnerability might be found in a number of places and might range from an identification with or membership of a particular group to his specific individual circumstances. By looking at vulnerability in this way, the sources of vulnerability may exist at two levels, at a group level and on an individual basis.

Adopting this approach to understanding what it means to be vulnerable is useful in that it provides a helpful guide to devising appropriate safeguards. Safeguards are determined by identifying the root/roots⁵² of the vulnerability, considering if the vulnerability can be removed or ameliorated and if not, how best to protect⁵³ the vulnerable population, bearing in mind that what may seem appropriate safeguards for a particular cohort of vulnerable subjects may be completely meaningless to another.⁵⁴

⁴⁹ The CIOMS International Ethical Guidelines for Biomedical Research identifies vulnerability with a limited capacity or freedom to consent or decline to participate in research. It recognises the unequal distribution of knowledge and power in the relationship between potential subjects and investigators. See Ruth Macklin, "Bioethics, Vulnerability, and Protection," *Bioethics* 17, no. 5-6 (2003). at 474

⁵⁰ B. Hoffmaster, "What Does Vulnerability Mean?," *Hastings Center Report* 36, no. 2 (2006). at 41

⁵¹ See Chapter 3 Section 3.2.1

⁵² This may vary depending on the population; it may be poverty, marginalisation or mental incapacity.

⁵³ Unlike a typical discussion on research ethics, the overarching value to be protected may not necessarily be autonomy as the vulnerability of a population may arise from an inability to be autonomous such as that found in very young children and some mentally ill.

⁵⁴ Different populations suffer from different types of vulnerabilities. For a discussion about some of the distinct problems faced by different vulnerable groups see Jason P. Lott, "Module Three: Vulnerable/Special Participant Populations," *Developing World Bioethics* 5, no. 1 (2005).

Therefore, applying this two-level approach, at the first and more general level, there needs to be an identification of the specific factors that render certain groups of people vulnerable. At a second and more specific level, there should be an appreciation of the special position of each individual subject in relation to the specific clinical trial being proposed, and at the heart of this enquiry should be concern for the protection and empowerment of the specific individual. This two-level approach is also valuable as it recognises the inherent tension between an administratively efficient system, which addresses the concerns of all members of a population, and the need for securing a just result for individuals within the population. It acknowledges the fact that while a certain population is made up of individuals who share certain characteristics, they nevertheless remain individuals within the population with individual needs and interests. It is this understanding of vulnerability that is employed in Chapter 3 in the discussion of what it means to respect the dignity of mentally incompetent patients.

Mentally incapacitated patients and clinical trials

If vulnerable populations are susceptible to exploitation, it may then be argued that the most prudent course of action would be never to include vulnerable populations in research trials so as to avoid any sort of abuse at all. This is not a feasible option as this may lead to further marginalisation. Refugees for instance, very often live in camps where clean drinking water is in very short supply. Meaningful research into managing hydration levels may require the participation of people living in refugee camps. Refusing to allow any sort of research in this area cannot be in the interest of refugee populations.

Similarly, if treatment modalities are to be developed for people suffering from conditions that lead to mental incapacity, research must be carried out and at some point, clinical trials must be run before treatments are made available to the public. Until these treatments are tested on the very populations that suffer from the disorders that affect capacity, there will be no reliable evidence concerning the efficacy or the safety profiles of the treatments.

Disorders that affect capacity and that may render individuals unable to make certain decisions for themselves mostly involve psychiatric or neurological conditions. Dementia, delirium, schizophrenia, depression and severe mental retardation are among the conditions that are most commonly associated with impaired decision-making.⁵⁵ Notably, these conditions affect a significant proportion of society. In 2001, the World Health Organisation recognised that mental and behavioural disorders were estimated to account for 12% of the global burden of disease and that mental disorders represented four of the 10 leading causes of disability worldwide.⁵⁶ Moreover, the economic and social impact of mental disorders is described as being 'wide ranging, long lasting and huge'.⁵⁷ It is evident that these disorders, which are likely to impact on decision-making abilities, are both prevalent and impact heavily on the lives of individuals as well as society in general. There is in short, a need to develop effective treatments for these disorders.

⁵⁵ United States. National Bioethics Advisory Commission, "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume II," (Rockville, Md. (6100 Executive Blvd., Suite 5B01, Rockville 20892-7508): National Bioethics Advisory Commission, 1998) at 1-2

⁵⁶ WHO, "The World Health Report 2001: Mental Health: New Understanding. New Hope," (World Health Organisation, 2001) at 3

⁵⁷ *Ibid.* at 7

Unfortunately, notwithstanding the fact that calls⁵⁸ have been made for greater support for mental health research, there is still a great imbalance in the amount of current research into mental health disorders. A survey evaluating the relation between the global burden of disease and conditions studied in randomised clinical trials published in general medical journals found that only 2.44% of clinical trials targeted mental disorders.⁵⁹ Similarly, a search of the ISI Web of Science database from 1992 – 2001, found that only 3.57% of health-related publications were related to mental health.⁶⁰ Taking into consideration the current burden of mental disease, much more research is needed to attain new knowledge and discover better ways to treat and manage mental disorders.

Therefore, mentally incapacitated patients represent an important cohort of research subjects. First, because at some point on the research continuum, mentally incompetent patients will inevitably need to participate in clinical trials if treatment modalities are to be developed for their disorders. Second, the growing burden of disorders that affect capacity coupled with recent pharmacological advances, have created a greater demand for research into these disorders, which will mean an increasing number of mentally incapacitated adults will be invited to participate in clinical trials.

Objective, scope, outline of chapter, terminology and research methodology

Objective of the research

The objective of this research is to analyse and evaluate the adequacy of the ethics review process in providing an adequate level of protection

⁵⁸Ibid. at 112, United States. Department of Health and Human Services, "Mental Health: A Report of the Surgeon General," (Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institutes of Mental Health, 1999). at 453

⁵⁹ Paula A. Rochon et al., "Relation between Randomized Controlled Trials Published in Leading General Medical Journals and the Global Burden of Disease," *CMAJ* 170, no. 11 (2004).

⁶⁰ Shekhar Saxena et al., "The 10/90 Divide in Mental Health Research: Trends over a 10-Year Period," *Br J Psychiatry* 188, no. 1 (2006) at 81

to mentally incapacitated adults who participate in clinical trials in Malaysia, and to offer a framework for ethics decision-making in the context of clinical trials. Even though the main focus of this thesis is the Malaysian ethics review process, many of the comments and discussions put forward in the following chapters are also very relevant to the ethics review processes in other jurisdictions given the international regulatory scheme that currently governs the conduct of clinical trials in many parts of the world.

This thesis aims to achieve the above objective by evaluating three aspects of the ethics review process. First, there is a consideration of the underlying principles that inform medical research on human subjects and whether or not ethics committee members are in fact able to provide adequate protection to mentally incapacitated subjects by engaging in meaningful ethical discussions during the review process. Second, the thesis looks at the current regulatory framework under which ethics committees operate and considers the adequacy of these guidelines in protecting human subjects. Finally, this thesis considers the notion of conflicts of interests in the clinical trials arena and calls into question the independence of the ethics review process and how this impacts on the interests of human subjects in general and mentally incapacitated adults in particular.

Scope of the study and outline of the chapters

This study assesses the adequacy of the protection afforded by ethics review committees to mentally incapacitated adults in clinical trials and focuses on three main aspects of ethics review: the underlying principles that inform ethics decision-making, the guidelines under which ethics review is carried out, and the prevalence and influence of conflicts of interests in the ethics review process.

While this thesis raises some crucial questions and provides a taste of what the answers to those questions might be, it is beyond the scope of this thesis to explore fully all these issues. For example, much more should and hopefully will be said in the future about the notion of respecting human dignity as raised in Chapter 3. What this thesis does seek to achieve is to argue convincingly that current ethical frameworks and guidelines are not providing ethics committees with the right tools and language to engage in meaningful discourses and that there needs to be a new way of looking at the ethical basis of research which is sufficiently rich to encompass the needs and interests of diversity within communities; but which also at the same time sets objective standards that hold persons accountable when necessary. Another example is the very important observation made in Chapter 5 about the impossibly compromised position of the researcher/physician in the informed consent process and the complete lack of recognition of the need for an independent informed consent facilitator in these situations.

It is also not within the scope of this thesis to make detailed recommendations relating to the weaknesses and insufficiencies uncovered by the discussions in the earlier chapters. At the end of the day, it is hoped that this thesis represents a first step in a journey towards reshaping the philosophy and process of human subject protection. To this end, much more empirical evidence will need to be collected to understand how ethics committees function and how within the political, economic and social realities of a developing country, improvements can be made to the way in which ethics review is carried out.

The following chapter, Chapter 2, provides an overview of the medical research industry in Malaysia in general and the machinery of clinical trials specifically. There is also a discussion of the Malaysian laws and guidelines that govern the enrolment of mentally incapacitated adults

into clinical trials. This sets the stage for the following three chapters, which analyse three main aspects of the ethics review process.

Chapters 3 and 4 deal with how ethics committees make decisions and whether or not they are able to engage in meaningful ethics discussions, which have at their heart, the interests of mentally incompetent patients. This is dealt with at two levels: first, by looking at the big picture, the very basic ethical principles that have been drawn up to provide for the protection of human subjects and considering if they are effective guides, and second, by analysing a specific guideline that is today considered the main document that ethics committees need to comply with. Chapter 3 begins with an examination of the current ethical guidelines and principles that are meant to guide decision-making in medical research involving human participants and contends that these guidelines and principles fail to provide a workable and coherent framework for ethics committees. Following this, by setting this discussion in the historical narrative of research misconduct, it is demonstrated that the notion of the undervaluation of human life lies at the heart of research misconduct and that this understanding is crucial to the construction of a rational and coherent ethical basis because it invites the question of what is the appropriate value of human life, the answer to which is presented as being respect for human dignity.

Chapter 4 then proceeds to look specifically at the ethics review process, putting it in its historical context. The Chapter also closely examines the document, which for all intents and purposes guides the way in which ethics committees are set up and under which they operate, namely the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Guideline for Good Clinical Practice E6 (R1). It argues

that this guideline falls far short of providing ethics committees with a framework for meaningful decision-making.

Chapter 5 considers the issue of the independence of ethics review committees. Beginning with a brief discussion of the notion of what it means to have a conflict of interest, it demonstrates the importance of the notion of independent ethics review by considering both the historical context and the impossibly compromised position of physicians/researchers in the informed consent process. Finally it demonstrates, how at a number of levels, ethics review committees possess or at least appear to possess conflicts of interests.

Research Methodology

This thesis relies on both desk and empirical research. Materials were obtained from libraries and the Internet. In-depth interviews were also conducted with 8 members of Malaysian ethics committees to understand how committee members see their roles as well as to get a better understanding of how they make decisions. The interviews, which on average lasted one hour, were taped and transcribed. Given the dearth of published information regarding clinical trials in Malaysia, informal interviews were also conducted with a number of psychiatrists/researchers, including the Chief Psychiatrist of Malaysia, Dr Suaran Singh⁶¹ to obtain an insight into how clinical trials are run on a day-to-day basis. Discussions were also held with some senior members of the civil service involved in the regulation of clinical trials to obtain a better picture of the regulatory mechanisms.

Insofar as materials obtained from libraries and the Internet are concerned, this thesis relies heavily on materials from the United Kingdom and the United States of America. This is because as noted

⁶¹ The interview with Doctor Suaran Singh elicited mainly factual information regarding psychiatric trials in Malaysia.

earlier, there is little, if any, Malaysian material. Apart from a few government publications, there is an absence of relevant textbooks or articles on the Malaysian position. Although there has been a heavy reliance on materials from other jurisdictions, the fact is that clinical trials are conducted under very similar guidelines across many jurisdictions and the primary points of references such as international guidelines and declarations apply equally in Malaysia as they would in the United Kingdom as well as in the United States of America. Consequently, many of the problems or issues faced in those jurisdictions would also apply to the Malaysian position and vice versa.

Interviews with ethics committee members were considered vital as the interviewees would have first hand experiences of the ethics review process and would be able to provide accurate and vivid narratives of their personal experiences. Selection of members from different backgrounds was important, as this would allow for a variety of perspectives, which would make for a richer, more nuanced, multi-dimensional view of the ethics review process.

Therefore, the basis of selection of interviewees was their experience, knowledge and the variety of perspectives that they bring to the topic. Interviews were thus conducted with laypersons, clinician/investigators and scientists. Interviewees were informed that their identities would not be revealed but as the pool of ethics committee members and investigators is a small one, interviewees were alerted to the fact that their identities may be quite easily discovered. They were told that transcripts of the interviews and sections of the research that made reference to them individually could be sent to them for comments before submission of the thesis, especially if they seemed reluctant to talk freely for fear of being misquoted or misunderstood.

There are two types of ethics committees in Malaysia, the Medical Research Ethics Committee (MREC), which reviews all applications to carry out research at any Ministry of Health (MOH) facility or using MOH resources; and ethics committees of academic institutions. Interviews were carried out with several members from both types of ethics committees. While letters asking for permission to interview ethics committee members were sent out to most of the ethics committees of academic institutions, only two positive responses were obtained: one from a relatively new medical faculty, which has yet to conduct any clinical trials in the areas of psychiatry or neurology; and another, from University A. University A has a well established medical faculty, with a proven track record in carrying out clinical research trials. In particular, the department of psychological medicine at University A has a very active research arm with five full time research co-ordinators and claims to have no less than five pharmaceutical related clinical trials being conducted at any one time. So far, they claim to have been involved in over 45 clinical trials. Moreover, University A's medical school is recognised as a pioneer in developing psychiatric services within the context of a general hospital and the model from which subsequent university hospital psychiatric services have been developed. Therefore, interviews were conducted with members of the ethics committee at University A, who were contactable and who agreed to be interviewed. The members interviewed are from a variety of disciplines: two lay members, one clinician-investigator and one scientist.

Various attempts were made to get permission to interview members of the MREC, but most of these attempts were met with refusals or silence. Given the fact that the MREC is a part of the Ministry of Health, this is perhaps unsurprising as civil servants in Malaysia are generally uneasy about releasing any information or discussing government policy. As a result of this, it was not possible to arrange for

interviews via the chairperson of the MREC. However, two members of the MREC were approached personally and agreed to be interviewed. One of them was the immediate past Chairperson of the MREC, who is still a member of the committee and is a clinician/investigator. The other person, who is also the Director of the Clinical Research Centre of Malaysia was also in the past a clinician/investigator. Another informal discussion was held with another member of the committee who is also a senior civil servant, as he declined a formal taped interview.

There are many different types of qualitative interviewing patterns ranging from open-ended unstructured interviews that provide a general flavour of the topic; to semi-structured/focused questions, which are either suggested by the answers to the initial question or when the researcher is interested in one core idea or specific piece of information. The type of interviewing pattern also depends on the subject of the approach. Using a two dimensional approach of breadth of focus and subject of focus, Rubin & Rubin⁶² construct a table of the variety of qualitative interviews patterns.

	Narrowly Focused Scope	In-Between	Broadly Focused Scope
Focused Mainly on Meanings and Frameworks	Concept clarification	Theory Elaboration	Ethnographic interpretation
In-Between	Exit interview	Oral histories Organisational culture	Life history
Focused Mainly on Event and Processes	Investigative interviewing	Action research Evaluation research	Elaborated case studies

The current study employed a mixture of open-ended unstructured questions and semi-focused questions. The questions asked were meant

⁶² Rubin, Herbert J. and Rubin, Irene, S. 2005 *Qualitative Interviewing: The art of hearing data*, 2nd Edition, Thousand Oaks, Sage Publications at 5

to generally guide conversational partners in an extended discussion to elicit depth and detail. Unlike survey research, each conversation is unique and the questions that are asked may vary depending on the flow of conversations. The idea of the interview was to generate depth of understanding rather than breadth. The aim of the questions was to obtain the interviewer's interpretations of their experiences and understanding of the processes and as such, the interviewer had to be aware of personal opinions, experiences and prejudices and be careful not to allow it to colour the conversation.

2 Chapter 2

The Malaysian Context

This chapter provides a brief snapshot of the context in which clinical trials are run in Malaysia. The discussion in this chapter on the environment in which clinical trials are run is meant to serve the following purpose; to demonstrate how over the last twenty years, the growth of biotechnology research in general and clinical trials specifically, have come to represent an important source of revenue for the government and how this has created a tension between creating an environment that is attractive to the sponsors of international clinical trials and ensuring that the rights and interests of subjects are protected.

Medical Research in Malaysia – A Brief History

Early days

The Institute of Medical Research (IMR),⁶³ Kuala Lumpur, established in 1900 by the British as a Pathological Institute to study tropical diseases⁶⁴ is the oldest medical research centre in Malaysia. The institute was meant to serve as a research outpost for the London School of Tropical Medicine, established a year earlier in 1899.⁶⁵ Early research was limited to tropical diseases such as malaria, beri-beri, dysentery and cholera.⁶⁶

⁶³ For further information see <http://www.imr.gov.my/about/history.htm> accessed August 17, 2010

⁶⁴ See <http://www.who.int/tdroid/publications/tdrnews/news64/imr.htm> accessed August 17, 2010 for further details.

⁶⁵ K. Ramanathan, Winnie C. Cheah, and Timothy J. Dondero, *75 Years of Medical Research in Malaysia : 1901-1976*, Rev. ed. (Kuala Lumpur: Institute for Medical Research, 1976) at 5

⁶⁶ Since then, the IMR has extended the ambit of its research into areas such as immunology, cancer research, herbal medicine and environmental health. Its research priorities are not commercially driven and remain directly related to health problems faced by the country, and it continues to excel in the management and treatment of tropical diseases. It is a WHO collaborating centre on taxonomy and immunology of Filariasis and clinical trials of drugs against Brugian Filariasis; ecology, taxonomy and control of vectors of Malaria, Filariasis and Dengue; and training for the Lymphatic Filariasis Elimination Program.

One of the earliest records of a clinical trial carried out in Malaysia is found in the 1907 issue of the *Lancet* entitled, "Rice and beri-beri: preliminary report on an experiment conducted in the Kuala Lumpur Insane Asylum."⁶⁷ Owing to a high incidence of beri-beri in the KL asylum, an experiment was carried out to determine if the cured (Siamese) rice supplied to the patients was the cause of the disease. Half the patients were provided with uncured (Indian) rice, while the other half remained on cured rice. The results showed that 34 out of 120 patients fed on cured rice developed beri-beri out of which 18 died, whilst there were no deaths among the 123 patients who dieted on uncured rice, and that the only 2 cases that were reported, had been suffering from the condition upon admission.⁶⁸ The experiment provided valuable insights into the causes of beri-beri, of which very little was known about at that time. Interestingly, no mention was made of the consent, willingness or even knowledge of the patients who were entered into the experiment; the researchers only sought the consent of the Government before starting the trial.

Apart from the primary research carried out by the IMR, the majority of clinical research trials carried out in Malaysia until recently have been Phase IV⁶⁹ marketing studies. These Phase IV studies tended to be "seeding trials", which were largely funded and managed by local or regional marketing offices of pharmaceutical companies, looking to promote the use of recently registered drugs among local doctors.⁷⁰ Running earlier phase clinical trials in developing countries was at

⁶⁷ W Fletcher, "Rice and Beri-Beri: Preliminary Report on an Experiment Conducted in the Kuala Lumpur Insane Asylum," *Lancet* 1 (1907).

⁶⁸ *Ibid* at 1776

⁶⁹ Clinical trials are run in a series of steps/phases where each phase is designed to answer a specific question. The phases run from Phase I to Phase IV. A Phase I trial is carried out on a small test population at an early stage of drug development to determine the safety profile of the drug. This is followed by Phase II trial that is carried out on a larger cohort of people to further evaluate the safety profiles of the drug. In Phase III, the trial drug is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely. Phase IV is done after the drug has been marketed to gather further information for marketing purposes.

⁷⁰ C.C. Lang, "The Current Status of Clinical Trials in Malaysia," *Drug Information Journal* 32, no. Oct-Dec 1998. at 1243S

that time viewed as pointless, because in order to register drugs in countries such as the US, Europe and Japan, drug developers needed to rely on decisions made by the regulatory authorities in these developed countries,⁷¹ which only permitted the use of data generated by trials in those countries. Big sponsors of clinical trials were reluctant to fund clinical trials in small developing countries such as Malaysia as the markets in these countries were too small to be of any significant interest to them. Also, because the regulatory authorities in developing countries themselves were relatively unsophisticated compared to developed countries such as the US and Japan, they tended to rely on the decisions made by the regulatory authorities in the developed countries, particularly the American Food and Drug Administration (FDA). Consequently, registration of drugs in these markets tended to rely on FDA approval. This meant that it was vital for new drugs to be approved by the relevant authorities in the US, Europe and Japan.

Emergence of the local clinical trial industry

The position has changed dramatically over the last fifteen years with a marked increase in the number of clinical trials run in Malaysia. In 1996, less than 10 trials were conducted in the country; whereas in 2008, 87 clinical trials were contracted to Malaysia, recruiting in 323 investigative sites, and targeting 5409 patients for enrolment.⁷² Malaysia is also emerging as a preferred destination for clinical research in South East Asia. A report by Pacific Bridge Medical,⁷³ describes Malaysia as a country where trials can be of 'decent quality and normally offer significantly lower costs than places like Taiwan, Singapore and Hong Kong.' Notably, the report remarks that Malaysia

⁷¹ Ibid. at1244S

⁷² Y. M. Ong, "Role of Crc in Promoting Malaysia to Industry," in *National Conference for Clinical Research, Malaysia* (Kuala Lumpur: 2009).

⁷³ Report from Pacific Bridge Medical, a leading Asian medical consulting firm, published in Speciality Pharma website <http://www.specialitypharma.org/>; Gross, A., Momoko H, *Conducting Clinical Trials in Asia*

is the most popular location for trials in Southeast Asia (not including Singapore) as it has a relatively developed hospital infrastructure and an advanced regulatory environment for drugs. In 2008, Malaysia was ranked 16 out of the 50 most active Asian cities based on the total number of study sites.⁷⁴

In terms of the phases⁷⁵ of clinical trials run in the country, there has been a steady increase in the number of Phase II and Phase III trials. In the year 2008, applications for Phase III trials accounted for 63% of the total number of applications, with Phase II trials coming in second highest with 29% of the total. This is in marked contrast with the situation in 1996, where there were no applications for Phase I and Phase II trials and Phase III trials accounted for less than a third of the total number of applications.⁷⁶ Clinical trials are primarily run in the following therapeutic areas: cardiovascular medicine, endocrinology, oncology, hepatology, infectious diseases, psychiatry and paediatrics.⁷⁷ Significantly, psychiatry ranked as the top therapeutic area of research.⁷⁸

The rapid expansion of the local clinical trial industry can be attributed to two developments. First, there was a growing acceptance by the FDA that its decision making process should make use of data from properly carried out trials in foreign countries. Allowing the use of data from foreign trials would serve several ends: it would dramatically improve the statistical significance of the findings, as

⁷⁴ J Karlberg, "Development of Sponsored Clinical Trials in Asia," *Clinical Trial Magnifier* 1, no. 5 (2008) at 82

⁷⁵ See Note 7 for a description of the different types of phases of clinical trials.

⁷⁶ ZH Zakaria, "Regulatory Aspects of Clinical Trials in Malaysia," ed. Ministry of Health National Pharmaceutical Control Bureau. at [http://www.research.kk.usm.my/pages/enrich/notes/Talk%2005%20-%20Regulations and Issues of Clinical Trials in Malaysia - Zaril%20Harza.pdf](http://www.research.kk.usm.my/pages/enrich/notes/Talk%2005%20-%20Regulations%20and%20Issues%20of%20Clinical%20Trials%20in%20Malaysia%20-%20Zaril%20Harza.pdf) accessed August 17, 2010

⁷⁷ PRA International, "Clinical Research in Taiwan, South Korea and Malaysia," PRA International, www.prainternational.com

⁷⁸ Ong, "Role of CRC in Promoting Malaysia to Industry.", National Conference for Clinical Research, Malaysia, 9 July 2009, Kuala Lumpur

more subjects would be recruited; it would also shorten the timeline for clinical testing as many more trials could be run concurrently; and finally, such trials, if carried out in developing countries, would be much cheaper to run. Following from this, in 1990,⁷⁹ the regulatory authorities for Europe, Japan and the United States initiated a 'joint regulatory/industry project to improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States',⁸⁰ in the form of The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH publishes guidelines that meet regulatory requirements for drug registration for the three jurisdictions, thus allowing for the running of multi-centre, international clinical trials for a single research protocol. The guidelines serve as a sort of quality control to ensure the integrity of data generated by any trial run in any country. The ICH guidelines are exhaustive and range from topics such as the clinical safety of drugs to terminology in pharmacogenomics. The guideline that is of specific relevance to the running of clinical trials is the ICH Good Clinical Practice: Consolidated Guideline (ICH-GCP Guideline),⁸¹ which describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and Institutional Review Boards. With the emergence of the ICH guidelines, large pharmaceutical companies who sponsor the majority of clinical trials were now able to rely on data obtained from clinical trials run anywhere in the world when applying to register their drugs in developed countries, as long as the trials adhere to the ICH standards.

⁷⁹ 2nd ICH Steering Committee Meeting in Tokyo, 23-24 October 1990

⁸⁰ History and Future of ICH at <http://www.ich.org/cache/compo/276-254-1.html> accessed on August 17, 2010.

⁸¹ E6(R1): Good Clinical Practice : Consolidated Guideline at <http://www.ich.org/cache/compo/276-254-1.html> (accessed August 21, 2007)

Second, because of the creation of the ICH process, pharmaceutical companies, which were looking at declining profit margins, became increasingly drawn to running trials in developing countries. Every year, Big Pharma⁸² spend US\$14 billion on testing drugs on human subjects.⁸³ Nevertheless, these companies are facing huge losses as investors begin to lose faith in their growth prospects.⁸⁴ The growth of generic firms, ending of patents on current drugs,⁸⁵ and increasing costs⁸⁶ incurred in developing new treatments have impacted heavily on the drug industry. The big money in pharmaceuticals lies in patented drugs. The highest selling twenty drugs in the year 2000 generated sales of about US\$100 billion, which was the equivalent of fifty percent of the total sales of the top 500 drugs.⁸⁷ Companies cannot invest heavily in research and development and at the same time expect to generate profits unless new drugs are developed and introduced into the market before current patents lapse. It is estimated that in order to maintain current levels of profitability, industry leaders will have to launch between 24 to 34 new drugs per year.⁸⁸ Therefore sponsors are constantly on the lookout for more cost efficient means of developing drugs and an increasing number of clinical trials are now run in developing countries. A review of 300 articles reporting the results of clinical trials in the *New England Journal of Medicine*, the *Lancet*, and the *Journal of the American Medical Association*, in

⁸² Big Pharma is a term that is used to describe the world's largest pharmaceutical companies. The top ten companies account for over 50% of global industry sales. See D. Jackson, "The Pharmaceutical Market Outlook to 2010," in *Reuters Business Insight - Healthcare*, ed. Reuters (Reuters, 2003). at 8

⁸³ D. Smith Evans, M. and Wilen, D., "Big Pharma's Shameful Secret," <http://www.bloomberg.com/specialreport/pharma.pdf>.

⁸⁴ An article in the Economist, cites a report by Accenture, which calculates that US\$1 trillion of future profitability has been wiped out because of lack of confidence on the part of investors. "Billion Dollar Pills," *The Economist*, Jan 25 2007.

⁸⁵ See Evans, "Big Pharma's Shameful Secret." Pharmaceutical companies that make 28 top-selling drugs will lose a total of \$50 billion in revenue as their patents expire from 2003 to 2008 according to Norwalk, Connecticut-based market research firm BCC Inc.

⁸⁶ It is estimated that the average cost of bringing a new drug to market in the United States is about \$500 million. Frank Davidoff et al., "Sponsorship, Authorship, and Accountability," *Ann Intern Med* 135, no. 6 (2001) at 463

⁸⁷ Jackson, "The Pharmaceutical Market Outlook to 2010." at 8

⁸⁸ Karine Morin et al., "Managing Conflicts of Interest in the Conduct of Clinical Trials," *JAMA* 287, no. 1 (2002) at 78

1995 and 2005, found that the number of trial sites outside the United States had more than doubled, whereas the proportion of trials conducted in the United States and Western Europe had decreased.⁸⁹

Clinical trials in Asian countries such as Malaysia, for example, are less expensive and less time-consuming than those carried out in developed countries. Because clinical research costs are largely driven by human labour, much of the cost difference is attributable to the lower salaries paid to investigators, nurses and study co-ordinators.⁹⁰ Also, patient recruitment in developing countries is reported to be generally easier and faster.⁹¹ This is significant as recruitment sometimes accounts for about half of the time required for the clinical trial. Another important reason why clinical trials are moving to developing countries is the increasingly bureaucratic and expensive regulatory environment in many developed countries; developing countries tend to have less complicated regulatory regimes, allowing for faster approval times and place less burdens on investigators and sponsors.⁹²

Government support of clinical trial industry

Developing countries in turn, have eagerly embraced this development and vie for the opportunity to conduct multinational trials in their countries. Malaysia for instance has put into place policies and programmes aimed at enticing sponsors to its shores. Among other things, it advertises the country as being an ideal place to carry out research owing to its pro-business government, political stability, cost-effective base for business, excellent transportation and ICT

⁸⁹ Glickman et al., "Ethical and Scientific Implications of the Globalization of Clinical Research," *N Engl J Med* 360, no. 8 (2009) at 816

⁹⁰ *Ibid.* at 816

⁹¹ Report from Pacific Bridge Medical, a leading Asian medical consulting firm, published in Speciality Pharma see <http://www.specialitypharma.org/>

⁹² Glickman et al., "Ethical and Scientific Implications of the Globalization of Clinical Research." at 818, Asprey, D. "UK Government Asks Academy to Review Regulation of Research." *BMJ* 340 (2010): c1770.

infrastructure, cost-competitive base of knowledge workers and its rich diversity in flora, fauna and population.⁹³

In 2005, the National Biotechnology Policy published by the Ministry of Science, Technology and Innovation, set out a series of financial incentives⁹⁴ such as grants and tax allowances, in the hope of 'attracting the best biotechnology ventures along the entire research and industry value chain.'⁹⁵ The policy among other things, establishes the Malaysian Biotech Corporation (MBC) that is entrusted with co-ordinating biotechnology initiatives from all relevant government ministries and is intended to be a dedicated one-stop agency with the main objective of developing the country's biotechnology industry.⁹⁶ In relation to health care matters, the MBC works together with the National Institutes of Health (NIH)⁹⁷, which was set up in 1996 to set research priorities and allocate research funding.⁹⁸ There are seven institutes⁹⁹ under the NIH and each institute has its own major research thrust, with the Network for Clinical Research Centres (CRC) as the clinical research arm of the NIH. The CRC is the main clinical research organisation in the country, with a network of 14 centres around the country, providing a single point of contact to access all Ministry of Health (MOH) hospitals and clinics nationwide¹⁰⁰. Apart from the Ministry of Health facilities, clinical trials are also run by the university hospitals. Private health care facilities as a rule do not carry out clinical trials. Recognising that at present very little basic research

⁹³ Ministry of Science Technology and Innovation Malaysia, "Bioetchnology for Wealth Creation and Social Well Being. The Way Forward," ed. Technology and Innovation (MOSTI) Ministry of Science (MOSTI, 2005). at 3

⁹⁴ The full list of incentives can be viewed online at www.mosti.gov.my

⁹⁵ Foreword by the Prime Minister of Malaysia, Datuk Seri Ahmad Badawi, in Ministry of Science Technology and Innovation Malaysia, "Bioetchnology for Wealth Creation and Social Well Being. The Way Forward." at 1

⁹⁶ Ibid. at 7

⁹⁷ Set up under the Ministry of Health (MOH)

⁹⁸ See the National Institutes of Health website, <http://www.nih.gov.my> accessed 9 July 2007

⁹⁹ Institute for Medical Research, Institute for Public Health, Network for Clinical Research Centres, Institute for Health Management, Institute for Health Systems Research, Institute for Health Promotion and National Institute for Natural Products, Vaccines and Biologicals.

¹⁰⁰ See http://www.crc.gov.my/default.asp?page=/about_us/index accessed 26 August 2007

on drug development is carried out in the country as it lacks the financial and technical resources,¹⁰¹ the main aim of the policy regarding clinical trials is to attract foreign investment. In a recent press interview, the Director-General of Health was quoted as saying; "I would like to see Malaysia position herself as the region's preferred clinical trial destination in the not-too-distant future."¹⁰²

Globalisation and the impact on human subject protection

The globalisation of clinical trials has been both a boon and a bane to developing countries such as Malaysia. Malaysia clearly benefits from the injection of money and technology into its health care system. However, there are two broad areas of concern that stem from the globalisation of clinical trials. First, there is the worry that because of the wide disparities that exist between developed and developing countries in respect of education, economic and social standing, and health care provision; there is a real danger that governments and companies of wealthy nations may exploit developing countries. Much ink has been spilled on both sides of the debate and an in depth discussion of these issues is beyond the scope of this paper.¹⁰³ However, some of the concerns raised in this regard go straight to the heart of human subject protection. An example of this is the issue of placebo-controlled trials. In a placebo-controlled trial, the efficacy of a new drug is tested against a placebo. Such a trial is generally considered unethical if there is a known effective treatment for that same

¹⁰¹ It is estimated that the average sum of US\$800 million is spent to develop a single drug from laboratory to marketplace. Economic Planning Unit Prime Minister's Department Malaysia, "Ninth Malaysia Plan 2006-2010," ed. Prime Minister's Department (Economic Planning Unit Prime Minister's Department Malaysia, 2006) at 414

¹⁰² T. T K Letchumy, Malaysia to position itself as region's clinical trial destination, *Malay Mail*, (Kuala Lumpur 2 June, 2010)

¹⁰³ A good discussion on the issue of exploitation and developing countries can be found in J S Hawkins and E. Emanuel, eds., *Exploitation and Developing Countries. The Ethics of Clinical Research* (Princeton: Princeton University Press, 2008).. Also see R Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge University Press, 2004), Garrafa, V, JH Solbakk, S Vidal, and C Lorenzo. "Between the Needy and the Greedy: The Quest for a Just and Fair Ethics of Clinical Research." *Journal of Medical Ethics* 36, no. 8 (2010): 500.

condition. It is unfair to offer subjects a placebo in place of an effective treatment. However, under current ethics guidelines, placebo-controlled trials are permitted where no current proven intervention exists.¹⁰⁴ This criterion usually obtains in developing and least developed countries because the existing intellectual property market regime of patent protection has meant that many developing countries, including Malaysia are often¹⁰⁵ unable to afford these proven interventions as standard interventions. It is thus permissible to carry out placebo-controlled trials in these countries. Therefore, subjects in Malaysia may be submitted to a clinical trial that would be otherwise considered unethical in U.K. Also, given the fact that clinical trials are only run in government facilities and academic centres, the cohort of patients tend to be drawn from the poorer sections of society. This situation is exacerbated in clinical trials involving mentally incapacitated persons. The worry is whether subjects drawn from marginalised sections of society are being exploited. The process of ethics review, if it is to mean anything, must be able to recognise and take into account the specific concerns that are raised by Malaysia being a developing country.¹⁰⁶

The second concern is that because the Malaysian government wants to become the venue of choice for the clinical trial industry, it may end up compromising human subject protection in its pursuit of economic prosperity. As is discussed in the following section, the clinical trial industry for all intents and purposes regulates itself. The only document that is used in practice to regulate clinical trials is the ICH-GCP. There is no local legislation that provides for local standards and

¹⁰⁴ Principle 31 World Medical Association, "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," (2008).

¹⁰⁵ In 2002, the world drug market was valued at \$406 billion, of which the developing world accounted for only twenty percent British Commission on Intellectual Property, "Integrating Intellectual Property Rights and Development Policy," in *Report of the Commission of Intellectual Property* (London: 2002). at 32

¹⁰⁶ The issue of placebo-controlled trials in clinical research trials involving mentally incompetent patients is discussed in more depth in Chapter 4 at 145-151

scrutiny of trials. The establishment and terms of reference of ethics review, is similarly based on ICH-GCP principles, which as discussed in Chapter 4, does not have human subject protection as its underlying philosophy. It is simply not in the interest of developing countries to have complex, time-consuming and expensive processes. Ethics committee review is carried out because it is mandated by the ICH-GCP; but the issue of whether or not the review process does in fact provide adequate protection to subjects by engaging in meaningful discussion, is rarely addressed. In fact, several studies of the existence and resources of ethics committees in developing countries in Africa and South America have raised troubling questions about the lack of training provided to members and composition of committees.¹⁰⁷ To date, there has been no similar research carried out in Malaysia, but preliminary evidence from interviews conducted for this thesis reveals a similar picture.

Regulation of clinical trials in Malaysia

Legislation

There is no law in Malaysia that specifically regulates the running of clinical trials. The only relevant legislation is the Sale of Drugs Act 1952 and its corresponding Control of Drugs and Cosmetics Regulations 1984, which regulate the importation and licensing of drugs for clinical trials. The act and the regulation fall under the purview of the National Pharmaceutical Board (NPB) of the Ministry of Health.

The body entrusted with developing government policies for the clinical trial industry is the National Committee for Clinical Research

¹⁰⁷ C Perrey et al., "Ethical Issues in Medical Research in the Developing World: A Report on a Meeting Organised by Foundation Merieux," *Developing World Bioethics* 9, no. 2 (2009). at 92

(NCCR).¹⁰⁸ There appears to be some interest in the NCCR for bringing the clinical trial industry under some sort of regulation,¹⁰⁹ but specific information as to how this would be accomplished could not be obtained because of the Official Secrets Act 1972.¹¹⁰ It is however quite clear that the government does not have any immediate plans to create a comprehensive piece of legislation to regulate clinical trials because of the many objections of interested parties; any control mechanisms are likely to be marginal and effected by extending the powers of the NPB under the Sale of Drugs Act 1952.¹¹¹ This light touch approach is as noted earlier a hallmark of clinical trial regulation in developing countries. It is telling that not one of the five terms of reference of the NCCR mentions human subject protection, but all five are geared towards expansion of the clinical trial industry. In fact, the final term of reference of the committee is “to take pro-active action *at all times*¹¹² in enhancing clinical research in Malaysia in tandem with the development in developed nations”.

Guidelines

Although there is no legislation currently in place, in practice, clinical trials are run in strict compliance with the ICH-GCP Guideline. The reason for this is that all clinical trials are carried out in public institutions¹¹³ that fall under the purview or influence of the Ministry of Health, and specifically the NCCR.¹¹⁴ Apart from developing broad government policies, the NCCR is also responsible for developing and publishing guidelines for clinical trials. To date, the NCCR has

¹⁰⁸ Established in 1997, The NCCR is a policy making body under the Ministry of Health. For more information see <http://www.nccr.gov.my>

¹⁰⁹ Interview with Dr Kamaruzaman Shah, Head of Clinical Research and Compliance Centre, National Pharmaceutical Control Board, Ministry of Health and also secretary to the NCCR on 2 March 2008

¹¹⁰ The Official Secrets Act 1972 restricts the dissemination of information classified as an official secret. Draft legislation is habitually classified as falling under the Official Secrets Act 1972.

¹¹¹ Interview with Professor Visweswaran Navaratnam, NCCR member, 22 November 2008

¹¹² Author's emphasis

¹¹³ Ministry of Health hospitals and university hospitals run by public universities.

¹¹⁴ For more information see, <http://www.nccr.gov.my>

published a Malaysian version of the ICH-GCP Guideline and Guidelines for Applications to Conduct Drug-Related Clinical Trials in Malaysia.¹¹⁵ Although the guidelines do not have the force of law, all public institutions or institutions that receive public funding, are bound to abide by the guidelines issued by the NCCR.

ICH-GCP Guideline

The Malaysian ICH-GCP Guideline¹¹⁶ is almost identical to the original ICH-GCP Guideline with very few minor amendments, which are mostly concerned with administrative matters such as the inclusion of local regulatory authorities in the glossary;¹¹⁷ allowing institutions without ethics committees to make requests to the ethics committee of the Ministry of Health or any of the University committees;¹¹⁸ requiring that all investigators receive approved training in Good Clinical Practice;¹¹⁹ and providing for thumbprints as evidence of consent where a subject or legal representative is unable to read.¹²⁰ The only amendment of any significance is the inclusion of para 4.8.10 (u) that requires investigators to inform subjects that the source of the investigational product may be culturally unacceptable. This was presumably added primarily for the benefit of Muslim subjects as some trial products contain porcine material.¹²¹ All centres currently conducting clinical trials in the country are bound by these guidelines issued by the NCCR, which for all intents and purposes will result in close compliance to the original ICH-GCP Guideline.

¹¹⁵ *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia*, 12 April 2007.

¹¹⁶ *Malaysian Guidelines for Good Clinical Practice 2004, 2nd Edition*.

¹¹⁷ *Ibid.*

¹¹⁸ *Ibid.* Para 3.2.7

¹¹⁹ *Ibid.* Para 4.1.1

¹²⁰ *Ibid.* Para 4.8.9

¹²¹ As a past member of the University of Malaya Medical Centre's Ethics Committee, I observed that concerns were only raised when investigational products had porcine material. It should be borne in mind that Hindu or Buddhist subjects might have objected to products of bovine origin, but these concerns were never dealt with.

Special emphasis is placed on adherence to the ICH-GCP Guideline because almost all drug trials carried out in the country, including the current drive by the government towards the expansion of the clinical trial enterprise, revolve around trials sponsored by multinational pharmaceutical companies. It is vital to these organisations that regulatory authorities in America and Europe accept the data generated by these trials. To this end, compliance with ICH-GCP standards is essential. An interesting point to note is that while the Malaysian ICH-GCP Guideline requires that all investigators receive approved GCP training; the current approved GCP workshops run by the Ministry of Health examine investigators not on the Malaysian version of the ICH-GCP, but rather on the original ICH-GCP Guideline.

Guidelines for Applications to Conduct Drug-Related Clinical Trials in Malaysia

The Guidelines for Applications to Conduct Drug-Related Clinical Trials in Malaysia¹²² issued by the NCCR, require that prior to the commencement of any clinical drug trial, approvals must be obtained from research and ethics committees and the National Pharmaceutical Control Bureau (NPCB).¹²³ Parallel submissions of applications are permitted and a recent industry report¹²⁴ estimates that the process takes approximately twelve to fourteen weeks. Research committees scrutinise the protocols for scientific merit while the principal task of ethics committees is to 'ensure that proposals comply with internationally accepted guidelines in the care and treatment of human

¹²² *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia.*

¹²³ The NPCB is responsible for issuing import licences and permits for drugs used in clinical trials under the Sale of Drugs Act 1952.

¹²⁴ PRA International, "Clinical Research in Taiwan, South Korea and Malaysia.". However, the Director-General of Health in a recent interview with a local daily placed the average time taken for approval at six weeks. See Star Online, "Clinical Trials in Malaysia," *The Star Online*, April 22 2007.

subjects.’¹²⁵ The specific responsibilities of the ethics committees is found in the ICH-GCP Guideline which mentions that clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).¹²⁶

Incapacitated subjects and clinical trials in Malaysia

Legislation

Malaysia has no specific law that regulates the participation of mentally incapacitated subjects in clinical research, but some guidance may be obtained from the laws that regulate decision-making for those who are considered unable to provide consent because of immaturity or infirmity. In the case of children, the parents or guardians of infants¹²⁷ are given powers to make health decisions for them under Section 3 of the Guardianship of Infants Act 1961,¹²⁸ which stipulates that the guardian of an infant shall be responsible for his ‘support, health and education’. There is no further mention of what it means to have this responsibility but it can be assumed that this empowers the guardian to make decisions on behalf of the child in relation to among other things, health care matters.

Mental Disorders Ordinance 1952

The answer as to who should be allowed to make health care decisions for mentally incapacitated adults is much less clear. A perusal of the Mental Disorders Ordinance 1952 (the Ordinance), which provides for

¹²⁵ Section A, Guideline 2.3 in *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia*.

¹²⁶ Guideline 2.1 World Medical Association, "Declaration of Helsinki: Ethical Principles For Medical Research Involving Human Subjects.", Guideline 2.1 *Malaysian Guidelines for Good Clinical Practice 2004, 2nd Edition*.

¹²⁷ Interestingly, the Act recognises that a Muslim child attains majority at the age of 18 years, whereas a non-Muslim child attains majority at the age of 21 years. Section 2(2) *Guardianship of Infants Act 1961 (Act 351)*.

¹²⁸ *Ibid*.

the care, reception and detention of persons of unsound mind does not provide any ready answers. The Ordinance primarily concerns itself only with matters concerning the reception and detention of persons in mental hospitals and is silent on matters relating to proxy decision-making. However, it is quite interesting to note that the Ordinance provides the courts with the power to appoint a committee or committees of the person and estate of a person¹²⁹ following a determination that such a person is mentally disordered.¹³⁰ There is unfortunately, no further mention of who should be appointed to this committee or what the powers or duties of the committee might be. It does however, seem to be the only provision in the Ordinance that comes close to giving another person/group of persons some decision-making power on behalf of the mentally disordered individual, and therefore merits closer scrutiny.

The notion of appointing a committee of a person is derived from archaic English mental health policy.¹³¹ This power was defined in the early fourteenth century and originated from the prerogative jurisdiction of the Crown, which was delegated to the Lord Chancellor.¹³² An inquiry was held where upon a determination of an appropriate degree of insanity, the care of the patient's person would be entrusted to a committee of the person. Unsworth¹³³ describes this sort of order as being a 'pre-carceral¹³⁴ mode of furnishing legal provision for the insane', which was property-driven rather than person-oriented, and in practice was usually reserved for cases where

¹²⁹ Section 10(1) *Mental Disorders Ordinance 1952, Federation of Malaya*.

¹³⁰ A mentally disordered person is defined as any person 'found by due course of law to be of unsound mind and incapable of managing himself or his affairs' Section 2 *Ibid*. The Court makes this determination following a formal inquiry Section 8 *Mental Disorders Ordinance 1952, Federation of Malaya*.

¹³¹ The Ordinance suffers from several weaknesses, one of which is the fact that it is painfully out of date.

¹³² See Clive Unsworth, "Law and Lunacy in Psychiatry's 'Golden Age'," *Oxford Journal of Legal Studies* 13, no. 4 (1993) for a more detailed discussion.

¹³³ *Ibid*. at 490

¹³⁴ It provided a means for caring for mentally incapacitated patients in a time before the *en masse* institutional detention. The power of psychiatry was at this time founded on the asylum.

control over family wealth was at issue. With the arrival of the carceral era, this jurisdiction was progressively marginalised and eventually disappeared. Clearly, the order in its inception was never intended to bestow proxy health care decision-making powers on the committee.

This would also suggest that as far as the Malaysian Ordinance is concerned, the committee of the person should not be assumed to possess proxy health care decision-making powers. Even if it were possible to infer proxy decision-making powers into the appointment, there are three further problems with the way in which these powers would operate under the Ordinance. First, much like the early English law,¹³⁵ there is almost no control exercisable over committees and while in England there was progressive law reform, which provided for oversight of the committees, no similar regulatory structures exist in Malaysia. A committee of the person appointed under the Ordinance would thus have an unfettered discretion to make decisions for the incapacitated individual.

Second, the Ordinance deals with the issue of incapacity as being either universally present or absent. When the court judges an individual to be mentally disordered, he is presumed to be universally unable to manage himself or his affairs and the committee of the person is entrusted with the management of all his personal affairs,¹³⁶ which would presumably include health care decisions. This view of incapacity is not in keeping with the current understanding of incapacity, which is based on a functional approach,¹³⁷ and would result in giving the committee a very wide power over the incapacitated individual.

¹³⁵ Unsworth, "Law and Lunacy in Psychiatry's 'Golden Age'." at 490

¹³⁶ The committee of the person is entrusted with the general care of the person and may among other things, commit him to an asylum; fix his residence and select his physician. See G. Pitt-Lewis, John Anthony Hawke, and Robert Percy M. D. Smith, *The Insane and the Law* (London: J. & A. Churchill: London, 1895) at 91

¹³⁷ The functional approach to capacity recognises that a person's ability to make a decision is determined in the context of a particular function or decision-making task.

Third, and most importantly, this power only comes into play in limited situations where the person is found to be not only mentally disordered but is also considered a danger to himself or to others.¹³⁸ Thus, it is only of restricted application and cannot be used as a general tool for proxy health care decision-making, much less deciding whether or not to enrol someone in a clinical research trial.

Parens Patriae Jurisdiction

As discussed earlier, the Mental Disorders Ordinance 1952 is not able to provide a satisfactory legal basis for adult proxy health care decision-making. In the absence of any specific legislative provision, the question arises as to whether the court's inherent *parens patriae* jurisdiction would extend to the care of mentally incompetent adults. There is no local case law on this matter and therefore guidance may be obtained from English common law. The English common law relating to proxy decision making for incompetent adults, is found in the case of *Re F (Mental patient: sterilisation)*¹³⁹ where the court declared that its ancient *parens patriae* jurisdiction originally vested in the Lord Chancellor only survived in relation to children and no longer existed in relation to adult persons of unsound minds with the coming into force of Section 1 of the Mental Health Act 1959.

It is unclear whether or not this jurisdiction still exists as far as the Malaysian courts are concerned. Section 3(1) of the Civil Law Act 1956 states that

¹³⁸ Section 10(2) *Mental Disorders Ordinance 1952, Federation of Malaya*. "If the Court finds that the person who is alleged to be mentally disordered is incapable of managing his affairs, but is not dangerous to himself or to others, the Court may appoint a committee of his estate, without appointing a committee of the person."

¹³⁹ [1990] 2 AC 1

‘Save so far as other provision has been made or may hereafter be made by any written law in force in Malaysia, the Court shall

- (a) in West Malaysia or any part thereof, apply the common law of England and the rules of equity as administered in England on the 7th day of April 1956’

Assuming that the appointment of the committee of the person under the Ordinance does not include proxy health care decision-making power based on the reasons discussed earlier, then this would appear to suggest that the appropriate position of the common law in Malaysia is pre section 1 of the UK Mental Health Act 1959, which means that the ancient prerogative jurisdiction remains. However, it is submitted that this should not be the case. The reason why the Mental Health Act 1959 was considered by the court in *Re F*¹⁴⁰ to be the point at which the prerogative ceased to exist, was presumably because it was at that point that decisions relating to the detention and treatment of mentally ill persons were taken away from the judiciary and handed over to an administrative process.¹⁴¹ Applying the same line of reasoning to the situation in Malaysia, the enactment of the Mental Disorders Ordinance 1952, which provided an administrative process for the detention and treatment of mentally incapacitated adults, should logically be the point at which the *parens patriae* jurisdiction of the Malaysian courts in relation to incapacitated adults ceased to exist.

Common Law Doctrine

This then leaves the option of the position at common law as stated in *Re F*, where the basis for making health care decisions for incompetent adults lies under the common law doctrine of necessity and that the doctor should act in the best interests of the patient. The application of

¹⁴⁰ Ibid

¹⁴¹ For a brief account of the history of mental health, see http://www.mind.org.uk/help/research_and_policy/the_history_of_mental_health_and_community_care-key_dates accessed August 17, 2010

this common law doctrine in cases of enrolling mentally incompetent adults in clinical research trials is not without its problems. It is difficult to see how one might argue that necessity demands that it is in a patient's best interests to be entered into a clinical trial. Much has been written regarding what is called the 'therapeutic misconception' and the importance of not confusing research with treatment; and in fact some argue that even the distinction between therapeutic and non-therapeutic trials should be abandoned.¹⁴² Accordingly, the Belmont Report has made clear that research and practice are mutually exclusive and

'that "practice" refers to interventions that are designed solely to enhance the well-being of the individual patient or client and that have a reasonable expectation of success. ... By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalisable knowledge.'¹⁴³

No research trial, therapeutic or otherwise is ever designed solely to enhance the well-being of a subject and it is never concerned with the best interests of the individual patient. It is therefore impossible to claim that based on necessity, is in the best interests of the mentally incapacitated adult to enrol in a clinical trial.

The situation thus appears to be that there is no legally sanctioned basis for enrolling mentally incapacitated adults into clinical trials.

Mental Health Act 2001

The state of the law will change once the Mental Health Act 2001(the Act) comes into force. The Mental Health Act 2001 replaces the

¹⁴² See Franklin G. Miller and Howard Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *The Hastings Center Report* 33, no. 3 (2003). for an excellent analysis of the therapeutic misconception

¹⁴³ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects Research," (Washington: Department of Health, Education and Welfare, 1979) at 2-3

existing Mental Disorders Ordinance 1952 and will be implemented once regulations have been agreed upon. The long title of the Act notes that it is an Act to consolidate the laws relating to mental disorder and to provide for the admission, detention, lodging, care, treatment, rehabilitation, control and protection of persons who are mentally disordered¹⁴⁴ and for related matters. The Act as a whole has not been particularly well drafted and many of the provisions leave much to be desired. Curiously enough, it retains the power of appointment of the committee of the person,¹⁴⁵ while at the same time, makes specific provision for proxy health care decision making for mentally incompetent patients. Which then begs the question, what are the responsibilities of a committee of the person?

Significantly, section 77 provides for proxy consent to participation in clinical trials. Section 77 (1) of the Act provides as follows:

Where a mentally disordered person is required to undergo surgery, electroconvulsive therapy (ECT) or clinical trials, consent for any of them may be given-

- (a) by the patient himself if he is capable of giving consent as assessed by a psychiatrist;
- (b) by his guardian in the case of a minor or a relative in the case of an adult, if the patient is incapable of giving consent;
- (c) by two psychiatrists, one of whom shall be the attending psychiatrist, if there is no guardian or relative of the patient available or traceable and the patient himself is incapable of giving consent.

The determination of whether a person is capable of providing consent, is provided for in section 77(5) as follows:

In determining whether or not a mentally disordered person is capable of giving consent under paragraph (1)(a), the examining

¹⁴⁴ Mental disorder here is defined as any mental illness, arrested or incomplete development of the mind, psychiatric disorder or any other disorder or disability of the mind however acquired. Section 2 *Mental Health Act 2001 (Act 615), Malaysia*. Unlike the earlier Ordinance where the issue of a person being mentally disordered was a question of law and it necessarily followed that such an individual was also incompetent, being mentally disordered in this Act does not inevitably lead to a conclusion that a person is incompetent.

¹⁴⁵ Ibid. at section 58

psychiatrist shall consider whether or not the person examined understands –

- (a) the condition for which the treatment is proposed;
- (b) the nature and purpose of the treatment;
- (c) the risks involved in not undergoing the treatment;
and
- (d) whether or not his ability to consent is affected by his condition.

Unfortunately, section 77 fails to provide any meaningful protection for mentally incompetent adults enrolling in clinical trials for four main reasons. First, the failure to recognise the difference between treatment and research leaves mentally disordered persons in a very unsafe position. There is a fundamental difference between medical treatment and medical research. The main aim of treatment lies always in the welfare of the individual patient whereas the ultimate goal of research is to gain further knowledge about a particular disease or condition. The decision to send a patient into surgery or for a course of ECT is likely to be made because it is considered to be the best option based on the patient's need for that specific intervention. Decisions to enrol patients in clinical trials are based on exclusion and inclusion criteria found in the trial protocols. The trial is not offered because it is the best option for the individual patient, it is offered because, all things being equal, it is as good an option as the standard available therapy, with the added bonus of providing valuable data to the investigators and sponsors. In addition, there is the added possibility that third parties may have competing interests in the participation of incompetent patients in clinical trials. Clinical trials should not be equated with medical treatment; additional safeguards need to be put in place. The section as it stands does not go far enough to protect these persons.

Second, paras (1)(a) and (b) of Section 77 provide proxy decision-makers with what appear to be unfettered decision-making powers. There is no mention of the best interests of the mentally disordered

person. In fact, there is no mention of his or her interests at all. There is nothing in the Act that requires either the relatives or physicians of persons declared incompetent to make any sort of enquiry regarding the interests of that person. The only protection afforded to the mentally disordered person is found in section 86, which renders it an offence to ill-treat or wilfully neglect a patient. It is possible to make a decision against the interests of a person, to fail to respect his human dignity without ill-treating or wilfully neglecting him.

The third point to note is that giving ‘a relative’ such broad powers as in para (1) (b) may not necessarily result in the best decision for the mentally disordered person. ‘Relative’ is defined in the Act as applying to any of the following persons of or above eighteen years of age: (a) husband or wife; (b) son or daughter; (c) father or mother; (d) brother or sister; (e) grandparent; (f) grandchild; (g) maternal or paternal uncle or aunt; (h) nephew or niece.¹⁴⁶ Relatives do not automatically know us better than anyone else. The intimacy of a relationship is not determined by kinship but rather by familiarity, friendship and companionship. The more progressive view is that whenever possible, to allow for the prior appointment of a health proxy decision-maker in the event that an individual loses his or her capacity. Carers are also increasingly being recognised as people whose interests are closely connected to their wards and who should be consulted in any decision-making process.

Finally, para (1) (c) appears to be flawed. It states that in the absence of any relative, two psychiatrists, one of whom shall be the attending psychiatrist, should give consent. Having regard to the fact that mental disorder is defined in the Act as ‘any mental illness, arrested or incomplete development of the mind, psychiatric disorder or any other

¹⁴⁶ Ibid. Section 2

disorder or disability of the mind however acquired',¹⁴⁷ not all mentally disordered adults will be suffering from psychiatric illnesses. A patient suffering from Alzheimer's disease is unlikely to even have an attending psychiatrist. If the basis for allowing doctors to make decisions in such cases is that they are best placed to do so, having regard to their medical knowledge, a psychiatrist cannot surely be in a better position than the patient's attending physician.

Guidelines

As discussed above, the law as it stands, provides little or no protection to mentally incompetent adult patients enrolling in clinical trials. Even when the Mental Health Act 2001 comes into force, the situation is unlikely to improve. As mentioned earlier, in practice, clinical trials are carried out in close compliance with the ICH-GCP Guideline; and therefore the protections afforded in it are at present the only real effective safeguards for trial subjects.

Research ethics approval¹⁴⁸ and the requirement for informed consent¹⁴⁹ are the main routes for protecting human subjects under the ICH-GCP Guideline. The guideline also stipulates that if a subject is unable to provide informed consent, the consent of a legally acceptable representative should be obtained.¹⁵⁰ Legally acceptable representative is defined as 'an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject to the

¹⁴⁷ Ibid. Section 2

¹⁴⁸ Section A, Guideline 1.2 *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia*. , Guideline 3.1.1 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)," in *ICH Harmonised Tripartite Guideline* (1996) , principle 13, World Medical Association, "Declaration of Helsinki: Ethical Principles For Medical Research Involving Human Subjects."

¹⁴⁹ Guideline 2.9 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." , *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia*.

¹⁵⁰ Guideline 4.8.5 *Malaysian Guidelines for Good Clinical Practice 2004, 2nd Edition*.

subject's participation in the clinical trial.'¹⁵¹ In practice, investigators enrolling mentally incompetent patients always obtain consent from who they believe to be the 'legally acceptable representative'. Anecdotal evidence suggests that investigators commonly identify the next of kin as being the appropriate legally acceptable representative. The earlier review of the law¹⁵² would suggest that this is not so and that there is in fact, no legally acceptable representative in the Malaysian context.¹⁵³

Ethics committee review

Ethics committee review as noted earlier, is a means of protecting human subjects who take part in clinical trials. In order to appreciate the way in which ethics review is carried out in Malaysia, it is necessary to understand the historical context of the ethics review process. A detailed account of the American experience is also provided for two reasons. First, there are many invaluable lessons to be learnt from the American experience. The American review system is commonly regarded as one of the oldest formalised independent review systems of research in the world and has been the subject of a great deal of rigorous scrutiny, debate and reform for well over three decades. This is particularly significant in the Malaysian context, as the Malaysian government is moving towards developing its research systems in the image of the American National Institutes of Health (NIH).¹⁵⁴ At the launch of the Malaysian NIH, the Minister of Health pointed out that the Malaysian NIH was modelled on the US NIH and that there would be close collaboration between the two agencies. In

¹⁵¹ Ibid. Guideline 1.42

¹⁵² See section 2.3.1.4 of this chapter on section 77 of the Mental Health Act 2001.

¹⁵³ For a discussion of the impact this has had on how clinical trials are conducted see Chapter 5, Section 5.4.3.2.1

¹⁵⁴ The NIH, a part of the Department of Health and Human Services (DHSS), is the primary Federal agency for conducting and supporting medical research in America

fact, he went so far as to say “I have instructed NIH Malaysia to benchmark themselves against the NIH USA.”¹⁵⁵

What is more, the influence of the American ethics review system goes beyond that of merely providing good lessons to countries that might be grappling with the limitations of their own systems. In matters relating to clinical trials for the purposes of drug development and registration, the American system stretches far beyond its shores. The long arm of the American Federal Drug Authority (FDA) extends into foreign jurisdictions, as it requires that contribution of non-US data to the FDA must be conducted under FDA regulations.¹⁵⁶ The impact of this is highly significant on developing countries such as Malaysia where a very sizeable proportion of clinical drug trials are international multi-site trials that are sponsored by pharmaceutical companies. These companies will undoubtedly be looking to submit their data to the FDA for registration and marketing purposes, which effectively means that most of the trials conducted in Malaysia will be subject to US regulation and FDA inspections. These reasons warrant a close consideration of the development of the US ethics review system within the context of its legislative framework.

History of ethics review

The first formal expression of the principle that proposals for research involving humans should be subject to prior independent peer review can be traced back to the first revision of the Helsinki Declaration, which was adopted by the World Medical Association (WMA) at its 29th general assembly in Tokyo in 1975 (the Declaration). Principle 2 of the 1975 Declaration, stated that:

¹⁵⁵ Speech by YB Dato’ Chua Jui Meng, Malaysian Minister of Health in conjunction with the launch of the “National Institutes of Health (NIH)” at Institute of Health Management, Jalan Bangsar, Kuala Lumpur, Malaysia, 11 August 2003, 9:30 a.m.

¹⁵⁶ 21 CFR 312 Subpart B for foreign studies under an Investigational New Drug Application (IND) or 21 CFR 312.120 for foreign studies not conducted under an IND

The design and performance of each experimental procedure involving human subjects should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

In 2000, the fifth revision of the Declaration at the 52nd WMA general assembly in Edinburgh, extended the role played by independent ethics review. Independent review is now found in principle 13, which states

... This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

U.S. Experience

At about the same time that the WMA was asserting its view that independent peer review was a necessary part of medical research on humans, developments in the United States were also moving policy makers in the same direction. In what is described by Levine¹⁵⁷ as a “highly emotionally charged atmosphere fuelled by public concern”,¹⁵⁸ the American Congress in 1974,¹⁵⁹ established the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. After intense study and detailed review of existing regulations, the commission published a set of reports and recommendations. These reports formed the basis for the creation of a

¹⁵⁷ Robert J. Levine and Louis Lasagna, "Demystifying Central Review Boards: Current Options and Future Directions: A Summary Report of Outcomes From "Central Irb Review of Multi-Site Trials," 27-28 October 1998," *IRB: Ethics and Human Research* 22, no. 6 (2000). at 5

¹⁵⁸ This concern was based on the many troubling reports about the abuse of research subjects and notably the article written by Henry Beecher in 1966. H. K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274, no. 24 (1966).

¹⁵⁹ Pub. Law 93-348, The National Research Act (1974)

series of federal regulations under the aegis of the Department of Health and Human Services (DHHS)¹⁶⁰ and Food and Drug Administration (FDA)¹⁶¹ that today govern the operation of the thousands of university and hospital institutional review boards that must review and approve research.¹⁶²

The most significant of these regulations is the Federal Policy for the Protection of Human Subjects (the Policy) promulgated in 1974 by the DHSS at Title 45 of the Code of Federal Regulations (CFR), part 46. Under this Title 45, the DHSS set out regulations aimed at protecting the rights of people enrolled in research. In 1991 this sphere of federal protection was extended to apply to a much broader range of research activities as the Policy was adopted by 16 federal agencies,¹⁶³ and has since become generally known as the “Common Rule”.

The approach taken by the US government in its development of the Common Rule was to create a highly regulated environment within which, the primary mechanism for delivering protection of human subjects was by way of independent review of research. Independent review was set up to address what was then recognised as the inherent conflict between the subject’s interest and the researcher’s quest for new information,¹⁶⁴ as “investigators should not have sole responsibility for determining whether research involving human subjects fulfils ethical standards. Others who are independent of the research must share this responsibility because investigators are

¹⁶⁰ Department of Health and Human Services Rules and Regulations 45 CFR 46

¹⁶¹ Food and Drug Administration Rules and Regulations 21 CFR 50, 56

¹⁶² Levine and Lasagna, "Demystifying Central Review Boards: Current Options and Future Directions: A Summary Report of Outcomes From "Central Irb Review of Multi-Site Trials," 27-28 October 1998." at pg 5

¹⁶³ United States Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, International Drug Development Cooperation Agency, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veteran Affairs, Environmental Protection Agency, National Science Foundation, Department of Health and Human Services and the Department of Transportation.

¹⁶⁴ John A. Robertson, "The Law of Institutional Review Boards," *UCLA L. Rev* 26 (1978-1979). at 487

always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research.”¹⁶⁵

The Common Rule provides for independent ethics review of research by way of the Institutional Review Board (IRB). IRBs are charged with reviewing all research protocols that are covered by the Common Rule,¹⁶⁶ before the research begins, as well as conducting continuous review of ongoing research at intervals appropriate to the degree of risk, but not less than once a year.¹⁶⁷ IRB membership is regulated¹⁶⁸ to the extent that there must be at least five members with varying backgrounds; at least one scientific and one non-scientific member; at least one member who is not affiliated with the institution; and a membership diverse in race, gender and cultural backgrounds who are sensitive to issues such as community attitudes.

When reviewing research, an IRB is required by the Common Rule¹⁶⁹ to ensure that the following requirements are satisfied: that the research design is sound; the risk-benefit ratio is reasonable; subjects are selected in an equitable manner; informed consent is obtained and appropriately documented and that additional safeguards have been included in studies involving vulnerable populations.

Vulnerable populations are described in the Common Rule as including children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons.¹⁷⁰ An IRB reviewing research that may involve vulnerable populations is

¹⁶⁵ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "Institutional Review Boards: Reports and Recommendations," ed. DHEW (Washington D.C.: U.S. Government Printing Office, 1978).

¹⁶⁶ The Common Rule applies to "all research conducted, supported or otherwise subject to regulation by any federal department or agency, which takes appropriate administrative action to make the policy applicable to such research." 45 CFR 46.101(a)

¹⁶⁷ 45 CFR 46.109(e)

¹⁶⁸ 45 CFR 46.107

¹⁶⁹ 45 CFR 46.111(a)

¹⁷⁰ 45 CFR 46.113(3)

generally required to ensure that additional safeguards have been included in the study to protect the rights and welfare of these subjects.¹⁷¹ In particular, an IRB is required to pay special attention to ensure that the selection of subjects is equitable by taking into account the purposes of the research and the setting in which the research will be conducted.¹⁷² Moreover, an IRB that regularly reviews research involving vulnerable populations is obligated to consider including on its committee, one or more individuals who are knowledgeable about and experienced in working with these subjects.¹⁷³

In addition to these general rules relating to vulnerable populations, there are specific regulations governing research on pregnant women, prisoners and children.¹⁷⁴ Surprisingly, there are no such specific regulations relating to research involving mentally incompetent persons. Concern for this cohort led to the 1998 publication of a National Bioethics Commission Advisory report, "Research involving persons with mental disorders that may affect decisionmaking capacity,"¹⁷⁵ which included twenty-one recommendations regarding additional protections for this group of subjects. It is noteworthy that none of the recommendations in this excellent report have ever been incorporated into the Common Rule as notwithstanding the general support of researchers, they feared that the protective spirit of the recommendations would result in stringent regulations that would slow down or even curtail potentially important research.

Ultimately, the responsibility for ensuring compliance with these regulations falls on the shoulders of an institution carrying out

¹⁷¹ 45 CFR 46.111(b)

¹⁷² 45 CFR 46.113(3)

¹⁷³ 45 CFR 46.107(a)

¹⁷⁴ Subparts B, C and D of 45 CFR 46

¹⁷⁵ United States. National Bioethics Advisory Commission., "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume I," (Rockville, Md. (6100 Executive Blvd., Suite 5B01, Rockville 20892-7508): National Bioethics Advisory Commission, 1998).

research and not on individual investigators. The Common Rule achieves this by requiring all institutions engaged in research covered by it to provide written assurances to the Office for Human Research Protections (OHRP) that they will comply with its requirements¹⁷⁶ as well as the Terms of the Assurance.¹⁷⁷ The only type of assurance currently accepted and approved by the OHRP is the Federalwide Assurance (FWA), which as the name suggests may also be relied on by other federal agencies and departments that have adopted the Common Rule. As part of the assurance, institutions are required to provide¹⁷⁸ (i) a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects; (ii) the designation of one or more IRBs¹⁷⁹ that will review the research covered by the FWA (If an institution does not have an IRB, it has the option to negotiate an agreement with an external IRB; establish an IRB; or negotiate an agreement with a commercial or independent IRB.); (iii) a list of IRB members identified by name; earned degrees; representative capacity; indications of experience; and any employment or other relationship between each member and the institution; (iv) written procedures which the IRB will follow; and (v) written procedures for ensuring prompt reporting to the IRB. An FWA is only effective for a period of three years and must be renewed at the end of that period of time to remain effective. Although institutions are only mandated to provide assurances for research supported by federal funds, they are permitted to voluntarily extend the assurance to cover all human subject research regardless of the source of support and most institutions have done so.¹⁸⁰

¹⁷⁶ 45 CFR 46.103

¹⁷⁷ The Terms of Assurance can be found on the United States Department of Health and Human Services website at <http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm> (accessed March 15, 2008)

¹⁷⁸ 45 CFR 46.103

¹⁷⁹ Each IRB must be registered with the OHRP before the FWA can be approved. See <http://www.hhs.gov/ohrp/IRBfaq.html> (accessed March 15, 2008).

¹⁸⁰ Levine and Lasagna, "Demystifying Central Review Boards: Current Options and Future Directions: A Summary Report of Outcomes From "Central Irb Review of Multi-Site Trials," 27-28 October 1998." at 6

In addition to the Common Rule, clinical drug trials, which are regulated by the FDA,¹⁸¹ must also comply with FDA regulations.¹⁸² Part 312.66 issued by the FDA, requires investigators to assure that a properly constituted IRB¹⁸³ is responsible for initial and continuing review and approval of a clinical trial. This means that where clinical drug trials are concerned, the duty to ensure IRB review falls not only on the institution carrying out research¹⁸⁴ as required under the Common Rule, but also on the individual investigators as provided by the FDA regulations.

Ethics Review in Malaysia

It was apparent since the early 1990s that if the Malaysian health care research institutions were to benefit from the development of harmonised standards that allowed for the outsourcing of clinical trials, they would need to have, among other things, ethics review systems in place. Thus, the Malaysian system of ethics committee review was conceived and continues to develop in accordance with the ICH-GCP Guideline,¹⁸⁵ which requires independent ethics review of protocols by Independent Ethics Committees or Institutional Review Boards.¹⁸⁶ As an expression of the commitment of the government to the ICH-GCP process, in 1999, the Ministry of Health (MOH) published the Malaysian version of the ICH-GCP Guideline. The sections¹⁸⁷ describing the responsibilities; composition, functions and operations; procedures and records of Institutional Review Boards in

¹⁸¹ Federal Food, Drug and Cosmetic Act ss 505(i) & 520(g)

¹⁸² Title 21 CFR

¹⁸³ As provided for in 21 CFR 56

¹⁸⁴ By way of providing an FWA.

¹⁸⁵ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

¹⁸⁶ While these terms are defined separately in the glossary: Guideline 1.27 describes an Independent Ethics Committee, and 1.31 describes the Institutional Review Board, they are used interchangeably in the rest of the document and are subject to the same responsibilities, functions and procedures.

¹⁸⁷ *Malaysian Guidelines for Good Clinical Practice 2004, 2nd Edition*. Guidelines 3.1-3.4

the Malaysian guidelines mirror those found in the original ICH-GCP Guideline.¹⁸⁸

In the same year, the Ministry released the Guidelines for Applications to Conduct Drug-Related Trials in Malaysia,¹⁸⁹ aimed at providing useful practical information to the pharmaceutical industry, sponsors and investigators. The guidelines describe the processes that need to be adhered to before a clinical drug trial may commence, including the requirement of ethics committee approval. Information is provided about the different ethics committees: contact details, workflow charts and average time taken for approval of protocols. The document reads more like an information leaflet as opposed to a set of norm prescribing guidelines as it is neither a standards framework nor does it set out any principles of good research. What it does do is spell out for the first time in an official publication, the existing structure of the ethics committee review system in the country.

Clinical trials in the country are run in two types of settings: Ministry of Health facilities; and universities or the private sector. As such, there are two corresponding types of ethics committees. The first, the Medical Research Ethics Committee (MREC), has the authority to review all health research conducted by MOH researchers and non-MOH researchers utilising facilities and resources of the MOH.¹⁹⁰ An application to conduct a multi-site trial in MOH facilities only requires the submission of a single application to the MREC, provided that all the investigators involved and all relevant directors of the institutions sign the application. However, an MREC approval for a multi-site trial

¹⁸⁸ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guidelines 3.1-3.4

¹⁸⁹ *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia.*

¹⁹⁰ The remit of the MREC was reiterated in the *NIH Guidelines for Conducting Research in the Ministry of Health (Moh) Institutions and Facilities 2007*, 3 February 2008.in policy no 2, which also requires that all submissions to the MREC for ethics review be conducted online at www.nmmr.gov.my

will not extend to any research conducted in universities or the private sector unless the said institution does not have an ethics committee.

The second type of ethics committee is the university/private institution ethics committee. Currently, all the ethics committees¹⁹¹ in this category are affiliated with universities with the exception of the National Heart Institute.¹⁹² There are no ethics committees operating in private healthcare facilities. These committees can be likened to the American IRBs in that their remit is limited to their institutional affiliation although they are permitted to review protocols from centres that have no ethics committee. Such instances are rare as ethics committees of universities and private institutions are very reluctant to take on the heavy burden of reviewing and monitoring clinical trials conducted in other centres and these sorts of applications, if any, are usually made to the MREC.

Notwithstanding the absence of legislation, there is close compliance with the standards set up in the ICH-GCPs. There are two main reasons for this. First, the guidelines contained in both the Malaysian ICH-GCP Guideline and the Guidelines for Applications to Conduct Drug-Related Trials in Malaysia are binding on all MOH institutions and institutions that receive funding or fall under the influence of the MOH, which include the universities. At the present time, all clinical trials running in the country are run in these institutions that are obliged to comply with the guidelines. Second and perhaps more importantly, as this would apply universally to all research centres throughout the country, the pharmaceutical industry, which is presently the biggest sponsor of clinical trials, has a vital interest in

¹⁹¹ University of Malaya, Universiti Sains Malaysia, Universiti Kebangsaan Malaysia, International Islamic University Malaysia, National Heart Institute, and Universiti Malaysia Sarawak.

¹⁹² The National Heart Institute was initially part of the Ministry of Health, but was corporatised by the state in 1992 when the Ministry of Finance bought it. It is now run as a semi-private institution.

ensuring that ICH-GCP standards are met. Sponsors run international multi-site clinical trials with the main aim of generating statistically significant data to support their applications to regulatory authorities for research or marketing permits¹⁹³ for their products. The largest drug regulatory authority in the world, the FDA clearly states¹⁹⁴ that it “may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review, by an IRB...” No sponsor would even consider running a trial without prior ethics committee review in spite of the absence of any legal compulsion.

Ethics committee review is thus firmly established in the Malaysian context. However, if ethics review is to fulfil its purpose as a mechanism for human subject protection, the enquiry that needs to be made is not whether the process has been put into place or institutionalised, but whether or not the deliberations and decisions made during the course of ethics review, as well as the way in which the committees are constituted, do in fact provide meaningful protection to mentally incapacitated adults. The rest of the thesis will take up this enquiry. The next chapter concerns itself with the big picture by reflecting on the fundamental ethical principles that are meant to guide decision-making in medical research.

¹⁹³ For purposes of this thesis the definition of an application for research or marketing permit is as provided by 21 CFR 50.3(b)(6)-(10), which includes new drug applications; investigational new drug applications; requests relating to bioavailability and bioequivalence data; and data submitted as part of drug classification.

¹⁹⁴ 21 CFR 56.103 (b)

3 Chapter 3

Ethics committee review and the ethics of clinical research

Whether or not ethics committees are effective protectors of the rights of human subjects will depend largely on the quality of their discussions. To engage in meaningful deliberations, they must understand the task set before them as well as possess the tools to carry out their mandate. To begin with, ethics committees need to be equipped with knowledge of, and the ability to engage in, rigorous ethical discourse. Ethics guidelines are meant to serve this purpose.

There is some evidence that ethics committee members who are key players in the protection of human subjects in the clinical trial process do not or are not able to use ethics guidelines effectively in their decision making.¹⁹⁵ Apart from the chairperson of the MREC and the director of the CRC, none of the persons interviewed had heard of or read the Nuremberg Code, the Belmont Report, the ICH-GCP Guideline or any other guideline apart from the Helsinki Declaration. Even though the majority of ethics committee members interviewed were able to cite the Helsinki Declaration as being the basis of ethical guidelines in medical research, none of them were able to articulate any of the principles contained within nor had any of them received any formal training in understanding or applying the principles contained in the declaration. One of the lay members described how she came upon the Helsinki declaration.

Because before I first went to the meeting, I said, ethics, something has got to be there, so I just got on the internet, put on medical ethics and then found that Helsinki appears... later on I knew I was on the right track because the [chairperson] mentioned it.¹⁹⁶

¹⁹⁵ As noted earlier, the two main mechanisms that exist to protect human subjects are ethics committee review and the informed consent process.

¹⁹⁶ Interview with Ethics Committee Member A, Institution A, 30 June 2008

The other lay member recalled reading the declaration but had no recollection of it and added thoughtfully, “yah, probably I should have looked into that more carefully.”¹⁹⁷ One ethics committee member who is also a physician/researcher when asked about the principles found in the Helsinki Declaration said,

I think once it is embraced as part of your professional guidelines it's got no impact because you're living within those rules and guidelines and I really haven't thought much about it.¹⁹⁸

In fact, these ethics committee members do not even appear to have a meaningful understanding of the length and breadth of their roles as protectors of the rights and interests of human subjects. Even as they recognised that their roles were to protect the interests of human subjects, their understanding of what this meant in practice seemed rather limited. The responses ranged from ones based on well-intentioned unawareness to hardened cynicism, neither of which bode well for the ethics review process. One of the lay members said that when looking at protocols, she was generally concerned with the patient's discomfort and whether or not taking part in the trial would incur additional costs to the patient; on a more troubling note, the same person was of the opinion that the main responsibility of the ethics committee was to ensure that the research carried out was scientifically valid.¹⁹⁹ Another lay member recognised that her role was to look out for the interests of the patients but saw that mainly as making sure that

Patients are not getting any less than what they should be getting normally... if there is anything more they should not pay for it. Even if it benefits them, they should not pay for it.²⁰⁰

The response from a senior member of the Ministry of Health, who sits on the MREC, was a cynical,

¹⁹⁷ Interview with Ethics Committee Member B, Institution A, 21 December 2007

¹⁹⁸ Interview with Ethics Committee Member C, Institution A, 28 June 2008

¹⁹⁹ Interview with Ethics Committee Member A, Institution A, 30 June 2008

²⁰⁰ Interview with Ethics Committee Member B, Institution A, 21 December 2007

It is all there in the GCP ... you know the party line again is protection of human research subjects. ... I am telling you the party line if that is what I do or how I actually behave in ethics committee, I don't know (laughs).

It was unclear whether he was being light hearted or genuinely cynical.

A considerable part of the problem is the lack of training provided to ethics committee members, a point that was raised by every person interviewed. Unlike investigators, who must be GCP certified before they can run clinical trials, ethics committee members are not required to undergo any formal training.²⁰¹ People are expected to learn on the job and according to a senior member of the MREC,

People who are freshly appointed ... will be guided by senior members of the committee. That is how most ethics committees learn, at least in this country, where it is still fairly informal.

Only one person interviewed recalled being given any specific training after joining the committee and could only recall being taught the different phases of a drug trial and "some guidelines, I can't remember exactly".²⁰² Ethics committee members are thus unlikely to be engaging in meaningful review because they are not adequately trained and they do not have the tools they need to construct a meaningful discourse. As is argued below, the tools that are currently on offer are inadequate; they are confusing, unclear and contradictory. A new paradigm is needed.

The next section makes the argument that the current ethical frameworks that exist in the research arena today fail to provide coherent and workable frameworks for decision-makers. Beginning with a consideration of the history of research misconduct and the

²⁰¹ Interestingly, even in the UK where there is an expectation that ethics committee members attend a certain amount of training, there is no centralised training or national or uniformed curriculum. It is up to the NHS authority to arrange for training. Telephone interview with David Neal, Deputy Director and Head of Policy, National Research Ethics Service. 19 March 2008, 4pm.

²⁰² Interview with Ethics Committee Member B, Institution A, 28 May 2008

subsequent articulations of three of the most influential guidelines and the problems with these guidelines, the proposition is made that the main failure of these guidelines is that they fail individually and as a whole to recognise that the underlying problem is that of undervaluing human life. Following from this, there is a short discussion of how and what it means to undervalue life and finally, offers a solution as being the idea of respecting human dignity.

History of clinical research misconduct

It is difficult to arrange and structure the history of clinical research misconduct as a consistent and coherent analytical narrative as the case studies recorded in the literature are not easily reconciled. Historians have approached this task in a number of ways such as framing the narrative as a reflection of the secularisation of society; placing it in the context of the history of informed consent; and telling the story in relation to the involvement of the State.²⁰³ Each one trying to make sense of why certain groups of people treated other people, who were often in no position to protect themselves, very badly; and by providing these insights, hopefully ensuring such misconduct would never recur. While it is beyond the scope of this thesis to delve into the murky depths of the history of research misconduct, it is possible to identify a select number of high profile exposés that ultimately led to the development of three very influential ethical guidelines that are discussed in the following section.

World War II Human Experiments and the Nuremberg Code Nazi Experiments

The atrocities carried out by German physicians and administrators during World War II shocked the world. On December 9, 1946, twenty-three German physicians and administrators were indicted for war

²⁰³ See J. Goodman, A. McElligott and L. Marks, *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century*, (Baltimore 2003), Chapter One

crimes and crimes against humanity before an American Military Tribunal in Nuremberg, commonly referred to as the Nuremberg Medical Trial.²⁰⁴ They were accused of murders, tortures, and other atrocities committed in the name of medical science. The experiments included but were not limited to high-altitude experiments; freezing experiments; malaria experiments; lost (mustard) gas experiments; sulphanilamide experiments; bone, muscle, and nerve regeneration and bone transplantation experiments; sea-water experiments; epidemic jaundice experiments; sterilization experiments; spotted fever (fleckfieber) experiments; experiments with poison and incendiary bomb experiments.²⁰⁵

The victims of these crimes were numbered in the hundreds of thousands. In the opening statement of the prosecution, Brigadier General Telford Taylor noted, ²⁰⁶

“... most of these miserable victims were slaughtered outright or died in the course of the tortures to which they were subjected. For the most part they are nameless dead. To their murderers, these wretched people were not individuals at all. They came in wholesale lots and were treated worse than animals. They were 200 Jews in good physical condition, 50 gypsies, 500 tubercular Poles, or 1,000 Russians. The victims of these crimes are numbered among the anonymous millions who met death at the hands of the Nazis and whose fate is a hideous blot on the page of modern history.”

The defendants tried to convince the judges that their experiments had not violated conventional standards for medical experimentation on human subjects, and that the extraordinarily cruel treatment of the subjects was not as much a sign of individual human failure as it was a testimony to the brutalising effect of the war. It was also argued,

²⁰⁴ See *The Nuremberg Medical Trial, The Holocaust and the Origin of the Nuremberg Medical Code*, Horst H. Freyhofer, Peter Lang Publishing, New York, 2004.

²⁰⁵ *Ibid.* The most famous examples of these experiments are the twin studies conducted by Dr Josef Mengele, one of the most notorious Nazi physicians. See Matalon Lagnado, Lucette, and Sheila Cohn Dekel. *Children of the Flames: Dr. Josef Mengele and the Untold Story of the Twins of Auschwitz*. London: Sidgwick & Jackson, 1991.

²⁰⁶ *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*. Nuremberg, October 1946 - April 1949. Washington D.C.: U.S. G.P.O, 1949-1953

among other things that it was necessary to sacrifice the well being of a few in the interests of the many. Significantly, however, it was clearly always the intention of the Germans that the 'few' should only comprise of members of certain groups such as Jews, gypsies, Poles and other such 'persons of lesser worth'. It would have been very unlikely that any Aryan Germans would have been included as subjects of these trials. To the judges, those arguments were unacceptable and demonstrated an urgent need for clear and binding standards capable of protecting human subjects from further abuse and an institutional framework capable of safeguarding these standards. The Nuremberg Medical Trial had made it obvious to many observers that the largely self-regulatory nature of the medical profession had failed miserably to prevent the atrocities committed in Germany. Consequently in their verdict, the judges introduced a set of medical principles. This set of principles is today known as the Nuremberg Code.

Japanese Experiments

Curiously, in contrast to the German experiments, which were revealed in all their gruesomeness to a shocked world, very little was known about the Japanese experiments that were also carried out during World War II. It has been claimed²⁰⁷ that the experiments carried out by the Japanese rivalled and at times exceeded those of the most inhumane Nazi doctors. Much like the Nazis, the Japanese believed that their race was superior to any other race or group and the military administrators and doctors did not regard other Asians and Westerners as truly human or worthy of the respect accorded to humans.²⁰⁸ It was not until the 1980s and 1990s that these events were brought to the attention of the world and even then, received very little public attention. The perpetrators of these crimes were never charged

²⁰⁷ Sheldon H Harris, Chapter 16 - Japanese Biomedical Experimentation During the World War II Era, *Military Medical Ethics, Volume 2*, page 466 Available at http://www.bordeninstitute.army.mil/ethicsbook_files/Ethics2/Ethics-ch-16.pdf Accessed 10 October 2005

²⁰⁸ Ibid at 471

or convicted and many of them went on to enjoy successful careers in medicine and science.²⁰⁹ It was not that the allied forces were unaware of the atrocities committed by the Japanese; it was that the Americans had an interest in the Japanese research results, specifically the human biological warfare data. Sheldon Harris describes²¹⁰ how the advent of the Cold War coupled with the availability of scientifically sound data resulted in the Americans coming to an agreement with the Japanese experts. The Japanese agreed to hand over their data in return for promises of immunity. There was never a 'Tokyo Trial' or a 'Tokyo Code'.

Both the Japanese and German researchers sought to justify their actions on the ground of sacrificing the few for the benefit of the many. But as pointed out earlier, it is vital to recognise that the selection of the sacrificial few was based on the notion that the lives of certain groups of people were worth less than the lives of the Japanese or Aryan Germans, and as a result, the sacrifice was negligible compared to the benefits that would be enjoyed by the 'superior' group. The fact that both countries were engaged in a protracted and horrific war led these researchers further to believe that they were entitled on utilitarian grounds forcibly to subject these sacrificial few to appalling medical experiments. Both these ideas - first, that some human lives are worth more than others; and second, that it is justifiable to sacrifice a few for the good of the many were inextricably linked and lay at the heart of the research misconduct during World War II.²¹¹

²⁰⁹ For a further discussion see Sheldon H. Harris, *Factories of Death: Japanese Biological Warfare, 1932-45, and the American Cover-Up*, London: Routledge 1995

²¹⁰ Sheldon H Harris, Chapter 16 - Japanese Biomedical Experimentation During the World War II Era, *Military Medical Ethics, Volume 2*, page 492 Available at http://www.bordeninstitute.army.mil/published_volumes/ethicsvol2/ethics-ch-16.pdf Accessed August 17, 2010

²¹¹ These ideas can also be seen as examples of ways in which human life can be undervalued. This argument that the greatest and most significant threat to human subjects who participate in clinical research is the undervaluation of human life is taken up again in Section 3.2

Nuremberg Code

This does not however; appear to be the way in which the judges at the Nuremberg Medical Trial approached the problem when they formulated the Nuremberg Code. It is worth examining the ideas that seem to have informed the development of the Nuremberg Code as it is generally viewed as being the first important declaration of ethical guidelines for medical research on human subjects and as such represents the “beginning of the story” of clinical research ethics. But more than this, as recognised by Capron, the principles²¹² prescribed by the Code continue to “guide the development of subsequent declarations, guidelines and regulations.”²¹³ The foremost principle is that which is set out as the very first, the requirement for free and informed consent:²¹⁴

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may

²¹² Need for free and informed consent from subjects, and that risk should be minimal and proportionate to scientific ends that are themselves reasonably attainable. A. Capron, "Experimentation with Human Beings: Light or Only Shadows" (2006) 6 Yale J. Health Pol'y L. & Ethics 431 at 436

²¹³ A. Capron, "Experimentation with Human Beings: Light or Only Shadows" (2006) 6 Yale J. Health Pol'y L. & Ethics 431 at 436

²¹⁴ Principle 1, Nuremberg Code at <http://ohsr.od.nih.gov/guidelines/nuremberg.html> Accessed August 17, 2010

possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility, which may not be delegated to another with impunity.

In presenting the principle of informed consent as the primary vehicle by which human subject protection might be achieved, the judges only addressed one of the underlying causes of the abuse - the utilitarian notion that the well being of an individual may be sacrificed for the good of society. Informed consent addresses this problem by recognising that every individual must be given the right to determine for himself whether or not to choose to participate in research and that this right cannot be taken away from him on the grounds that it would serve the interests of the many. However, by focusing on informed consent, the judges at Nuremberg failed to give recognition to what was perhaps the greater driving force behind the atrocious experiments, namely the undervaluation of certain groups of vulnerable people who were regarded as being of less value than the German Aryans. There was never any interest in obtaining any form of consent from these prisoners and because these prisoners were viewed as 'inferior' beings not worthy of full moral respect even if informed consent had been laid down in a code of practice or law in Germany or Japan before the outbreak of World War II, it would not have prevented the commission of the subsequent atrocities. The abuses occurred and were sanctioned by the state largely in part because the subjects were not recognised as possessing worthwhile lives.

What the Nuremberg Code should also have made perfectly clear is that all human beings regardless of race, religion or social standing must be accorded the same level of respect. It should have made it clear that in no situation should a human being belonging to one

section of society ever be used as a means to an end for any human being belonging to another section of society. It should have mandated that individuals or persons in power (state) be responsible to protect the interests of minorities and vulnerable populations. In failing specifically to address these issues, the Code failed to recognise that the undervaluation of human life²¹⁵ lay at the heart of the experiments.

Also, the Code at the time of its articulation did not have a great impact on the way in which clinical research was being carried out in other countries²¹⁶ as it was seen as only being of direct application to the physicians that were on trial, who were viewed as either products of something “inherently flawed in the German character or as the playthings of an evil race and totalitarian regime that had collectively abandoned its “civilized” qualities”.²¹⁷ This was evident from the fact that even after the revelations that were made at Nuremberg, there continued to be many instances of unethical trials being conducted on unsuspecting subjects in other countries, which led to the formulation of a number of international and national level ethical guidelines which are discussed in the next section.

Before proceeding to consider some of the events that led to the development of the abovementioned documents, there is one more noteworthy observation that can be made of the events that followed the German and Japanese World War II experiments –as to why there was never a Japanese equivalent of the Nuremberg Code. The main difference between the Japanese and German researchers was, as the

²¹⁵ A discussion of the idea of the undervaluation of human life is found in section 3.2

²¹⁶ *The Nuremberg Medical Trial, The Holocaust and the Origin of the Nuremberg Medical Code*, Horst H. Freyhofer, Peter Lang Publishing, New York, 2004 at 10

²¹⁷ J. Goodman, A. McElligott and L. Marks, *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century*, (Baltimore 2003) at 7

literature²¹⁸ suggests, that the Japanese had something of value to the Americans who were in power at that point of time. There can be no question that both the Germans and the Japanese had been unethical but only the Germans were called to answer for their crimes. It is ironic that the most famous medical research trial in history which resulted in one of the most important research ethics declarations was conducted by a government that was at the same time acting unethically by wilfully turning its back to a set of even more diabolical research trials. At the heart of this contradiction appears to be the fact that the then American government was acting on interests other than the interests of justice. It was acting on what it perceived to be American national security interests and it was the Americans who had the power to act on their interests and in doing so failed to act in the interest of justice. While this observation in no way undermines the validity of the principles laid down in the Code, it does serve as an illustration of the problems created by conflicting interests, an issue that is taken up in greater depth in Chapter 5

Henry Beecher's Article and the Declaration of Helsinki

Henry Beecher's Article

As noted earlier, few physicians at that time outside or inside Germany felt that the Nuremberg Code had any direct bearing on their work. The code was seen as only being of direct application to the physicians that were on trial.²¹⁹ In fact, in the period shortly after the end of World War II, physicians/researchers in America enjoyed high levels of autonomy in conducting human experiments that were "limited only by their individual consciences..."²²⁰ It was not until the publication of an

²¹⁸ Sheldon H Harris, Chapter 16 - Japanese Biomedical Experimentation During the World War II Era, *Military Medical Ethics, Volume 2*, Available at http://www.bordeninstitute.army.mil/published_volumes/ethicsvol2/ethics-ch-16.pdf Accessed August 17, 2010

²¹⁹ *The Nuremberg Medical Trial, The Holocaust and the Origin of the Nuremberg Medical Code*, Horst H. Freyhofer, Peter Lang Publishing, New York, 2004 at 10

²²⁰ D. J. Rothman, *Strangers at the bedside: a history of how law and bioethics transformed medical decision making*, Second ed., (Hawthorne, NY 2003) at 69

article by Henry Beecher²²¹ in 1966 that steps were taken to fetter the discretion of these physicians/researchers. In his article, Henry Beecher documented 22 problematic studies and referred to a personal communication from M.H. Pappworth²²² who had himself collected 500 examples of what he took to be unethical trials. Human subjects in these trials were placed in positions where their health and sometimes lives were placed at risk, and in almost all cases, without their knowledge or acquiescence. Notably, these trials were conducted by respected researchers in mainstream institutions, and were funded by well-respected sponsors such as the United States military, the National Institutes of Health and established pharmaceutical companies.

Among the more notorious experiments that caught the attention of the public were case studies 16 and 17, more commonly known now as the Willowbrook Hepatitis Study²²³ and the Jewish Chronic Disease Hospital Trial. In the Willowbrook study, mentally defective children who were residents at the Willowbrook State School for the Retarded were fed live hepatitis viruses in order that researchers might better understand the basic nature of the disease. The manner in which the study was conducted raised concerns about the use of children as subjects in clinical research and in particular, the use of what was essentially a captive and vulnerable population: institutionalised mentally retarded children. Moreover, there were problems with the way in which parental consent was obtained as there was evidence that

²²¹ Beecher H, Ethics and Clinical Research, *N Engl J Med* 1966; 274: 1354-60. For an excellent account of the events leading up to the publication of the article and the subsequent responses of various parties, see D. J. Rothman, *Strangers at the bedside: a history of how law and bioethics transformed medical decision making*, Second ed., (Hawthorne, NY 2003). Chapter 4

²²² Pappworth had earlier in 1962 reviewed a number of published studies that revealed similar abuses. See M. H. Pappworth, "Human Guinea Pigs: A Warning" (1962) *Autumn Twentieth Century* 66-75. Also see M. H. Pappworth, *Human Guinea Pigs: Experimentation on Man*, (Harmondsworth 1969).

²²³ For a detailed account of the experiment and an analysis of the arguments that were forwarded by the researchers in defence of the study, see J. Goodman, A. McElligott and L. Marks, *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century*, (Baltimore 2003).

parents had been coerced into providing consent.²²⁴ At the other end of the age spectrum, the Jewish Chronic Disease Hospital Trial recruited chronically ill and debilitated elderly patients who were residents at the Brooklyn Jewish Chronic Disease Hospital. The study, which was funded by the American National Institutes of Health saw investigators inject live cancer cells into 22 human subjects as part of a study of immunity to cancer. Although the investigators claimed to have obtained informed consent, it was revealed that many of the patients were incapacitated or did not speak English; and those that were able to provide consent were not told of the true nature of the cells or that the injections were unrelated to their normal therapy programme.²²⁵ Beecher notes in his article that, "... the subjects (hospitalized patients) were "merely told they would be receiving 'some cells' – ... the word cancer was entirely omitted."²²⁶

The publication of Beecher's article following close on the heels of the revelations made at Nuremberg prompted the medical profession to act. Under the aegis of the World Medical Association, the profession set out what was to become arguably the most important set of guidelines relating to the conduct of human research, the Declaration of Helsinki.²²⁷

²²⁴ The wards of this facility were closed to new admissions due to overcrowding and parents on the waiting list were told that their children would be admitted if they were placed in the research ward and would later be transferred into the facility. See E. J. C. Emanuel, Robert A. Arras, John D. Moreno, Jonathan D. Grady C. (ed.), *Ethical and regulatory aspects of clinical research : readings and commentary*, (Baltimore 2003), at 3-4

²²⁵ United States. National Bioethics Advisory Commission., *Ethical and policy issues in research involving human participants*, vol. 1, (Bethesda, Md. (6705 Rockledge Drive, Suite 700, Bethesda, 20892-7979) 2001). Appendix C, page 152 Also see J. Katz, A. M. Capron and E. S. Glass, "The Jewish chronic disease hospital case" (1972) *Experimentation with human beings*. New York: Russell Sage Foundation 36-65.

²²⁶H. K. Beecher, "Ethics and Clinical Research" (1966) 274 *New England Journal of Medicine* 367 – 372 at 371

²²⁷ At <http://wma.net> Accessed 21 October 2005

The Declaration of Helsinki

The Declaration of Helsinki was adopted by the World Medical Association (WMA) in 1964²²⁸ at its 18th Assembly in Helsinki and since then has been modified on several occasions.²²⁹ More recently, amendments have been made that reflect the changing nature of the research enterprise such as concerns about the growing internationalisation of research especially in relation to research in developing countries,²³⁰ and the problem of conflicts of interests. It is recognised by the Council for International Organisations of Medical Sciences²³¹ as,

‘... the fundamental international document in the field of ethics in biomedical research and has influenced the formulation of international, regional and national legislation and codes of conduct.’

The declaration was primarily developed to provide guidance to physicians²³² involved in research on human subjects.²³³ Because of this, the declaration takes a more flexible approach to clinical trials,²³⁴ unlike the stern and uncompromising tenor of the Nuremberg Code.²³⁵ For example, the Nuremberg Code is rigid in that it only permits research on subjects who are able to provide informed consent and never in a therapeutic setting; whereas the Helsinki declaration while

²²⁸ For a discussion of the historical development of the Declaration of Helsinki see Brody B.A. ‘A historical introduction to the requirement of obtaining informed consent from research participants.’ in L Doyal and JS Tobias (eds) *Informed Consent in Medical Research* (BMJ Books 2001) 7 - 14

²²⁹ The declaration, which was originally tabled in 1961, was revised several times before its final adoption in 1964. It was substantially revised in 1975; reviewed and minor revisions made in 1983; amended in 1989, 1996 and 2000; and 2 notes of clarification made in 2002 and 2004. In 2008, the Assembly passed a revised version, which included 3 new paragraphs.

²³⁰ In particular Principles 29 and 30 of the Declaration of Helsinki and notes of clarification on both these paragraphs

²³¹ Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* CIOMS, Geneva 2002, 15

²³² The Nuremberg Code by comparison, is of wider application to the scientific community in general.

²³³ Declaration of Helsinki Principle 1

²³⁴ J F Childress, Nuremberg’s Legacy – Some ethical reflections, *Perspectives in Biology and Medicine*, 43,4, (Spring 2000), 347 at 356 describes Nuremberg as being ‘protectionist’ and Helsinki as ‘inclusionist’

²³⁵ Which was unsurprising, given the fact that it was set out by judges in response to scientists who were on trial for committing horrific acts of abuse.

recognising the primacy of informed consent, also allows for the idea of proxy consent for incompetent patients.²³⁶ In addition it allows for the combination of medical research with medical care.²³⁷ Significantly, it introduced for the first time a requirement for independent ethics review²³⁸ of trials; and the idea of balancing risks and benefits of the research. With this, the Helsinki declaration brings together in one document for the first time, the two main safeguards for human subject protection: informed consent and independent ethics review.

The fact that the Helsinki declaration represents a significant milestone in the development of human subject protection is not in dispute. Nonetheless it is unsatisfactory as it suffers from two main weaknesses: first, like the Nuremberg Code, it diminishes the wrongs visited on human subjects by failing to recognise the underlying basis of unethical trials;²³⁹ and on a more practical front, it saddles investigators and ethics committee members with an unworkable framework for making ethical decisions. Decision-makers relying on the declaration will be hard pressed to derive from its text any coherent or consistent basic ethical principle or set of principles; this in turn is exacerbated by the open textured language of its text, leaving the guideline open to a very wide range of interpretations.

Take for example the fact that on the one hand, there is a clear rejection of the type of utilitarian arguments forwarded by the German scientists in Principle 5, which states, 'In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.' On the other hand, utilitarianism appears to inform principle 18 where it states, 'Medical research involving human subjects should only be

²³⁶ Principle 24 Declaration of Helsinki

²³⁷ Part C, Additional Principles for Medical Research Combined with Medical Care, Principles 28 – 32 Declaration of Helsinki

²³⁸ Principle 13 Declaration of Helsinki

²³⁹ A further discussion of this is found in section 3.2

conducted *if the importance of the objective outweighs the inherent risks and burdens to the subjects...*' These principles are at odds with each other. If the interests of the human subject always take precedence over the interests of science and society, any calculation as to the importance of the objective (which presumably means the advancement of science or benefit to society) should never outweigh the inherent risks and burdens to the subjects.

Another case in point is the principle allowing for proxy consent. One of the developments of Helsinki as noted earlier, was to adopt an inclusionist approach by allowing proxy consent for incompetent subjects. However, the qualification of allowing for proxy consent is that 'these groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent patients.'²⁴⁰ This means that incompetent people can only participate in research relating to the particular diseases or disorders that have rendered them incompetent.²⁴¹ Therefore, a person suffering from severe mental retardation who subsequently contracts a terminal form of cancer will not even be considered for enrolment into a trial that might offer access to new therapies for his cancer. The inclusionist principle that brings in the idea of allowing incompetent patients access to the research arena is offset by this exclusionist qualification, which denies them access to potentially beneficial treatments.

An instance of the vague and imprecise language of the text is evident in principle 8, which introduces the idea of vulnerable populations in a manner that is less than helpful. It provides too broad a description of vulnerability that ultimately leaves it with very little meaning. It describes vulnerable populations as: the economically and medically

²⁴⁰ Principle 24 Declaration of Helsinki

²⁴¹ This is the only way to achieve advances in the treatment and management of some of these diseases and disorders.

disadvantaged, those who cannot give or refuse to give consent, those who may be subject to giving consent under duress, those who will not benefit personally from the research and for those for whom the research is combined with care. Ultimately, all participants save the wealthy, healthy, strong-willed and self-interested fall under the term vulnerable populations. The physician is then enjoined to give special protection and special attention to these populations. There is no further elaboration of what special protection or special attention might include. Such vague and imprecise terms render the principle unworkable at best and subject to manipulation at worst.

The Tuskegee Syphilis Study and the Belmont Report

The Tuskegee Syphilis Study²⁴²

Even as Henry Beecher was writing his exposé on research misconduct, one of the most infamous human experiments in the history of the United States was well on its way. Curiously, neither the public outcry that followed the publication of Beecher's article, nor the articulation of the Declaration of Helsinki seemed to have had any discernible effect on the conduct of the trial where for forty years from 1932 until 1972, the United States Public Health Service conducted a study on the effects of untreated syphilis on poor and illiterate black men living in the county of Tuskegee. The only goal of the study was to compile data on the effects of the evolution of the untreated disease. It had nothing to do with treatment and the men did not even know that they had syphilis and one subject recalled that he was only told that he had 'bad blood'.²⁴³ Not only were these men denied treatment, they were tricked into believing that they were receiving a "blood tonic" that would help them and were even threatened with being dropped from the study if

²⁴² For a detailed case study of the experiment, see James H. Jones, *Bad Blood : The Tuskegee Syphilis Experiment*, New and expanded ed. ed. (New York: Free Press ; Toronto : Maxwell Macmillan Canada ; New York : Maxwell Macmillan International, 1993).

²⁴³ Ibid. at 5

they took any other treatment for their 'bad blood'.²⁴⁴ Although apologists for the study pointed out that there were no effective treatments for syphilis in the 1930s, the study became indefensible when after 1945, penicillin was discovered to be an effective treatment for the disease and investigators withheld this treatment from the men in the study. When the story broke on July 25, 1972, the press reported that as of 1969 at least 28 and perhaps as many as 100 men had died as a direct result of complications caused by syphilis. These disturbing disclosures triggered a national debate on research ethics, which led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research²⁴⁵, which, in 1979, published the Belmont Report.²⁴⁶

The Belmont Report

The Belmont Report is a significant document for two reasons. First, unlike the Declaration of Helsinki, which merely lists twenty-four basic principles that are meant to promote ethical behaviour, it sets out a different approach to determining ethical research conduct. It is the first guideline to adopt²⁴⁷ a 'principled' approach to ethical decision-making in human subject research. Three basic ethical principles are identified which are then meant to inform the application of the specific principles expressed within the rest of the report. The three basic ethical principles are: respect for persons, beneficence and justice.²⁴⁸

²⁴⁴ Ibid. at 6

²⁴⁵ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created by the National Research Act (Pub. L. 93-348).

²⁴⁶ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects Research."

²⁴⁷ This approach has been since taken up by other guidelines such as the International Ethical Guidelines for Biomedical Research Involving Human Subjects, by the The Council for International Organizations of Medical Sciences (CIOMS), an international, non-governmental, non-profit organization established jointly by the World Health Organisation (WHO) and UNESCO in 1949. See Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* at http://www.cioms.ch/publications/guidelines/frame_guidelines.htm accessed August 17, 2010

²⁴⁸ Beneficence establishes a duty to help others by doing what is best for them and justice requires that benefits and burdens should be distributed equitably

These principles form the bedrock of what is then flagged as the three requirements for ethical research on human subjects: informed consent, assessment of risks and benefits and subject selection. The other important attribute of the Belmont Report is that unlike the earlier ethical guidelines, it articulates specific considerations and protections for vulnerable populations.²⁴⁹ It does this by way of the idea of respect for persons. Respect for persons is recognised as incorporating two ideas: that individuals should be treated as autonomous agents and that people with diminished autonomy are entitled to protection.²⁵⁰

By setting out three basic principles that are meant to guide decision making, the Belmont Report provides a more workable framework as compared to the Helsinki declaration. Researchers and ethics committee members need not plough through a list of twenty-four principles and try to make sense of what often appear to be competing and unclear provisions. However, it is submitted that the framework adopted by the report is nevertheless still far from satisfactory. Two main criticisms can be levelled at its approach. First, the lack of guidance as to how these principles should be applied leaves the guidelines open to a wide variety of interpretations, which leaves them uncertain and possibly ineffective. Second, the principles of beneficence and justice are of themselves open to different interpretations and their insertion essentially weakens the first principle of respect for persons.

The first criticism flows from the fact that the principles are not ranked in any hierarchical order and that there is no guidance as to how much weight each principle might carry and when any particular principle

²⁴⁹ The needs of vulnerable populations is found in Part C of the report see National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects Research."

²⁵⁰ See Part B of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report* at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

should take precedence over another. The application of the three basic principles is described as follows,²⁵¹

In varying circumstances they may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

It may be true that varying circumstances may require different considerations. For instance, recruiting subjects into a clinical trial on HIV drugs might raise concerns about the release of personal information of subjects, which may be potentially harmful or prejudicial to subjects. In such a situation, the principles of respect for persons and beneficence may be the primary principles in guiding the decision making process. On the other hand, when a trial using a placebo as a comparator rather than an established effective intervention proposes to recruit subjects in a poor country, concerns about the applications of the principles of justice and beneficence are likely to dominate ethical discussions. Nevertheless, it is submitted that it does not help to provide decision makers with alternative and possibly competing principles without any guidance as to how they should be applied. Taking the latter example of placebo trials: on the one hand, it is possible to present a persuasive argument that as a rule, when there is an established therapy for a particular condition, placebo trials are unethical because they violate the principle of beneficence, as subjects are harmed by not being offered an effective treatment. Moreover, these trials remain unethical when run in developing countries where subjects may not generally have access to established therapies. This is because they violate the principle of respect for the persons, as they are essentially a form of exploitation of the poor. On the other hand an equally compelling argument can be presented as to why trials should be allowed because they will at least offer some subjects some benefit, and that no is harmed because the established therapy is

²⁵¹ Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* CIOMS, Geneva 2002, 17

not available as standard therapy - and so this serves the principle of beneficence.

The second criticism or problem is that the principles of beneficence and justice, being open to different interpretations, may weaken the idea of respect for persons. The principle of beneficence is defined as “the ethical obligation to maximise benefit and to minimise harm ... Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, *nonmaleficence*²⁵².” The problem with this principle is that the notion of harm and benefit may vary tremendously depending on an individual’s personal value system.

For instance, some people consider active euthanasia as a form of harm in that it is harmful to shorten a person’s life, whereas others view it as a benefit in that it is a good thing to help someone who is suffering to end his life. A doctor who holds the former view might rely on the principle of beneficence to claim that to end a life is an infliction of harm, whereas another physician who holds the latter view may perceive ending the patient’s life as a beneficial action. Both these physicians will have arrived at opposite decisions relying on their personal moral compasses without any regard to the feelings of the patient involved. The question of whether the ending of the patient’s life is beneficial or harmful to *him* may never be asked. If researchers are left to choose and pick between the three principles without the benefit of some hierarchical ordering or overarching guideline, the choices they make may not result in the best possible outcomes.

In the sixty-three years following the pronouncement of the Nuremberg Code, many international and national guidelines and declarations concerning ethical conduct in human subject research have been

²⁵² Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* CIOMS, Geneva 2002, 17

published. Most if not all of them have drawn on the structures and principles enunciated in the three guidelines discussed above, and because of this, most of them have missed the main point. The main point is that the basis of research misconduct is the undervaluation of human life. This idea is explored in the next section. Before taking up this discussion, mention must be made of what is now undoubtedly the most significant set of guidelines that guide clinical research trials worldwide; the guidelines issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and specifically its Good Clinical Practice: Consolidated Guideline E6 (R1)²⁵³ (ICH-GCP Guideline), which has been referred to briefly in the previous chapter. A critical analysis of the ICH-GCP is found in Chapter Four, but suffice to say at this point that unlike the other guidelines, its genesis did not lie in the quest for human subject protection, but rather the drive for economic efficiency. As such, it is largely concerned with procedural and administrative matters and does not offer any useful contribution to the present discussion.

Basis of research misconduct - Undervaluation of Human Life

As submitted earlier, the main reason why existing codes and guidelines fail to provide a workable ethical basis for human subject research is that they failed to appreciate the underlying cause of the unethical treatment of human subjects and that this cause is the undervaluation of human subjects. This undervaluation can take two forms. First, it may be class based in the sense that a particular group or class of persons are considered to be less worthwhile owing to the fact that they may possess or fail to possess certain characteristics. Second, it may be based on an undervaluation of individuals' lives; this

²⁵³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

can occur in one of two ways: the establishment of a moral duty to participate in research or paternalistic decision-making practices.

Group based undervaluation of human life

People may be undervalued because they are members of what might be regarded as inferior races or religions, if they are poor or old, or if they are mentally immature or incompetent. This undervaluation is often driven by discrimination and contempt for people who are viewed as being inferior. The inferiority may be based on extrinsic or intrinsic grounds.²⁵⁴ Extrinsic racism and discrimination lie in the belief that certain groups of people differ in respects that warrant differential treatment. Certain qualities are considered morally relevant and the presence or absence of these qualities justifies treating groups of people differently. For instance, people who are mentally retarded might be viewed as lacking sufficient intelligence. Following from this, if intelligence is viewed as being morally relevant, this group of people are considered less valuable to society and can be treated differently. Intrinsic racism differentiates between members of different races, believing that every race possesses a different moral status quite independent of morally relevant qualities. Some races are simply regarded as superior to other races. Such racist and discriminatory attitudes result in the dehumanisation of its victims as recognised by Chief Justice Dickson of the Canadian Supreme Court when he commented that "[t]he message of [racial vilification] is that members of identifiable groups are not to be given equal standing in society, and are not human beings equally deserving of concern, respect and consideration."²⁵⁵

World War II Nazi Experiments

²⁵⁴ Based on the idea that there are two types of racism, extrinsic racism and intrinsic racism from David Theo Goldberg, *Anatomy of Racism* (Minneapolis: University of Minnesota Press, 1990). at 5

²⁵⁵ *R v Keegstra* [1991] 2 WWR 1 at 50. This was a case on anti-Semitic speech

A striking example of this sort of undervaluation is the type of racist and eugenic policy pursued by the Nazi regime. They were apparently heavily influenced by social Darwinism²⁵⁶ which among other things considers that humans are nothing more than highly evolved animals; that natural selection should only allow for the survival of the fittest and that policies which bring about the death of those not fit for survival are justified. Hitler and others believed that there were gradations of human fitness; that race and physical and mental abilities were determinants of the fitness of humans; and that at the lower end of the spectrum, some lives were so worthless as not to be worth living. Unwilling to submit to the unhurried pace of natural selection, the Nazi regime chose to exterminate those they considered unfit or sacrifice their lives to serve the ends of the superior race by using them as subjects in their medical experiments.

Tuskegee Syphilis Study

The Tuskegee Syphilis Study was driven by similar ideas.²⁵⁷ Black men were considered far behind white men in terms of evolution and according to their physicians, their 'lust and immorality, unstable families, and reversion to barbaric tendencies made blacks especially prone to venereal diseases.'²⁵⁸ The doctors who formulated and ran the study accepted this view of blacks and justified not treating their condition on the premise that blacks, being promiscuous and lustful, would not seek or continue treatment.²⁵⁹

The group-based undervaluation of human life can take many forms. In the above-mentioned examples, it was grounded on mainly racial

²⁵⁶ D P O'Mathuna 'Human dignity in the Nazi era: Implications for contemporary bioethics' *BMC Medical Ethics* 2006, 7:2 at <http://www.biomedcentral.com/1472-6939/7/2> accessed April 5, 2006

²⁵⁷ For a brief description of the study, see section 3.1.3.1. Also, an excellent article which places the study in a historical context is AM Brandt 'Racism and Research: The Case of the Tuskegee Syphilis Study' *Hastings Center Report*, December 1978, 21-29

²⁵⁸ AM Brandt 'Racism and Research: The Case of the Tuskegee Syphilis Study' *Hastings Center Report*, December 1978, 22

²⁵⁹ *Ibid* at 23

arguments. It may also be gender-based, age-based²⁶⁰ or disability-based.²⁶¹ Some forms of undervaluation may be particularly insidious as they are masked by good intentions. The past practice of sterilising mentally retarded women serves as an example of this. Between 1907 and 1963 there were eugenical sterilisation programmes in 30 American states. It is estimated that more than 60,000 persons were sterilised pursuant to state laws. Both men and women were sterilised but beginning around 1930, there was a dramatic increase in the number of sterilised women.²⁶² It was thought that sterilising mentally retarded women was not only in their best interests but also in the interests of the unborn children and society as a whole, as it was then believed that mental retardation was passed on from one generation to another. Carrie Buck, an American woman was sterilised in 1927 because she had been committed to the State Colony for Epileptics and the Feeble Minded. The judge in her case,²⁶³ Justice Holmes commented that, “ It is better for all the world if instead of waiting to execute degenerate offspring for crime, or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind.”²⁶⁴

Undervaluation of the individual person

Imposition of a moral duty to participate in clinical research trials

²⁶⁰ For example, the Brooklyn Jewish Chronic Disease Hospital trials where in July 1963 a researcher at the hospital injected live cancer cells into debilitated elderly patients without their fully informed consent. See Ezekiel J. Crouch Emanuel, Robert A. Arras, John D. Moreno, Jonathan D. Grady C., ed., *Ethical and Regulatory Aspects of Clinical Research : Readings and Commentary* (Baltimore: Johns Hopkins University Press, 2003). at 3

²⁶¹ One of the more infamous cases is the Willowbrook study; in which researchers deliberately exposed children and adolescents with disabilities to hepatitis at a New York state facility. See *Ibid.*

²⁶² P. R. Reilly, "Involuntary Sterilization in the United-States - a Surgical Solution," *Quarterly Review of Biology* 62, no. 2 (1987). at 161

²⁶³ *Buck v Bell*, 274 U.S. 200, 47 S.Ct. 584, 71 L.Ed. 1000 (1927)

²⁶⁴ Interestingly, in 1980, Carrie Buck was discovered living in the Appalachian Hills and was found to be mentally competent and disappointed that she was never able to bear a child. See B Furrow, T Greaney, S Johnson, T Jost and R Schwartz *Bioethics: Health Care Law and Ethics* Third Edition (West Publishing Co, 1997) 77

As society tastes the fruits of successful research, it grows eager to savour new cures and treatments. One of the consequences of this is that there is a growing demand for new treatment possibilities and diagnostic tools, which place an enormous pressure on researchers to deliver new solutions. A leading American bioethics scholar, Callahan uses the metaphor of war²⁶⁵ to describe the zeal with which medical research is at present pursued. Researchers are seen as engaged in a battle against death and disease, and the attainment of victory may require some sacrifices. This in turn has led some besieged researchers to view human participation in research as an obligation to society.²⁶⁶ Some have gone so far as to propose that certain patients should only be offered treatment if they agree to participate in research.²⁶⁷

This obligation is commonly rooted in an account of morality known as utilitarianism, which states that the rightness of any particular enterprise is calculated based on the total benefit gained by all individuals in a society. The argument for establishing a moral duty to participate in research would be that it is in the interest of society as a whole that new drugs and methods of treating illness and diseases are discovered and that the risks undertaken and the possible harms that might befall subjects are outweighed by the gains obtained by society as a whole. One of the grounds on which the Nazi scientists sought to defend their experiments was based on utility where they argued that there was a greater good to be achieved in bringing World War II to an end by assisting the military triumph of the German army and that it was morally acceptable and in fact necessary to sacrifice the rights of a few individuals to achieve that greater good.

²⁶⁵ Daniel Callahan, *What Price Better Health? Hazards of the research imperative*, University of California Press, 2003 at 59. For examples of statements made by politicians and researchers regarding the need to pursue research, at 57

²⁶⁶ This was recognised by the National Bioethics Advisory Commission in their report entitled United States. "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume I." Rockville, Md. National Bioethics Advisory Commission, 1998.

²⁶⁷ D Orentlicher 'Making research a requirement of treatment – why we should sometimes let doctors pressure patients to participate' *Hastings Center Report* 35, no 5 (2005): 20-28

John Harris²⁶⁸ has put a more contemporary but nevertheless similar argument forward. He attempts to establish a duty to participate in clinical research trials based on the twin principles of doing no harm and fairness. In the first instance, he argues that when the actions of an individual may serve to prevent serious harm occurring to others, he is under a moral obligation to perform those actions. Since medical research contributes to a reduction in human suffering, there is among other things, an obligation to participate in medical research. Second, he relies on the principle of fairness to say that because individuals have accepted the benefits of past medical research, they have an “obligation in justice to contribute to the social practice that produces them.”²⁶⁹ It is interesting to note that Harris utilises two of the more commonly²⁷⁰ recognised ethical principles of bioethics, which are generally associated with protecting the rights of individuals. The edict to do no harm is rooted in the belief that Mr A should not be harmed by the action of Mr B and that what amounts to harm should be determined by reference to the interests of Mr A and not Mr B. The application of the principle of justice in bioethics would require fairness in the distribution of limited resources, that every person should be treated equally. However, Harris has employed these principles to construct what is essentially an argument that is utilitarian in nature.

²⁶⁸ J Harris ‘Scientific research is a moral duty’ *J Med Ethics* 2005: 31; 242-248. Also see Shapshay, S, and KD Pimple. “Participation in Biomedical Research Is an Imperfect Moral Duty: A Response to John Harris.” *British Medical Journal* 33, no. 7 (2007): 414 for a good critique of Harris’ article where the authors argue that the only thing Harris has succeeded in showing is that participating in research is a moral good among many other moral goods and not that there is a moral duty to participate in research.

²⁶⁹ Ibid at 243

²⁷⁰ Bioethics has over the past 20 years developed a set of ethical principles that serve as a sort of checklist when considering biomedical issues. This checklist includes at least the principles of autonomy, doing no harm, beneficence, confidentiality and justice

When Harris puts forward the principle of doing no harm²⁷¹ to others as being the foundation of a moral obligation to participate in research, he presents a typical consequentialist argument of attaching negative responsibility. Consequentialism attaches significance to states of affairs and therefore, a person is just as responsible for things that he fails to prevent as for things that he himself does.²⁷² The rightness of an action is ascertained by reference not to the action itself but rather to the consequences of the action. When he relies on the notion that the obligation to participate in clinical research arises from the enjoyment of benefits obtained from previous human research participation in clinical trials, he is proposing that the risks undertaken and benefits enjoyed by people in a society can be off set against each other. Duties are imposed on people today based on the consequences of the actions of individuals who have gone before them, for the benefit of members of society in the future. We enjoy the beneficial consequences of past research projects and therefore we should be responsible for ensuring that future generations continue to enjoy the same advantageous consequences.

The utilitarian position is not an unattractive one. The utilitarian does not look exclusively to his own comfort or benefit, but rather considers the interests of all other members of society. Every person counts as one and there is no place for discrimination or favouritism. However, the contention that the maximisation of utility is an appropriate basis for establishing a moral obligation to participate in research cannot be accepted because it is among other things, predicated on the undervaluation of the individual human life.

²⁷¹ This is a distortion of the ordinary use of the principle of doing no harm in the field of bioethics, which is limited to actions performed by healthcare providers engaged in providing health care services to specific individuals. It is a duty owed by one individual to another individual and not by one individual to society. It is based on the notion of respecting the individual's right to not be harmed by another individual.

²⁷² See Smart and Williams, *Utilitarianism For and Against* (Cambridge University Press 1990) at 95-96

In a utilitarian world, the primary concern of an instrument regulating research practice such as the Helsinki Declaration would be that a determination be made to assess the good and bad consequences of a research project. This determination would include amongst other things, considerations of the scientific validity of the research; the potential value of any result obtained; the number of people currently suffering from the condition; the level of suffering caused by the condition; the number of people likely to benefit from the research; the number of subjects that might be put at risk and the level of risk that subjects might be exposed to. If at the end of the calculation, the potential benefits of proceeding with the research are greater than the possible harms, there should no question that the research should continue and that individuals should be duty bound to participate in the project. Informed consent would no longer be needed, as the individual no longer determines whether he is willing to accept the risks of research participation. No consideration of the rights and interests of individual subjects is required as their interests will already have been included as part of the initial calculation of utility. When this is done, people are no longer treated as valuable individuals with rights and interests; instead they are treated as tokens.

People are treated as objects or tokens that are traded against each other when a greater value is placed on consequences rather than the interests of individual lives. Jonas eloquently describes the problem with treating people in this way:

“What is wrong with making a person an experimental subject is not so much that we make him thereby a means (which happens in social contexts of all kinds) but that we make him a thing - a passive thing merely to be acted on, and passive not even for real action, but for token action whose token object he is.”²⁷³

²⁷³ Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, *DAEDALUS* 98, (Spring, 1969), 219-247 at 221

People are neither tokens nor things that can be subjected to experiments for the benefit of others. Every individual is committed to projects and actions that make his life worthwhile and to devalue a person's commitments is to attack his integrity.²⁷⁴ To demand that a person gives up his projects is to "alienate him in real sense from his actions and the source of his action in his own conviction."²⁷⁵ Utilitarian principles undervalue the commitment of individuals to projects that make their lives worthwhile and in short, they undervalue the individual human life. An example might be given of a person Ms F, who suffers from severe arthritis and who is invited to enrol in a randomised, double blind study of a new painkiller. There is some evidence that the new painkiller, X may be more effective than the standard treatment, Y. Ms F is an extremely fearful person and cannot abide uncertainty. The thought of being enrolled in a trial where neither she nor her doctor will know the medication she is taking is deeply distressing to her. To force her into this trial because it is in the best interests of society is to violate her sense of integrity by undervaluing her preferences.

Moreover, we should not mistake what is morally praise-worthy for what should be morally obligatory. When we declare that a particular action is obligatory, we take away the element of individual choice; we do not distinguish between the courageous and the timid but compel all to take such action. Harris' assertion that fairness requires that we should participate in medical research trials because we have benefited from the advances in health care provided by past medical research projects places an unduly heavy burden on individuals. Consider the case of a middle-aged woman, Eve, who when she was a child, was saved from a burning building by her elderly neighbour. While on her way to work one day, she notices that another neighbour's house is on

²⁷⁴ See Bernard Williams attack on utilitarianism in Smart and Williams, *Utilitarianism For and Against* (Cambridge University Press 1990) particularly 116-117

²⁷⁵ Ibid at 116

fire and that a young boy is trapped in the building. Does she have a moral duty to risk her life to save the young boy? If she attempts to save him, we would praise her for her bravery but it would seem unreasonable to suggest that her failure to do so was morally blameworthy. It is unlikely that her elderly neighbour thought he was creating a debt when he saved Eve and in fact it diminishes his heroic act by suggesting this.

Harris' appeal to fairness is in fact mistaken in that he assumes that a duty to reciprocate is an obligatory response to a gift, which is freely given.²⁷⁶ At most, the obligation is that the beneficiaries should be grateful for the gift.²⁷⁷ Moreover, if reciprocity were to apply, it is hard to see how the duty could be owed to anyone other than those who participated in past research projects. In the example above, if Eve owes anyone a duty for her rescue, she owes that duty only to her elderly neighbour.

Certain levels of illness, disease, disability and death have been a part of society since the beginning of time. No amount of research will eradicate these phenomena and society will not be destroyed by their existence.²⁷⁸ It would certainly be a laudable aim to embark on research to reduce the suffering and sickness in this world but it cannot be a moral obligation on individuals in a society.

Paternalistic decision-making

The second way in which the individual life may be undervalued is when decisions are made for people based on what other people perceive to be in their best interests. This may lead to situations where

²⁷⁶ See A L Caplan, "Is There an Obligation to Participate in Biomedical Research," in *The Use of Human Beings in Research with Special Reference to Clinical Trials*, ed. Stuart F. Spicker, *Philosophy and Medicine. Vol 28* (Dordrecht: Kluwer Academic, 1988). at 235

²⁷⁷ Caplan goes on to point out that it is naïve to think that all who participated were acting altruistically as many compensated, others tricked or coerced into participating in trials, and it is certainly difficult to derive an obligation from trickery or coercion. *Ibid.* at 235

²⁷⁸ This is based on normal expected mortality and morbidity rates in a society

investigators make decisions based on beliefs and suppositions close to the hearts of the investigators, but that may be alien to the research subjects.

These sorts of decisions undervalue the individual by rejecting his or her personal beliefs as being inferior or unacceptable. This sort of undervaluation is often found in situations where health care givers have to deal with patients from migrant communities that have very different cultural ideas. The case of Miss Tai,²⁷⁹ a 42-year-old Vietnamese immigrant, suffering from metastatic cancer illustrates how conflicting notions of respect for autonomy can occur. In interviews, Ms Tai suggested that her brother was her primary decision-maker concerning her health care. The physician viewed Ms Tai's traditional views on decision making as being inferior to his idea of respect for individual autonomy and in fact described the family as being abnormal. Ms Tai's brother was against her being told about her cancer because he did not think that she would be able to cope with the knowledge. Her physician opposed this view and against her brother's wishes, informed her of her diagnosis and expressed frustration that she did not seem to want to make decisions on her own. The physician undervalued Ms Tai in this case when he chose to disregard her wishes to leave the decisions to her brother.

Ethical Basis for Clinical Research Involving Human Subjects

When medical research is pursued relentlessly or in an unethical manner it may bring about a great deal of harm, and as shown above, the root of that harm is the undervaluation of human life. This then begs the question, how do we ensure that human life is not undervalued? What is the appropriate value that should be placed on

²⁷⁹ See P Marshall, B A Koenig, P Grifhorst and M V Ewijk 'Ethical Issues in Immigrant Health Care and Clinical Research' *Handbook of Immigrant Health* ed Loue (Plenum Press 1998 New York) 208-209

human life? This thesis proposes that the answer is that the value of human life should be based on the single principle of respect for human dignity. The following discussion will demonstrate how by grounding the moral basis of human research in the idea of respecting human dignity, it is possible to tease out the idea of human dignity to provide a framework for ethical decision-making that is not only coherent but also and perhaps more importantly, that provides a discourse that is accessible to the parties who are required to make decisions in the interest of human subjects.

How to value human life?

Addressing the issue of how persons should be treated so as to not undervalue their lives involves asking questions that range from what is human life – when does life begin, to when does life matter morally and what that entails in relation to different groups of people? As this thesis is primarily concerned with the way in which mentally incapacitated adults are treated, there is little to be gained²⁸⁰ by delving into the fundamental questions at the edges of human life - when does human life begin and end? Accepting the fact that human life exists, the next step of the enquiry is to consider questions revolving around how human life is valued: is all human life morally significant, and whether there are different degrees of morally valuable human lives? If, as many bio-ethicists would suggest, that not all human life is equally morally valuable; and that moral significance is dependent on the existence of certain criteria and indicators, the question then must be asked as to what these criteria or indicators are?

Valuing life based on capacities – personhood

²⁸⁰ This is in no way suggesting that the issue is of no importance, but simply that given the limitations of this current research paper, it is not feasible to engage in this deliberation

The notion of a morally valuable life has often been connected to the notion of personhood, where theories of personhood distinguish what it means to be 'human' from what it means to be a 'person'.²⁸¹ The criteria range from very the stringent criteria such as requiring the possession of concept of a self as a continuing subject of experiences²⁸² to the very low requirement of simply being conceived by human parents²⁸³ (at which point the argument collapses into all human life is morally valuable). The problem with relying on the idea of respecting personhood emerges at the higher end of the spectrum where what it means to be human is distinguished from what it means to be a person.

Persons are individuals who possess certain properties. There are nonhuman persons such as angels, devils, fictional cartoon characters such as Donald Duck; and there are human non-persons such as anencephalic infants and individuals in persistent vegetative states.²⁸⁴ Personhood is dependent on the possession of a range of capacities²⁸⁵ and only persons are considered to possess morally valuable lives.²⁸⁶ Harris puts forward the view that the connection between personhood and moral value arises in two ways, possession of the capacity for self consciousness coupled with minimum intelligence; and the capacity of an individual for valuing his own life and taking an interest in his own future. He observes that evidence of the latter presumes the existence of the former and thus

²⁸¹ For an excellent overview of the concept of personhood in bioethics, see Ruth Macklin, "Personhood in the Bioethics Literature," *The Milbank Memorial Fund Quarterly. Health and Society* 61, no. 1 (1983). Ideally, the present discussion would encompass the entire spectrum of human life from the infant to the aged individual, but the present enquiry is limited to the adult human. While the matter of how we should value the lives of infants and children is without doubt of great importance and should be given close consideration, it is beyond the scope of this thesis to delve into these matters at present.

²⁸² Michael Tooley's criteria, see Ibid. at 44

²⁸³ John Noonan, see Ibid. at 41

²⁸⁴ J Harris 'The concept of person and the value of life' *Kennedy Institute of Ethics Journal* 9.4 (1999) 293-308 at 293

²⁸⁵ These are by and large cognitive abilities such as self-consciousness, capacity of act on reason, rationality and capacity to communicate.

²⁸⁶ Beauchamp distinguishes between metaphysical personhood, which is determined by possession of psychological properties and moral personhood, which is determined by possession of properties or capacities for moral agency and moral motivation. However, this distinction does not help in the discussion, as he does not show why this distinction is important as he concludes that moral standing does not depend on moral personhood. See T L Beauchamp 'The Failure of Theories of Personhood' *Kennedy Institute of Ethics Journal* 9.4 (1999) 309-324

the capacity of an individual for valuing his own life and taking an interest in his own future is the criterion for recognising morally valuable lives.

Connecting the value of an individual's life to his own capacity to value it would allow for the killing of any individual who is assumed to have lost this capacity. An individual suffering from a severe form of cerebral palsy would not count as a person and according to Harris' account would not have any moral value. Harris would agree that as long as he was killed in a humane manner, he could be put to death without harming him. The only prohibition would be not to harm him by causing gratuitous suffering.

Harris' theory is wanting in that it alienates us from our sense of what it means to be human. It reduces the value of human life to an instrumental value in that it is only valuable because the person living that life values it. It opens the door to the first type of undervaluation of human life mentioned in the earlier section. It prejudices certain classes of individuals as being less valuable and unworthy of moral protection because they fail to possess certain capacities. It leaves them vulnerable. The history of research misconduct as set out earlier is very much a history of undervaluing people with impaired cognitive abilities.

Valuing life based on human dignity

An alternative to basing the value of human life on notions of personhood as possessing certain capacities is the idea of respecting human dignity. The concept of human dignity is not a new one and has been extensively used in various discourses. Schulman²⁸⁷ highlights four key sources of the idea of human dignity that have come to shape

²⁸⁷ Adam Schulman, "Bioethics and the Question of Human Dignity," in *Human Dignity and Bioethics: Essays Commissioned by the President's Council on Bioethics*, ed. President's Commission on Bioethics (US Independent Agencies and Commissions, 2008) at 6. Also see Schüklenk, U., and A. Pacholczyk. "Dignity's Woolly Uplift." *Bioethics* 24, no. 2 (2010)

the way in which the term is understood. First, dignity as used in classical antiquity to mean something rare and exceptional; second, the use of the term in the context of religious discourse which is generally associated with the Catholic tradition;²⁸⁸ third, as used in Kantian moral philosophy where the notion of dignity is grounded in human rational thinking; and lastly, in the use of the term in the 20th century where since the end of World War II, dignity has been used as a foundational concept in human rights instruments²⁸⁹ and state constitutions. Schulman argues that because of the disparate nature of these sources, the application of the term human dignity in the bioethics discourse has been rather uncertain and wonders if “it is a useful concept that sheds important light on a whole range of bioethical issues ... or is it a useless concept at best... or at worst a mere slogan that camouflages unconvincing arguments and unarticulated biasness?”²⁹⁰ Schulman is right when he points out that the term human dignity is useful when used to shed light on issues, and dangerous when employed to substantiate biasness; but much the same can be said about the term personhood. What matters is not the term that is used but the way in which that term is understood.

Beyleveld and Brownsword²⁹¹ on the other hand, suggest that there are two conceptions of the notions of human dignity: human dignity as empowerment and human dignity as constraint. Human dignity is used as a tool for empowerment in human rights instruments²⁹² where it provides the justification for the recognition of human rights; and is

²⁸⁸ In fact, the Catechism of the Catholic Church devotes no less than 23 pages to explaining the concept and its implications. R J Neuhaus, "Human Dignity and Public Discourse," in *Human Dignity and Bioethics. Essays Commissioned by the President's Council on Bioethics*, ed. President's Council on Bioethics (Government Printing Office, 2008). at 227

²⁸⁹ Universal Declaration of Human Rights 1948, International Covenant on Economic, Social & Cultural Rights 1966 and International Covenant on Civil & Political Rights 1966. In each case, human dignity is specifically mentioned as one of the foundational ideas.

²⁹⁰ Schulman, "Bioethics and the Question of Human Dignity." at 3

²⁹¹ Deryck Beyleveld and Roger Brownsword, *Human Dignity in Bioethics and Biolaw* (Oxford: Oxford University Press, 2001).

²⁹² The term is described as the “rock on which the superstructures of human rights is built.”Ibid. at 12

used as constraint primarily in the bioethics context where it restricts individual choice by representing a collective good that society deems worth pursuing at the expense of the individual. Beyleveld and Brownsword provide what appears to be a very narrow understanding of how human dignity is understood in the bioethics arena and focus a great deal of their arguments on two particular instruments: the Council of Europe's Convention on Human Rights and Biomedicine and the preamble to UNESCO's Universal Declaration on the Human Genome and Human Rights. But there is much more to how human dignity has been employed in the bioethics literature. For example, human dignity is commonly employed as a principle that should guide ethical action in caring for the elderly. Calls are made in the name of human dignity to defer to choices made by elderly patients even if such decisions may hasten death.²⁹³ The Social Care Institute for Excellence²⁹⁴ in the United Kingdom sets out eight dignity factors, which are considered vital in the care of the elderly. These factors are choice and control, communication, personal hygiene, practical assistance, privacy and social inclusion. Dignity in this sense is far more about empowerment rather than constraint. Therefore, while Beyleveld and Brownsword are not wrong to say that dignity may be used as constraint and empowerment, it is untrue that it is used primarily as constraint in bioethics and recognising that it may exist as constraint or empowerment does not help in clarifying the way in which the term should be used.

Richard Ashcroft provides what appears to be the most useful if not practical description of how the term human dignity is used in bioethics.²⁹⁵ He identifies four distinct ways in which current bioethics scholars regard the term 'dignity'. First, as incoherent and unhelpful;

²⁹³ Schulman, "Bioethics and the Question of Human Dignity." at 5

²⁹⁴ This is an independent charity funded by the Department of Health and the devolved administrations in Wales and Northern Ireland. SCIE identifies and disseminates the knowledge base for good practice in all aspects of social care throughout the United Kingdom.

²⁹⁵ R E Ashcroft 'Making sense of dignity' *J Med Ethics* 2005 31:679-682 at 679

second, as ‘illuminating but reducible to autonomy as extended to cover some marginal cases’; third, as ‘concepts about capabilities, functionings, and social interactions and fourth, as “a metaphysical property possessed by all and only human beings, and which serves as a moral foundation for moral philosophy and human rights.” The following discussion will demonstrate that the concept of dignity should be accepted in the fourth and last sense of being a characteristic accorded to all humans and which serves as the moral foundation for moral philosophy and human rights.

The following section proposes a framework for understanding human dignity that serves two main functions. First and most importantly, it provides a rich account of the notion of human dignity that is not only inclusive in that it embraces all human life, but that also recognises that not all humans are able, or choose to value their lives in the same way and that what it means to treat different individuals with dignity may mean different things to different people. Second, by anchoring the ethical treatment of research subjects onto the single principle of respecting human dignity, it provides decision makers such as ethics committee members with not only a coherent framework for their deliberations but it provides this framework in a simple language that is accessible to both lay and professional members of ethics committees.

It is proposed that human dignity should be understood as applying to all humans by recognising both the subjective and intrinsic value of human life.

Human Dignity as accorded to all humans

If human dignity is understood as essentially being about autonomy, or capabilities and social functionings, then there is very little to separate dignity from the account of personhood described above. This account as noted earlier fails to adequately provide for persons with impaired

capabilities and social functionings. If human dignity is to address the problem of the undervaluation of human life, it must be not only an inclusive concept that embraces all human life, but also a rich concept that recognises the complex nature of human life. It should allow us to not only recognise the value of individuals who possess rationality but also to accept our moral duties to those who do not possess this capacity based on the idea of the intrinsic value of human life. The idea of personhood forwarded by Harris only permits of a simplistic and one-dimensional explanation of the value of human life as it is based solely on the ability to value one's life. Human life is valuable not just because some humans value life. To this end, Dworkin²⁹⁶ offers a richer and more accurate understanding of the values attached to human life.

Human dignity reflects the subjective and intrinsic value of human life

Dworkin argues that human life possesses value in three ways: instrumental value, which is based on how a person being alive serves the interests of others; subjective value, which is based on how much a person values his own life; and intrinsic value, which is a value that is independent of what people happen to enjoy or want or need or that is good for them.²⁹⁷ It is proposed that when speaking of the idea of respecting human dignity, it is most appropriate to look to the second and third components of the value of human life.

Subjective value of human life

The subjective value of an individual's life is derived from the capacity it protects, which is the capacity to express one's own values, commitments and convictions. In recognising the subjective value of human life as being a reason for according it respect, we recognise the importance of the integrity of the person and from this derive the

²⁹⁶ R Dworkin *Life's Dominion* Harper Collins Publishers 1993

²⁹⁷ Ibid at 72

principle of respect for autonomy of the person. Therefore, when speaking of respecting the human dignity of an individual, this is often connected to the idea of respecting his autonomy, allowing him to make choices even though society may think that he has made the wrong choices. In recognising that each person has a right to choose against the wishes of others, the individual life is not undervalued.

The subjective value of an individual's life is shaped by many factors, for instance: a person's genetic makeup, his personal experiences, cultural influences and religious beliefs. In seeking to respect human dignity, there must be a certain level of deference to how an individual chooses to shape his or her own subjective value. For example, in some African and Asian²⁹⁸ countries, one's tribe, village or social group defines an individual's identity. It may be necessary to obtain consent from a tribal village head, head of a family or religious authority before obtaining individual consent to participate in a clinical research trial. An individual living in that community may see the subjective value of his life as being primarily attached to the interests of the tribe. While this notion may be alien to a decision maker whose subjective value is strongly tied to the notion of individual autonomy, respecting the human dignity of the African individual would require the decision maker to honour his choice to defer to the interests of the tribe.

In the research arena, the recognition of the subjective value of human life of competent subjects is most often reflected in the principle of autonomy and actualised by requiring that subjects provide informed consent before they enter into any trial. Therefore, in most cases, ethics committee members focus their discussions on the adequacy of informed consent forms and patient information sheets. So long as

²⁹⁸ Differences may even exist within a country; Mala Ramanathan notes that a research project carried out in India which involved both urban and rural subjects required that consent be obtained from local leaders in rural areas before obtaining informed consent, whereas in urban areas, consent was obtained solely from the subjects. Mala Ramanathan, Cultural Absolutism vs. Cultural Relativism: Ethical Issues in International Health Research, *Program on Ethical Issues in International Health Research*, Harvard School of Public Health, June 14-18, 2004

patients are provided with sufficient information that maximises their decision-making abilities by allowing them to make free and informed choices, the subjective values of their lives are respected.²⁹⁹ However, it is erroneous to presume that persons who lack the capacity to provide informed consent have no subjective interests at all.

Capacity and subjective value

A person is typically determined as lacking capacity to provide informed consent when he is unable to do any of the following: understand the relevant information, weigh the information as part of the decision-making process, or communicate his decision. This does not mean that the incapacitated person has no interests at all as to how his life is lived. Take for example, Mr Y, who is extremely musical and loves to play the piano. He is also suffering from severe dementia, which has profoundly affected his decision-making abilities. His doctor wants to enrol him in a clinical trial for a new treatment for dementia. There is a risk that the new drug will affect his co-ordination, and while it does not present a risk to his health, it may affect Mr Y's ability to play the piano. If it is evident that playing the piano gives Mr Y pleasure, (even if he cannot articulate this fact himself) it must reflect a subjective value in Mr Y's life, and as such, should be taken into account in determining whether he should be enrolled in the trial. Therefore, when decisions to enrol mentally incapacitate persons into clinical trials are taken, they should inasmuch as is possible, require inquiry into the interests and commitments of the persons and incorporate these values into the decisions. More so if a person once was competent, regard should be given to the person he once was.

²⁹⁹ Although it is debatable as to whether or not it is actually ever possible to obtain truly informed consent.

Intrinsic value of human life

But if this is all that is meant by dignity, then Macklin³⁰⁰ is correct when she claims that dignity is a useless concept because it means little more than respect for persons or their autonomy and at the end of the day, this means nothing more than respecting personhood. It is suggested that Macklin is wrong because she has failed to appreciate that dignity means more than just respecting the subjective value of life.

Consider the case of an elderly man X, suffering from late stage Alzheimer's Disease living in a nursing home. He generally appears to be unaware and unresponsive to his surroundings. He is led to the living area on a daily basis, where he sits for a few hours, not talking to anyone or responding to any external stimuli. One day, he soils himself in the living area. Supposing that there are two carers working at the home with two very different philosophical outlooks and each of them is asked how they would manage him. Carer A says that he would lead X to the bathroom, disrobe him, clean him up, put on a new set of clothes and lead him back to the living area. Carer B however, says that he would take off X's clothes in the living room, lead him out into the garden, hose him down, lead him back into his room and dress him in a new set of clothes. We instinctively feel that B's manner of tending to the needs of X is wrong and would say that he has treated him in an undignified manner. However, assuming that X does not resist the ministrations of either A or B and if we accept that dignity is limited to respecting autonomy; it cannot be said that X has been treated without dignity by B. But this account of dignity does not recognise central features of our convictions about dignity, that it embraces both the subjective and intrinsic value of human life. When an individual has lost his capacity to value his own life and no longer has a coherent

³⁰⁰ R Macklin 'Dignity is a useless concept' *BMJ* 2003; 3227; 1419-1429

sense of self, his life may not have any subjective value, but it retains an intrinsic value.

Human life has an intrinsic value in that it is valuable 'for its own sake' or 'in its own right'. Even if that human life does not enjoy instrumental or subjective value, it is a unique creation. It possesses a sacred³⁰¹ and inviolable value and as Dworkin proposes, it is sacred because it exists and it is inviolable because of what it embodies.³⁰² The typical human life embodies the idea that it is not just important that human life exists but that it flourishes, that there more to being human than being alive. However, even when this life is 'flawed' and unable to flourish in the ordinary sense, it remains a representation of what it is to be human and as such should be afforded a measure of respect. We respect the sacredness of life by not destroying it and we respect the inviolable value of life by acknowledging that life has moral value beyond mere existence, that it is objectively important how that life goes and we insist that "nothing be done to or for him, that in our community's vocabulary of respect, denies him dignity."³⁰³ In the case of X, we respect his dignity by treating him as carer A would.

Human dignity means much more than merely possessing the capacity for autonomous choice. Even when a person is unable to appreciate the value of his or her own life, the notion of dignity requires that this person be treated with a measure of respect. The more difficult questions to answer are: what factors should be taken into account in deciding what the intrinsic value of life should mean, and how might ethics committees use this notion of intrinsic value in their deliberations? As noted above, the intrinsic value of human life exists independently of any instrumental or subjective value that life might hold for the individual himself, therefore, what counts as the intrinsic

³⁰¹ The word sacred is not used in the religious sense but is used to show that human life should be regarded with a sense of reverence or respect.

³⁰² R Dworkin *Life's Dominion* Harper Collins Publishers 1993 at 74

³⁰³ Ibid at 237

value of human life should be independent of the personal characteristics or capacities of a person, his culture, community or religion.

While it is beyond the scope of this thesis to consider fully the factors that are relevant to an enquiry into intrinsic value, the following four factors are presented as being relevant criteria that should be taken into account particularly in cases involving medical research enrolling mentally incapacitated adults.

1. No person should be killed or caused to suffer undue pain or distress or be put in risky situations. It is impossible to eliminate all risks in a clinical trial but incompetent patients should only be exposed to the lowest possible levels of risk and each patient should be assessed to determine whether or not any of the procedures involved would cause him any distress.
2. No person should be treated in a discriminatory fashion. There should be no distinction based on factors such as intellectual ability, cognitive powers, race, gender, national origin, and religious beliefs.
3. No person should ever be treated solely as a means to an end. No one should be used to serve the ends of another individual or a group of people.. There is a greater risk of this happening when deciding for incompetent patients because the people who care for them and who are involved in trials have interests of their own and that there must be a determination that these interests do not override the interests of the incompetent patient thus making him a means to an end.
4. Identity goes to the heart of what it means to be a human being and this identity is rooted in the cultural, societal and religious norms of a community. It is thus important to look to a community's vocabulary of respect when considering the intrinsic value of an incapacitated patient's life. For example, a patient living in a

conservative Muslim community should not be enrolled into trials, which would involve him ingesting capsules made of porcine material.

Human dignity and vulnerability - mentally incapacitated adults

In certain circumstances a population might be deemed vulnerable. This should put ethics committees on alert and they should pay particular attention to ensuring that the dignity of this population is respected. While much ink has been spilled on unpacking the notion of vulnerability,³⁰⁴ there is little doubt that mentally incapacitated persons are considered vulnerable and history has borne witness to the fact that many unethical trials have been carried out on persons who have lacked capacity.³⁰⁵ How then should the principle of respecting human dignity be applied in cases involving vulnerable populations? How should ethical decision-making proceed in such cases?

When considering situations involving vulnerable groups, the first step should be to locate the sources that contribute to the vulnerability. In the case of mentally incapacitated adults, there are internal and external sources that feed into their vulnerability. Mentally incapacitated adults inevitably suffer from cognitive defects or deficiencies that render them unable to make autonomous decisions or to communicate such decisions; and as such, these internal pathologies are sources of their vulnerability. However, it is not internal pathology alone that makes this group vulnerable, although it is certainly a necessary prerequisite. The vulnerability and sense of powerlessness of the decisionally impaired is also driven by external factors: the manner

³⁰⁴ See discussion in Chapter One, Section 1.2.1

³⁰⁵ See discussion in Section 3.1

in which capacity judgments are made, and the mechanisms by which decisions are made for mentally incompetent patients.³⁰⁶

How capacity is determined

Once a person is judged as not having capacity to decide whether or not to enrol in a clinical trial, he loses the right to make a choice based on what he believes is the subjective value of his life and at best, others will decide whether he should take part in the research based on what they can ascertain of his subjective interests and their understanding of the factors that make up the intrinsic value of life. A finding of incapacity deprives a person of a vital element of the subjective value of human life – the right to autonomy - to make choices free from external interference.

A person who faces a determination of incapacity is more or less powerless. He has no power to decide what sort of information will be provided to him; no choice as to which capacity test will be administered; no say in the determination of capacity, which will lie in the hands of the physician; and any protestations on his part, are likely to be viewed as further evidence of his incapacity. Szasz suitably demonstrates the vulnerability of an individual who is subject to a determination of incapacity when he compares the difference between the situations where a person is accused of a crime with that of a person facing a determination of incapacity.³⁰⁷

‘The defendant has a right to deny his crime and disagree with his accusers. His insistence on his innocence is not interpreted

³⁰⁶ There is no doubt that persons who are denied decision-making powers regarding their own lives are vulnerable. They are subject to the decisions of others and particularly susceptible to having decisions made for them contrary to their wishes or being exploited. Proxies do not always make decisions that tally with what patients might really want. A systematic review of 16 studies involving 151 hypothetical scenarios and 2595 surrogate-patient pairs, which collectively analyzed 19,526 patient-surrogate paired responses found that surrogates wrongly predicted the end-of-life preferences of patients in one third of the cases. D. I. Shalowitz, E. Garrett-Mayer, and D. Wendler, "The Accuracy of Surrogate Decision Makers - a Systematic Review," *Archives of Internal Medicine* 166, no. 5 (2006).

³⁰⁷ T. Szasz, "'Idiots, Infants, and the Insane': Mental Illness and Legal Incompetence," *J Med Ethics* 31, no. 2 (2005).at 80

as evidence of his guilt. The person diagnosed as mentally ill loses this right. His disagreement with the psychiatrist is interpreted as “lack of insight into his illness” or “denial of his illness”. His insistence on his sanity is interpreted as evidence of insanity.’

Given the consequences of a determination of incapacity and the fact that the person on whom this determination is being made is more or less powerless to contest it; unless the judgment is beyond question, a person whose capacity is called into doubt is placed in an extremely vulnerable position. It is therefore troubling to note that problems have been raised concerning the tests of capacity. To begin with, there appears to be a lack of consistency across instruments in what is being measured. A study³⁰⁸ that conducted searches on PubMed (MEDLINE), PsycINFO, ArticleFirst, LexisNexis and Westlaw for English-language articles from January 1980 through to December 2004 describing or using structured instruments designed to assess adults’ capacity to consent to clinical treatment or research found that “definitions of “reasoning” vary from the ability to provide “rational reasons” for one’s choices to making the “reasonable” choice in a given situation to the underlying cognitive processes used in reaching a decision.”³⁰⁹ Moreover, definitions and measurements of appreciation were also found to be variable with the focus ranging from appreciation of the consequences of a choice to acknowledgment of the presence of a disorder and its treatment potential to the absence of “patently false beliefs” driving one’s appreciation.³¹⁰

Second, there is a large subjective element present in the assessment of capacity. The lack of standardized means of measuring dependent variables noted above has resulted in investigators frequently “devising their own measures of understanding, appreciation, and

³⁰⁸ L. B. Dunn et al., “Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments,” *American Journal of Psychiatry* 163, no. 8 (2006).

³⁰⁹ *Ibid.* at 1331

³¹⁰ *Ibid.* at 1331

rational manipulation, with varying psychometric properties.”³¹¹ Significantly, observers³¹² have pointed out that that patients are rarely found to be incompetent when they agree with the choices of their physicians.

Linked to the first and second points is the argument that assessment of patient capacity is to a certain extent a matter of social construction and therefore subject to the injection of bias. Capacity is a continuum concept that ranges from full capacity through to complete incapacity and as there are no discernable breaks in the continuum, cut-offs stationed on it are based largely on practical and policy reasons³¹³ and these reasons are partially based on the dominant moral and socio-political values of a society.³¹⁴ A person who does not conform to socially accepted norms of behaviour runs the risk of being found to lack capacity.

Third, sometimes the poor performance of patients may not be solely dependent on their cognitive disabilities as sometimes this may be due to the way in which information is provided to them. Patients have no control over the manner in which information is provided to them. Schizophrenic patients who performed poorly on initial capacity tests and who were subsequently given added learning opportunities, were found to be able to bring their scores into a range of comparative group

³¹¹ Paul S. Appelbaum and Thomas Grisso, "The MacArthur Treatment Competence Study. I," *Law and Human Behavior* 19, no. 2 (1995). at 111. Jos Welie and Sander Welie, "Patient Decision Making Competence: Outlines of a Conceptual Analysis," *Medicine, Health Care and Philosophy* 4, no. 2 (2001). at 131 notes that in the absence of a generally agreed-upon theory of health care benefits, the views of individual clinicians inevitably will affect their assessment of patient's decision-making competence.

³¹² James F. Drane, "The Many Faces of Competency," *The Hastings Center Report* 15, no. 2 (1985). at 17, Welie and Welie, "Patient Decision Making Competence: Outlines of a Conceptual Analysis." at 131.

³¹³ Ruth R. Faden, Tom L. Beauchamp, and Nancy M. P. King, *A History and Theory of Informed Consent* (New York ; Oxford: Oxford University Press, 1986). at 289

³¹⁴ Barbara Secker, "Labeling Patient (in)Competence: A Feminist Analysis of Medico-Legal Discourse," *Journal of Social Philosophy* 30 (1999). at 297

of people who did not suffer from the condition.³¹⁵ A study examining 154 consent forms approved by the Internal Review Boards (IRBs) of the Massachusetts Department of Mental Health found a discrepancy between the readability of consent forms and the reading ability of potential study participants.³¹⁶ Furthermore, consent forms became more difficult to read as risk levels of the studies increased. There is a danger that determinations of incapacity may be made too summarily based on consent forms that are too complicated for certain individuals.

Having ascertained that a source of vulnerability is the manner in which capacity is determined, and recognising that the danger is that persons who are subject to this process may lose their right to make choices based on the subjective values of their lives; ethics committees that are presented with research protocols that include the participation of mentally incapacitated adults adhere to the principle of respecting human dignity by engaging in rigorous examinations of the way capacity determinations are made.

Respecting human dignity – interplay between subjective and intrinsic values

How an ethics committee might decide how the pertinent factors that make up subjective and intrinsic values bear on a particular case and whether subjective or intrinsic values are more important when they point in different directions will depend on the protocol that is set before the committee. These decisions are not always easy to make. Subjective values may sometimes clash with intrinsic values. There may be instances where the treatment of a person violates the intrinsic

³¹⁵ W. T. Carpenter et al., "Decisional Capacity for Informed Consent in Schizophrenia Research," *Archives of General Psychiatry* 57, no. 6 (2000). 537

³¹⁶ Even by the most conservative estimate, approximately 35% were found to lack the educational level required to read the average informed consent form. P. P. Christopher et al., "Consent Form Readability and Educational Levels of Potential Participants in Mental Health Research," *Psychiatric Services* 58, no. 2 (2007) at 230

value of that person notwithstanding the fact that the individual chooses that treatment based on cultural and religious influences.

For example, it is one thing to respect the tradition of consulting a village elder before proceeding to ask individuals in a community for their consent to conduct a clinical trial in a community; and another thing altogether to acquiesce to the demand from a village elder that consent for giving women a trial drug should only be obtained from their husbands and that researchers should make no attempt to engage the women in any conversations. Even if the wives appear to accept that they have no choice in the matter and do not resist the treatment once their husbands instruct them, it is still a violation of the intrinsic value of life. Culturally defined notions of identity and subjective value should not to be confused with culturally based discrimination and bias. However, these judgments are not easily made and Macklin³¹⁷ provides an illuminating approach to distinguishing between the two. She suggests that there are different levels of ethical significance and that within and across cultures some values have greater importance than others. Some deal with “basic ways humans treat each other and others shade into what is more like etiquette.”³¹⁸

There is no easy prescription for locating what it means to respect human dignity in any particular case and ethics committees must make that journey every time they are presented with a research protocol. But at the same time, what amounts to respecting human dignity cannot be a matter of ineffable intuition provoked mysteriously by some factor and not another. By unwrapping the notion of human dignity into the factors as described above, ethics committee members have at their disposal a set of building blocks that they can use to

³¹⁷ Macklin, Ruth. *Against Relativism: Cultural Diversity and the Search for Ethical Universals in Medicine*. New York; Oxford: Oxford University Press, 1999. Also see Gupta, V.B., and D Mukherjee. "Conflicting Beliefs." *Hastings Cent Rep* 40, no. 4 (2010): 14-15 of a case study of an incapacitated Hindu man.

³¹⁸ *Ibid* at 11

construct their own understandings of what respecting human dignity requires in each case. While there is still much work to be done in fully unwrapping this notion of respecting human dignity and what it means to other potentially vulnerable cohorts such as children and refugees, it is submitted that this approach presents ethics committees with a coherent and workable framework for meaningful ethics discourse in a language that is accessible to all parties.

It is evident from the discussion at the beginning of this chapter that Malaysian ethics committee members do not or are not able to engage in meaningful ethics review. Much of this is attributed to the lack of training provided to committee members. However, as is argued above, the tools that are presently on offer are flawed. Therefore, offering ethics committee members these tools will not necessarily remedy the situation. Guidelines such as the Helsinki Declaration are too complex and difficult to apply. This is evidenced by the fact that eventhough some ethics committee members did receive some training on the Helsinki Declaration, none of them was able to articulate any of the principles contained within. The reality is that ethics committee members need new tools. Because ethics committee members come from a variety of backgrounds,³¹⁹ they need to be provided with an ethics framework that is coherent and in a language that is accessible to every member, but which at the same time is rich enough to reflect the complex issues raised by medical research. The framework offered above is the first step in that direction.

³¹⁹ Scientists, clinicians, researchers, lawyers and lay persons.

4 Chapter 4

Ethics Committee Review and the ICH-GCP Guideline

Chapter 3 considered whether Malaysian ethics committees were providing adequate protection to research subjects by examining the quality of their review process by looking at the principles that they were using in their discussions. What was apparent from the interviews that were conducted was that ethics committee members were generally not relying on established research ethics guidelines because they were either unaware of the guidelines or unable to remember the principles contained within. One of the reasons forwarded for this is that the current guidelines and principles that are meant to guide ethics committee decision-making are as a whole, incoherent and difficult to apply. To this end the principle of respecting human dignity was proposed as being a sounder basis for meaningful ethics review. Another reason why ethics committee members are largely ignorant about research ethics is that for all intents and purposes, the clinical trial industry in Malaysia is regulated by a the ICH process³²⁰ and ethics committees are run in strict compliance with the ICH-GCP guideline.³²¹

This chapter sets out to describe and analyse the roles and responsibilities of ethics review as set out by the ICH-GCP, and demonstrates that taken as a whole, this framework reveals two major concerns. First, ethics committees (IRBs)³²² are not provided with sufficiently clear and coherent guidance in carrying out their mandate to protect human subjects. Second, the guideline places a disproportionate emphasis on duties that are administrative in nature,

³²⁰ For a brief account of the development of the ICH process and the implications for developing countries such as Malaysia, see Chapter 2, Section 2.1.2 and 2.1.3

³²¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

³²² The term IRB is used in this chapter when referring to ethics committee because this is the language used by the ICH-GCP. There is no difference between an ethics committee and an IRB.

which does not necessarily ensure effective protection of human subjects. Subsequently, even where the guideline does set out valuable rules, for example the rules relating to disclosure of information, because of the amount and nature of the information disclosed, it lands up placing an unduly heavy burden on ethics committees. By then focusing on the issue of how clinical trials are designed, it further becomes clear that if ethics review is to achieve its goal of protecting human subjects, ethics committee members need to be able to identify and focus their attention on information that is relevant to the issue of subject protection and to do this they need to be able to understand the impact certain aspects of trial design have on human subjects in general and the local population in particular.

While these arguments clearly have a direct impact in the Malaysian context, it is worthwhile to note the growing influence of the ICH-GCP process in other jurisdictions such as the UK as well as with the American FDA. Research Ethics Committees (RECs) reviewing clinical drug trials in the UK operate under very similar standards as the Medicines for Human Use (Clinical Trials) Regulations 2004³²³ incorporate the principles of “the GCP Directive”,³²⁴ which correspond in broad terms to the ICH-GCP principles. In America, the FDA currently recognises the ICH-GCP guideline as a guidance document³²⁵ and more significantly, it is also proposing to revise its regulations of foreign clinical studies under 21 CFR 312.120. Under this revision, the requirement to conduct studies in accordance with principles stated in the Declaration of Helsinki will be replaced by a requirement that the

³²³ *The Medicines for Human Use (Clinical Trials) Regulations 2004 (as Amended by S.I 2006/1928 & 2984).*

³²⁴ The directive mentioned therein is the Commission Directive 2005/28/EC, which according to the title is “laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.”

³²⁵ A guidance document represents the Agency’s current thinking on a particular subject. For more information, see

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformation/SheetsandNotices/default.htm> (accessed August 17, 2010).

studies be conducted in accordance with GCP, including review and approval by an independent ethics committee.³²⁶ Given the increasing influence of GCP principles in the context of clinical trials, it is surprising to note that there is no literature on how this might impact on the ethics review process and the protection of human subjects.

Thus it becomes imperative to analyse whether the ICH-GCP principles adequately protect subjects in clinical trials and if not, what the alternatives might be.

Ethics committees' roles and responsibilities and ICH-GCP

Safeguarding rights safety and well-being of all trial subjects – substantive duties

The first and overarching responsibility of an IRBw as recognised by the guideline is to safeguard the rights, safety, and well-being of all trial subjects while paying special attention to trials that may include vulnerable subjects.³²⁷ The IRB responsibility as contained in the guideline is twofold. First, to safeguard the rights, safety and well-being of all subjects; and second, to pay special attention to vulnerable subjects. Both these aspects involve what can be described as substantive duties as opposed to administrative duties. The ICH-GCP in general, imposes two types of duties on IRBs, which can be described as being administrative and substantive. Administrative duties are those that relate to tasks that are more or less clerical in nature and do not require any exercise of discretion or judgment. For example, where the committee is charged with obtaining certain documents and providing review within a stipulated time.³²⁸ Substantive duties on the other hand, require that the IRB perform certain tasks or secure

³²⁶ Food and Drug Administration, DHSS, Docket No 2004N-0018, Federal Register Vol 69, No 112, June 10 2004.

³²⁷ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1).", Guideline 3.1.1

³²⁸ Ibid. Guideline 3.1.2

certain outcomes, which will require some exercise of discretion or judgment. In this case, the IRB is assigned the responsibility to ensure an outcome: that is safeguarding the rights, safety and well-being of subjects, and is further tasked to pay special attention to vulnerable subjects with presumably the same outcome in mind.

Lack of clear guidance in relation to substantive duties

It is undoubtedly true that the *raison d'être* of ethics review of clinical research is to safeguard the interests of human subjects, but, if the guideline is to act as an effective framework for ethics review, it must also provide IRBs with the tools to enable them to achieve this outcome. This then raises two questions: first, what sort of guidance should be provided to IRBs and second, is this guidance provided in the ICH-GCP document? In order to answer these questions, it is necessary to return to the concept of a substantive duty. A substantive duty, by definition, is made up of two aspects: first, what can be termed an “outcome” aspect, in that it requires that a certain outcome be achieved, in this case, the safeguarding of certain rights and interests of human subjects; and second, what can be called a “process” aspect, which refers to the process by which the outcome is achieved. A consideration of process aspects would involve asking questions about the types of properties or features of a system that need to be put into place in order to achieve the desired outcome. Therefore, for an IRB to successfully fulfil its responsibility as set out by the ICH-GCP, it must be given sufficient guidance regarding both the outcome and process aspects of its responsibility.

Outcome aspect

As mentioned earlier,³²⁹ the desired outcome or outcome aspect of ethics review is that the rights, safety and well-being of subjects are protected. If an IRB is to achieve this outcome, it surely must have a clear conception of what it means to safeguard the rights, safety and well-being of subjects. It will be difficult if not impossible for an IRB to arrive at this desired outcome of protecting these elements if it is not provided at the outset with a comprehensible notion of the content of each element. If an IRB is to safeguard the stated interests of a subject, it needs to know what rights a subject has and whether they are absolute or relative, what levels of safety a subject should be provided with and what is meant by the well-being of a subject. There is no specific detailed explanation of any of these matters in the guideline.

Moreover, in cases involving vulnerable subjects, IRBs are tasked with paying special attention. Vulnerable subjects³³⁰ under this guideline include individuals who may be unduly influenced by benefits or fear of reprisals from senior members of a hierarchy; as well as “patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent.”³³¹ There is no further mention of vulnerable subjects in the document apart from its definition and the fact that trials involving these populations should be given special attention. Having set out this requirement, the guideline stops short of providing an IRB with any assistance about what “paying special attention” should mean. The very fact that the guideline charges an

³²⁹ See Chapter One, section 1.1.2

³³⁰ For a discussion of the concept of vulnerability see Chapter 1, section 1.2.1

³³¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 1.61

IRB to pay special attention in such cases must mean that there are different or extra considerations that need to be taken into account in determining the scope of the rights, safety and welfare of incompetent subjects. The guideline simply fails to provide IRBs with a clear idea of what they need to achieve in order to protect human subjects in general and vulnerable subjects in particular.

In contrast to this, the American Common Rule sets out much clearer guidance regarding what an IRB needs to achieve. Under the CFR 46.111, an IRB must make a determination that it is satisfied that all the requirements provided for in the section have been met before it approves any research.³³² These include providing: for the minimisation of risks to subjects by ensuring that procedures are consistent with sound research design, that risks to subjects are reasonable in relation to anticipated benefits, the equitable selection of subjects, appropriately documented and obtained informed consent, and the protection of subjects' confidentiality. In addition to this, the Common Rule spells out in detail what extra criteria IRBs are required to take into account when reviewing research trials involving certain vulnerable populations such as pregnant women, human foetuses and neonates, children, and prisoners.³³³

Process-oriented aspects

In seeking to achieve the outcome of human subject protection, an IRB engages in a process of reviewing research protocols to decide whether or not certain trials should be allowed to carry on. What this might or should entail is still very much open to debate. To date, very little research has been carried out into this aspect of ethics review and most of the literature has focused on administrative matters: such as how

³³² 46 CFR 46.111

³³³ 46 CFR Subparts B, C and D

long it takes committees to make decisions,³³⁴ and the amount of time and money wasted on bureaucracy.³³⁵

It is submitted that there are two features, which are integral to the process of meaningful ethics review. First, conditions must exist that allow for meaningful discussions, which are accessible to all members of an IRB; and second, there must be a framework for rational decision-making. These features are closely interrelated: when IRB members engage in meaningful discussions, they will in all probability identify and consider the relevant principles and facts that will in turn, promote rational decision-making. Similarly, if IRB members are provided with an appropriate framework that sets out the relevant principles they should take into account when making their decisions, this will in turn, result in a more focused and meaningful discussion.

Both these features will require as a starting point, some sort of framework that sets out the principles and considerations that underlie the review process. The guideline does provide some guidance in this respect under Guideline 2 where there is a list of general principles that apply across the board to the conduct of clinical trials.³³⁶ The principles listed under this section deal with both issues of human subject protection as well as scientific merit. Significantly, eight³³⁷ out of the thirteen principles go to the issue of scientific merit and only four³³⁸ principles are directly concerned with human subject

³³⁴ Joanna Tully et al., "The New System of Review by Multicentre Research Ethics Committees: Prospective Study," *BMJ* 320, no. 7243 (2000).

³³⁵ Alysun M. Jones and Bryony Bamford, "The Other Face of Research Governance," *BMJ* 329, no. 7460 (2004)., Paul Glasziou and Iain Chalmers, "Ethics Review Roulette: What Can We Learn?," *BMJ* 328, no. 7432 (2004)., David Hunter, "Efficiency and the Proposed Reforms to the Nhs Research Ethics System," *J Med Ethics* 33, no. 11 (2007)., Hilary Hearnshaw, "Comparison of Requirements of Research Ethics Committees in 11 European Countries for a Non-Invasive Interventional Study," *BMJ* 328, no. 7432 (2004)., David S. Wald, "Bureaucracy of Ethics Applications," *BMJ* 329, no. 7460 (2004).

³³⁶ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 2

³³⁷ Ibid. Guidelines 2.4, 2.5, 2.7, 2.8, 2.10, 2.11, 2.12 and 2.13

³³⁸ Ibid. Guideline 2.1, 2.2, 2.3, and 2.9

protection. The principles provided in the guideline were most likely never intended to serve as a framework for IRB decision making as the title of the section itself suggests that these are simply principles of ICH GCP. The best option for basing a framework for IRB decision making is guideline 2.1, which states that clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirements.³³⁹ This however, is not without its problems. As discussed in chapter 3, the Declaration of Helsinki is plagued with conflicting principles and the open-texture of the language used exposes it to many different and possibly contradictory interpretations.

In addition to having a coherent and meaningful set of principles to guide the ethics review process, two other elements are vital to ensure that an IRB engages in rational decision-making. First, an IRB must be properly constituted and second, the committee must be provided with sufficient, relevant information. The issues of the composition of an IRB and the documents that must be submitted for review are covered in great detail in the guideline and discussed in greater depth in later parts of this chapter as well as in Chapter 5

As such, as in the case of the “outcome” aspect discussed above, the Guideline fails also in formulating a process that satisfactorily aids an IRB in achieving the outcome of subject protection in clinical trials.

Administrative duties

The guideline stipulates the composition, function and operation of ethics committees; the procedures it should follow; and matters relating to record keeping. The content of these sections is to all intents

³³⁹ Ibid. Guideline 2.1

and purposes, administrative in nature and is aimed at ensuring that the operations of a committee are well documented. It is worth pointing out that three³⁴⁰ out of the four sub-topics under the heading of Institutional Review Board/Independent Ethics Committee cover matters that relate to the administrative duties of an IRB. Moreover, even guideline 3.1 that deals with the responsibilities of the IRB has as many subsections prescribing administrative duties³⁴¹ as it has prescribing substantive duties.

This really goes to the heart of what the ICH process is all about. It is concerned with two things: first, ensuring that regardless of where drug development and manufacturing takes place, drugs are developed, tested, registered and monitored in a manner that ensures their quality and safety; and second, making the process of developing new drugs more efficient and less expensive. It does these things by prescribing harmonized standards for what are mostly scientific and quantitative processes, which mainly involve close observation and documentation. Apart from the ICH-GCP, all the other ICH guidelines prescribe standards for scientific and quantitative processes and it is therefore not surprising that the ICH-GCP is to a large extent made up of administrative duties.

Admittedly, these administrative processes lend themselves well in the scientific arena as a manner of demonstrating compliance to standards. Take for example the ICH Guideline on Structure and Content of Study Reports that sets out the standards for adverse event reporting.³⁴² Close monitoring of adverse events is a crucial part of ensuring the safety profile of drugs in clinical trials. Adverse events

³⁴⁰ Ibid. Guidelines 3.2-3.4

³⁴¹ See Ibid. Guidelines 3.1.2, 3.1.3, 3.1.4, 3.1.9

³⁴² International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Structure and Content of Clinical Study Reports E3." In *ICH Harmonised Tripartite Guideline*, 1995. at para 12.2, Study reports must document all adverse events in a brief narrative supported by more detailed tabulations and analyses.

during the course of a trial may indicate that a certain drug is generally unsafe or unsafe when used in certain populations. To ensure that a drug is safe for use, information needs to be compiled regarding how many people have had bad reactions during the trial; the type of reactions; the severity of the events; the possible causal links between the reactions and the drugs; and so on. The accurate and careful compilation of relevant data is essential to any meaningful analysis. Moreover, when a trial is run across several countries in hundreds of institutions involving thousands of subjects, this can only be successfully achieved if there is detailed and accurate documentation of identical data. For this reason, standardization of documentation is key to ensuring the quality of the analysis and this is what the ICH process sets out to ensure.

The question is whether or not this same approach is appropriate in situations that involve non-science based activities such as the activity of ethics review? Ethics review is concerned with human subject protection, and as noted earlier imposes substantive duties on an IRB. The endpoint of a successful ethics review should be determined by whether or not the safety and well being of subjects have in fact been adequately protected. The fact that a committee is required to scrutinise an exhaustive series of documents is certainly important as it serves as evidence that its attention has been drawn to pieces of relevant information, but it surely cannot on its own, be evidence of the quality of the decision made based on the documents provided to it. Similarly, evaluating whether or not an ethics committee has performed its functions according to written standard operating procedures, and whether it has maintained written records of its activities and minutes of its meetings is valuable but only to the extent that it speaks to its good organisation rather than its success in protecting human subjects. While there is undoubtedly a great deal of value in these procedural requirements, they cannot and should not be

the last word on setting the standards of ethics review. The fact that the largest portion of the guideline concerns itself with administrative duties rather than giving flesh to the bare bones of the few substantive duties set out, renders it much less valuable as a tool for protecting human subjects.

This then raises the question as to what is needed to give flesh to the bare bones of the substantive duties set out in the guideline? Undeniably, ethics review in the “real” sense does not lend itself easily to accurate measurement. There are a series of questions that might be considered. How does one measure whether or not human subjects are protected? Should we ask subjects or physicians? How do we know that ethics committees have taken the right principles into account? Are there any right principles to begin with, or should these committees be free to come up with their own principles, or choose from a list of pre-approved declarations and guidelines? How do we ensure that these committees are free from the types of conflicts of interest that bedevil investigators, institutions and the pharmaceutical industry? This would involve asking questions such as what principles should guide decision-making, particularly in cases involving vulnerable populations such as mentally incompetent patients and whether or not ethics committees are taking such principles into account and if they are not, why?

In answering these questions, and in seeking to enable IRBs to perform their substantive duties satisfactorily, it is necessary to return to the origins of ethics review and the concerns that needed to be met at that time; and place them against the current setting of clinical trials. In so doing, three broad themes emerge. First, the importance of the notion of independence. Second, the essential need for a coherent and inclusive set of general principles that underlie the decision-making framework and third, the need for institutional structures that allow

for high-quality review. These themes go far beyond the guidelines found in the ICH-GCP and bring to sharp focus the shortcomings of a system that has chosen to rely on this document to shape the manner in which ethics review of clinical trials is conducted.

Having said this, it is important to recognise that some aspects of the ICH-GCP have the potential to play a very important part in ensuring effective ethics review. This is particularly true in relation to the rules relating to documents that must be provided to ethics committees.

Rules relating to Disclosure of information

There is no doubt that the ethics review process as required by the ICH-GCP guideline provides an extra level of detailed scrutiny of research trials. Investigators are required to submit a number of documents³⁴³ relating to the clinical trial for ethics review including: the trial protocol, written informed consent forms, subject recruitment procedures, written information to be provided to subjects, Investigator's Brochure,³⁴⁴ available safety information, information about payments and compensation available to subjects and the investigator's current curriculum vitae.

A typical research application submitted to an ethics committee easily runs into several hundred pages, as very detailed disclosure is required by the guideline. For instance, the trial protocol alone should include at the minimum, the following topics³⁴⁵: general information regarding the title of the trial, names and addresses of the sponsors, medical experts, investigators, clinical laboratories and institutions involved in the trial; background information of the investigational product,

³⁴³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 3.1.2

³⁴⁴ The Investigator's Brochure is a compilation of the clinical and non-clinical data on the investigational product which is relevant to the study of the product in human subjects, Ibid. Guideline 1.36

³⁴⁵ Ibid. Guideline 6

including summaries of findings from relevant non clinical studies and known potential risks and benefits; reference to relevant literature and data; a detailed description of the objectives and purposes of the trial; the trial design in detail, which would include specific statements of endpoints, whether it is randomised, placebo-controlled, double-blinded, the dosage regiment, duration of the trial, stopping procedures and accountability procedures; the selection and withdrawal criteria of subjects; the treatment provided to subjects; assessments of efficacy and safety of the trial; statistical methods to be employed; IRB access to source data and documents; quality control and assurance; ethics considerations; data handling and record keeping; financing and insurance and publication policy.

The fact that investigators are required to submit for ethics review such an exhaustive amount of data for every trial that they hope to run has both positive and negative aspects. On the positive side, sponsors and investigators are compelled to articulate in detail almost every aspect of the research trial. This is in stark contrast to the practice in the immediate post-World War II period where investigators were, for all intents and purposes, left to decide whether or not to submit their research trials to any sort of peer review and if so, how much information they chose to divulge. The autonomy they enjoyed was only limited by their individual consciences and the manner in which this discretion was frequently abused eventually became the focus of several exposes,³⁴⁶ demonstrating the dangers of leaving investigators to their own devices. The ICH-GCP guideline in requiring not just cursory but comprehensive disclosures of the different aspects of a clinical trial makes it very difficult for an investigator to hold back any information, which in turn, allows for a more effective ethics review process.

³⁴⁶ Beecher, "Ethics and Clinical Research.", M H Pappworth, *Human Guinea Pigs: Experimentation on Man* (Harmondsworth: Pelican Books, 1969).

In addition to this, the very fact that investigators and sponsors have to spell out each aspect of the trial so specifically, lends to a much more thoughtful and careful planning and development process. Clinical trial design and development has evolved into a complex activity. Teams of people are often involved in writing protocols with input from many different parties. The development process involves collaboration among study statisticians, scientists, clinical investigators, editors, protocol co-ordinators and managers.³⁴⁷ When protocol development teams sit down to design a trial and write a protocol, they do so with a clear picture of the issues they will need to address and clearly describe. In addition to detailing the scientific aspects of the trial, they will also have to draw up patient information sheets, describing the nature of the trial in lay terms, together with descriptions of the potential risks and benefits of the trial. This would mean that by the time the research protocol is presented for ethics review, a great deal of work will have already been put in to ensure that the trial will pass ethics review.

There are two potentially negative aspects of requiring such detailed disclosure. First, ethics committee members are required to look through a voluminous amount of material as a single application for ethics review usually runs into hundreds of pages. A typical ethics committee meets once a month and at each meeting peruses approximately between eighteen to twenty research protocols. As a conservative estimate, if each protocol runs into 150 pages and there are eighteen protocols submitted each month, ethics committee members will need to read through on average, 2,700 pages every

³⁴⁷ An example of this is the American Clinical Trials Co-operative Group Program, which is sponsored by the National Cancer Institute. It works with the Institute to identify important questions in cancer research and to design clinical trials. This programme involves more than 1,700 institutions and thousands of investigators. For more information see <http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group> (date accessed 22 May 2008)

month. Most committee members are employed on a full time basis and serve on ethics committees as volunteers, and as such will be hard pressed to find the time and energy to carefully scrutinise thousands of pages of information.

In addition to this, because the guideline requires not just detailed disclosure of information, but detailed disclosure of information across a wide range of topics; ethics committee members land up struggling with not only just reading through thousands of pages, but also with trying to understand the different types of information provided in the protocols. For example, a standard protocol would include among other things: scientific information relating to the characteristics of the product being studied; the treatment regime involved, which would include the route of administration, dosage and treatment period; details of the statistical analysis employed; information about data collection, handling and record keeping; details of the trial design; an informed consent sheet; information to be provided to patients about the trial procedure, risks and benefits; and pharmacovigilance³⁴⁸ measures. The language used in most of these topics will be highly technical and often, inaccessible to the lay reader. A clinician might find it easy to understand and assess the treatment regime proposed and the type of disorder being studied, he might not however, find it so easy to understand the details of the characteristics of a new product that is being proposed for study. A pharmacologist on the other hand, may find that he has the opposite problem, and both of them might have trouble understanding the type of statistical analysis that is being proposed.

So, ethics committees are likely to struggle with both the volume and content of the material submitted for review. The logical solution to the

³⁴⁸ This is a branch of pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects of medicines.

latter problem is to have a committee that is made up of a sufficiently broad range of experts who will be able to assess effectively the different types of information provided in a trial protocol. This is provided for in the guideline, which states, “The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects and ethics of the proposed trial.”³⁴⁹ The guideline does not specify what sorts of qualifications ethics committee members should have apart from requiring that at least one member’s primary interest must lie in a non-scientific area,³⁵⁰ and that one other member must be independent of the institution or trial site.³⁵¹ In practice, both academic ethics committees as well as the MREC are made up of clinicians, scientists and lay representatives. Members of the ethics committee at University A, and the MREC are primarily appointed by virtue of the positions they hold in their respective institutions. At University A, the ethics committee is comprised of:

- Chairman – The Dean of the Faculty of Medicine or named representative, in this case, a senior Professor of the Faculty of Medicine,
- Hospital Director or representative,
- Head of the Department of Medicine or named representative, Faculty of Medicine,
- Head, Department of Psychological Medicine or named representative, Faculty of Medicine,
- Head, Department of Surgery or named representative, Faculty of Medicine,
- Dean, Faculty of Law, or named representative

³⁴⁹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 3.2.1

³⁵⁰ Ibid. Guideline 3.2.1 (b)

³⁵¹ Ibid. Guideline 3.2.1 (c)

- Head, Department of Pharmacy/Pharmacology, Faculty of Medicine, or named representative, on rotation through a two-yearly term
- Head, Pharmacy Unit, or named representative and
- 2 public representatives

The composition of the MREC is as follows:

- Deputy Director-General of Health (Research & Technical Support) – permanent chairman
- Director of the Institute for Medical Research
- Director of the Institute of Public Health
- Director of the Network of Clinical Research Centres
- Two Public Health Medical Specialists
- Two Clinical Medicine Specialists
- Three Medical Research Specialists
- Three Senior Research Officers
- One Senior Pharmacist
- One Nurse
- One Medical Laboratory Technologist
- One Lay Person
- One Representative from the Academy of Medicine

Theoretically these committees, which are made up of clinical physicians, scientists, lay representatives, and legally trained representatives are well placed to evaluate the different aspects of trial protocols. In fact, this would also appear to solve the problem of the high volume of material that is submitted for review. If physicians are confident that their scientist counterparts are carefully reviewing the scientific aspects of protocols and vice versa; and if lay members are confident that the scientists and physicians are reading through the medical and scientific descriptions carefully, they might be satisfied with merely looking through the informed consent sheets and patient

information sheets. The latter certainly appears to be the case as one lay member commented that

‘We basically focus on the objective and then the procedure and the patient consent form. So we think the rest of it is okay.’³⁵²

Another member from the MREC³⁵³ said that

‘Some of them who are not well versed in the clinical part of it will look at the informed consent part for instance, and try to see from a layman’s point of view or from a non doctor’s point of view, whether what information which is given, whether it was enough or appropriate. Those who are doctors tend to ask a bit more questions about the clinical part of the trial.’

It is submitted that if this is true, then ethics committee members are not paying enough attention to aspects that they think are beyond their expertise or understanding but that are integral to meaningful ethics review, and by conducting separate, disjointed reviews of different aspects of the protocols and by seemingly relying on each other to function in a uncoordinated manner, they are placing all human subjects at risk and especially incompetent adult patients.

The following section will demonstrate how this can occur in relation to the issue of how trials are designed. It might be maintained that an evaluation of the way a trial is designed, is more a matter of scientific review rather than ethics review. It will be argued that this is not necessarily the case and where trials are sponsored by the industry, the issue of trial design becomes very much a concern for ethics committees, and that what at first appears to simply be a question of science, turns into an ethical dilemma with rather surprising paradoxical consequences. The fact is that the problem of having to review large amounts of information, most of which is highly technical, cannot be solved by apportioning review of different aspects of trial protocols to committee members who have special qualifications. Because the ICH-GCP guideline throws such a voluminous amount of

³⁵² Interview with Committee Member B, Institution A, 21 December 2007.

³⁵³ Interview with Ethics Committee Member A, MREC, 25 November 2008

information in the way of ethics committees it is not easy for committee members to know which aspects of a protocol require their combined attention and review and the solution must go further than the appointment of a variety of experts. Among other thing, ethics committees need to be provided with sufficient and appropriate training that will allow them to engage in meaningful ethics review.

Industry-sponsored trials and trial design

The majority of trials run in Malaysia are industry-sponsored trials. These trials are usually carried out to prove that the experimental therapy, which is usually a drug or compound manufactured by the sponsor, is superior to existing treatment modalities. Numerous studies have indicated that industry-sponsored trials are far more likely to report in favour of experimental therapy compared to publicly funded research.³⁵⁴ Significantly, this apparent bias has not been attributed to defects in the scientific quality of the research as some authors have even suggested that the design of industry sponsored trials are of a higher quality as compared to publicly funded research.³⁵⁵ Among the various reasons³⁵⁶ forwarded to explain these favourable results is that research trials supported by the industry

³⁵⁴ See Sameer S. Chopra, "Industry Funding of Clinical Trials: Benefit or Bias?," *JAMA* 290, no. 1 (2003)., Benjamin Djulbegovic et al., "The Uncertainty Principle and Industry-Sponsored Research," *The Lancet* 356, no. 9230 (2000)., Richard Davidson, "Source of Funding and Outcome of Clinical Trials," *Journal of General Internal Medicine* 1, no. 3 (1986)., Roy H. Perlis et al., "Industry Sponsorship and Financial Conflict of Interest in the Reporting of Clinical Trials in Psychiatry," *Am J Psychiatry* 162, no. 10 (2005)., Mildred K. Cho and Lisa A. Bero, "The Quality of Drug Studies Published in Symposium Proceedings," *Ann Intern Med* 124, no. 5 (1996)., R.M. Procyshyn et al., "Prevalence and Outcomes of Pharmaceutical Industry-Sponsored Clinical Trials Involving Clozapine, Risperidone, or Olanzapine," *Can J Psychiatry* 49, no. 9 (2004).

³⁵⁵ Julio S. G. Montaner, Michael V. O'Shaughnessy, and Martin T. Schechter, "Industry-Sponsored Clinical Research: A Double-Edged Sword," *The Lancet* 358, no. 9296 (2001). citing Davidson, "Source of Funding and Outcome of Clinical Trials." and K. I. Kaitin, N. R. Bryant, and L. Lasagna, "The Role of the Research-Based Pharmaceutical Industry in Medical Progress in the United States," *J Clin Pharmacol* 33, no. 5 (1993).. See also Procyshyn et al., "Prevalence and Outcomes of Pharmaceutical Industry-Sponsored Clinical Trials Involving Clozapine, Risperidone, or Olanzapine."

³⁵⁶ Other reasons include, drug companies beings less willing to sponsor studies in the absence of evidence of effectiveness of a compound, delays in publishing negative findings, inappropriate use of statistical analysis or misleading presentation of data. See Chopra, "Industry Funding of Clinical Trials: Benefit or Bias?," Djulbegovic et al., "The Uncertainty Principle and Industry-Sponsored Research." and Montaner, O'Shaughnessy, and Schechter, "Industry-Sponsored Clinical Research: A Double-Edged Sword."

may be subject to methodological bias. This is to say that the study question or the design of the trial may be structured in a way that might affect the outcome of the research. For example, clinical trials might use inappropriate controls such as inferior comparative therapies or placebos. A study looking at trials of non-steroidal anti-inflammatory drugs in the treatment of arthritis, found that almost half of industry-sponsored trials used dosing which favoured the experimental drug.³⁵⁷ Enrolling relatively healthy patients into a trial and extrapolating these results to the broader spectrum of patients may be another way in which the design of the study might inject bias into the results. For instance, a trial looking at the effectiveness of a treatment for schizophrenia might only allow the enrolment of patients with a very mild form of the disease and exclude patients with more moderate or severe forms of the disease, or patients presenting with co-morbidities. Assuming that schizophrenic patients typically suffer from moderate forms of the disease or suffer from co-morbidities, the favourable results of such a trial may not translate into an effective treatment regime for the broader group of schizophrenic patients. This then raises the question as to whether such a trial is ethically sound? If the trial drug cannot be safely or effectively administered to the general patient population, the time and money spent, and more importantly, the risks borne by trial subjects cannot be justified. Having regard to the fact that virtually all trials run in the country are industry-sponsored, it is essential that all protocols be carefully reviewed to minimise the risk of methodological bias.

Scientific validity vs. scientific value

As pointed out earlier, the question of trial design would appear to be more a question of scientific merit rather than one that raises ethical concerns. This in turn raises the issue as to the proper remit of ethics

³⁵⁷ P. A. Rochon et al., "A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis," *Arch Intern Med* 154, no. 2 (1994).

review and the appropriateness of using the vehicle of ethics review to gauge the scientific merits of a protocol. The Malaysian Guidelines for Applications to Conduct Drug Related Trials³⁵⁸ requires both ethics as well as scientific review of every application. Each academic institution in the country has a scientific review process in place that is separate from its ethics review and the Research Review Committee of the Ministry of Health reviews the scientific merit of trials run in government hospitals. With these mechanisms for reviewing scientific merit in place, it may well be argued that ethics committees should eschew documents relating to the science of the trial and focus on patient information sheets, informed consent forms, and information about payments and compensation available to subjects. Focusing on these documents would also mean that ethics committee members would be able to spend more time examining these aspects in greater detail resulting in better ethical review.

On the other hand, it is well established that if research on human subjects is to be ethical, it must have scientific merit.³⁵⁹ However, there has been little discussion of what is required of ethical review in this context, and given that research protocols are subject to prior scientific review, ethics review of scientific merit seems superfluous. Freedman³⁶⁰ in his illuminating explication of scientific merit in research ethics makes sense of this apparent dilemma. He distinguishes between what he calls readings of “validity” and “value” and asks whether the ethical review of research should examine scientific validity or value.

³⁵⁸ *Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia 2000.*

³⁵⁹ Guideline 1 Council for International Organizations of Medical Sciences, "International Ethical Guidelines for Biomedical Research Involving Human Subjects.", Para 11 World Medical Association, "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects."

³⁶⁰ Benjamin Freedman, "Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication," *IRB: Ethics and Human Research* 9, no. 6 (1987).

Validity is simply concerned about whether the “study is designed to yield reliable information, according to accepted principles of research practice, concerning the hypothesis being tested”³⁶¹ and therefore only involves judgments of intrinsic elements,³⁶² and as such requires expertise in the form of members with knowledge of research design, statistics, and clinical and bench sciences. Value, on the other hand, starts with an assumption of validity but proceeds to consider the significance of the hypothesis itself.³⁶³ Is the hypothesis useful or interesting? What is useful or interesting may depend on a variety of factors including clinical or social implications and might even require a trade-off with other elements of ethical research, such as the quality of consent.³⁶⁴ Interdisciplinary expertise is thus required in making judgments of scientific value.

A trial that might be scientifically valid may not be scientifically valuable. The previous example of a clinical trial involving schizophrenia treatment is a case in point. The trial protocol might be scientifically valid in that it would provide information to support a hypothesis that drug A is superior to a placebo for treating schizophrenia by enrolling patients with mild schizophrenia and who have no other pre-existing conditions into a double-blinded, randomised trial. If this cohort of subjects does not represent the general population of schizophrenic patients, the protocol may not be scientifically valuable in that the hypothesis will have hardly any practical clinical significance. The time and money spent, and risks incurred by subjects might not be warranted, given its limited practical applicability.

³⁶¹ Ibid. at 7

³⁶² Freedman contends that proposals contain two elements, those that are intrinsic and those that are presumptive. The absence of an intrinsic element is fatal to a proposal, whereas the absence of a presumptive element will, as a matter of judgment, make it less likely that a proposal will succeed. Typical examples of presumptive elements include the experience and track record of the investigator. Ibid. at 9

³⁶³ Ibid. at 9

³⁶⁴ Ibid. at 9

Having established that the assessments of validity and value involve different types of judgments, that validity is a necessary and discrete condition of value, and that assessments of value need to be made in the context of the other elements of the research; Freedman convincingly argues that a prior technical adjudication of scientific merit should only encompass judgments of validity as scientific review committees are not made up of a broad enough range of expertise to adjudicate on issues of scientific value, leaving this determination in the hands of ethics review committees.

Trial design and scientific value

Accepting this argument that scientific review is rightly concerned with judging scientific validity and that judgments of scientific value are best left to ethics review; it is contended that the role played by ethics review of scientific value in clinical trials is in fact a critical one. Hence, what at the outset would appear to be an area requiring a scientific evaluation by either a scientific review board or by members of an ethics review board that are scientifically trained / qualified, is in fact an area requiring a non-scientific review, i.e. an ethics review by the combined members of the IRB (including in particular the lay persons or ethics experts, i.e. the non-scientifically trained members). This will ensure that the trial is of scientific value as well as being scientifically valid.

This proposition is clearly demonstrated upon an examination of clinical trials that potentially involve mentally incompetent adults. Trials (e.g. clinical trials of psychiatric drugs / therapy) that meet the highest standards of scientific validity are likely to adversely affect the interests of mentally incompetent adult patients (and hence lack scientific value) for two reasons. The first reason is based on the fact that a successful trial is one that generates statistically significant

findings, and this in turn is dependent on large numbers of subjects completing the trial. If mentally incompetent patients are considered unreliable and unlikely to complete, or if there are problems associated with enrolling this cohort, they risk being excluded from the trial altogether and the following section discusses how in the Malaysian context in particular, this exclusion of mentally incompetent subjects might not be a good thing. Second, the most scientifically reliable results are those obtained from clinical trials that are able to minimise any bias, and the best way to minimise bias in a clinical drug trial is to run a randomised, double-blinded, placebo-controlled trial; preferably with a washout period, if subjects are on any medication for the condition that is being studied. This type of clinical trial, i.e. randomised controlled trials (RCT), which are considered the most scientifically reliable, and hence valid, have the downside of potentially adversely affecting mentally incompetent adults where such subjects are included in the trials, and hence, carries the danger of lacking scientific value. The last section of this chapter will demonstrate the manner in which RCTs potentially expose mentally incompetent adults which are included in such trials to unacceptable levels of risk. In addition to this, the greater problem identified in the Malaysian context is that although mentally incompetent patients are as a rule excluded from trials as described earlier; because of the lack of consistent and clear standards for determining capacity, there is a very real danger that they be inappropriately admitted into such trials without the benefit of any extra safeguards.

Trial Design - Subject selection criteria and exclusion from trials

In the Malaysian context, incompetent³⁶⁵ adults suffering from psychiatric disorders are not enrolled into industry-sponsored clinical trials and in fact, competency is as a rule, listed as an inclusion

³⁶⁵ The criteria for determining competency itself raise a number of concerns that are dealt with in Chapter 3. The following discussion assumes that such determinations are appropriately made.

criterion. So at the outset, the design of the trial excludes the participation of mentally incompetent adult patients. One of the reasons cited for excluding incompetent adults from psychiatric trials is the great difficulty in ensuring compliance with treatment plans. Incompetent patients by definition suffer from cognitive defects and are unlikely to be able to understand the complex treatment regimes required of them or the need for a greater number of follow-up sessions with investigators. In the absence of caregiver or institutional support, these patients are unlikely to be able to adhere to the strict regimens prescribed by the protocols.

Another reason provided is that sponsors are unwilling to proceed without informed consent. Sponsors are said to be

‘very, very keen and cautious about consent and everything must be written by the patient....must be the patient’s own handwriting and they are very, very strict about that.’³⁶⁶

This is rather surprising as the ICH-GCP guideline clearly envisages proxy-decision making and makes provision for this by way of recognising legally acceptable representatives.³⁶⁷ Moreover, if industry players adopt the attitude of being unwilling to accept anything short of informed consent, this will result in a smaller pool of potential subjects, which in turn, will weaken the statistical significance of the results. On the other hand, it is undoubtedly true that validly obtained informed consent is ethically preferable to proxy consent. Ethically, informed consent, is one, if not the most important tool in securing the respect of human dignity of a competent adult, by allowing an individual to give voice to the subjective value he places on his life³⁶⁸ Proxy consent is by far a much weaker and more ethically suspect

³⁶⁶ Interview with Psychiatrist/Investigator A, practicing at University A, 30 June 2008

³⁶⁷ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 1.37

³⁶⁸ For a discussion of the idea of respecting human dignity which is made of up subjective and intrinsic values, see Chapter 3

device³⁶⁹ and raises many questions such as who should decide, what standards should apply and what factors should be taken into account? Also, given the greater potential liabilities associated with proxy consent,³⁷⁰ this stance may be partially attributable to the risk adverse nature of commercial entities. However, it does not explain why trials run in other jurisdictions such as the United Kingdom and United States are not routinely subject to such strict restrictions.

A more likely explanation is that in Malaysia it is difficult if not impossible, to ascertain who might be considered a legally acceptable representative as defined by the ICH-GCP. The guideline defines a legally acceptable representative as “an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial.”³⁷¹ Until the Mental Health Act³⁷² comes into force, there is no law in Malaysia that authorises a proxy to make health care decisions for an incompetent adult patient. In the event that a Malaysian court is called on to determine a case involving the treatment of an incompetent adult, it will most likely rely on the English decision in *Re F*³⁷³ where the court recognised that in such cases, treatment proceeded without any consent but did not invite any legal liability as reliance was placed on the defence of necessity, requiring that the doctor should act in the best interests of the patient. If this is the case, there is currently no legal basis for authorising proxies to make health care decisions on behalf of mentally incompetent adults. Given the uncertainty regarding the legality of proxy decision makers in Malaysia, it is not surprising that sponsors are unwilling to accept any

³⁶⁹ Some of the concerns raised by proxy consent are discussed further in Chapter 4

³⁷⁰ Questions may be raised regarding the appropriateness of an appointed proxy; standard limitation periods for tortious liability do not apply when the claimant is considered of unsound mind.

³⁷¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 1.37

³⁷² *Mental Health Act 2001 (Act 615), Malaysia.*

³⁷³ *Re F (Mental patient: sterilisation)* [1990] 2 AC 1

form of proxy consent, which for all intents and purposes has resulted in a blanket exclusion of this population from participation in clinical trials.

Significantly, the exclusion of mentally incompetent patients is achieved in this context by relying on subject selection criteria, that is by either making incompetency an exclusion criterion or alternatively, competency, an inclusion criterion. Inclusion and exclusion criteria are important features of a trial design and if properly drawn up, help to produce reliable results. These criteria are typically based on factors such as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.³⁷⁴ If the main purpose of subject selection is to enhance the dependability of the results, there must be some correlation between the criterion stated and its likely effect on the data produced. It would also mean that subject selection goes to the question of scientific validity and would therefore be more appropriately considered during scientific review. However, in the case of psychiatric trials in Malaysia, the exclusion of mentally incompetent patients seems to be based on two factors unrelated to the question of scientific validity. First, a broad and general assumption that incompetent subjects will be unable to comply with the requirements of the protocol, and second, a cautious approach to what appears to be the uncertain legal authority of proxy decision-makers. Neither of these reasons have any direct association to the question of the reliability nor quality of the trial results. They do however seem to go to the issue of scientific value, which falls under the remit of ethics review. The larger social implications of designing trials that exclude mentally incompetent adults as whole are not insignificant and require the close consideration of ethics committees.

³⁷⁴ See US. National Institutes of Health write-up on Understanding Clinical Trials at <http://clinicaltrials.gov/ct2/info/understand> (accessed 20 May 2008)

Exclusion of mentally incompetent adults

While on the topic of exclusion from industry-sponsored clinical trials of incompetent adults in the Malaysian context, it is useful to digress briefly to examine the general issue of exclusion of mentally incompetent adults. The exclusion of certain populations from clinical trials has been the cause of some concern in the recent past. Rothman³⁷⁵ suggests that while the flurry of regulations changed the face of clinical research and that the horrors described by Beecher could not now occur, they have had the unintended effect of patients being denied access or fair opportunity to enter a protocol. “The nightmare image has shifted from an unscrupulous researcher taking advantage of a helpless inmate to a dying patient desperate to join a drug trial and have a chance at life.”³⁷⁶

This debate came to a head in America in the early 1990s. Up till then, American women of childbearing age were routinely excluded from clinical research because of concerns about risks to fetuses *in utero*. Investigators and sponsors were fearful of among other things, incurring large monetary losses in the event of lawsuits being brought against them. As a result of this, women were not only denied the opportunity to receive new and innovative drugs, but there was also a lack of adequate information regarding the metabolism of drugs in women of child-bearing age. Similar arguments were raised in relation to minority groups who claimed that they were being unfairly excluded from participating in clinical research.³⁷⁷

³⁷⁵ Rothman, *Strangers at the Bedside : A History of How Law and Bioethics Transformed Medical Decision Making*. at 251-252

³⁷⁶ Ibid. at 252. The view that research participation is something that is generally beneficial and should be sought after is rejected by Menikoff in his book Jerry Menikoff and Edward P. Richards, *What the Doctor Didn't Say : The Hidden Truth About Medical Research* (New York ; Oxford: Oxford University Press, 2006).

³⁷⁷ In 1993, then President of the United States, Bill Clinton, signed the NIH Revitalization Act, which directed the NIH to establish guidelines for inclusion of women and minority groups in clinical research. It mandated the inclusion of minorities and women in clinical research unless “clear and compelling rationale and justification establishes ... that inclusion is inappropriate with

These same arguments are also easily applied in the Malaysian context. Blanket exclusions of mentally incompetent adults will deprive them of new and innovative treatment. Also, as pointed out by a psychiatrist at one of the larger psychiatric research facilities in the country, patients that he would deem incompetent are more often than not, those suffering from the severest forms of the disease. If these severely ill patients are denied access to trials, there will be a paucity of reliable data about the effectiveness and side-effects of the trial drug on this group of patients.

This matter of excluding specific populations and denying them access to certain treatments takes on an added dimension in relation to trials run in developing countries. In developed countries, the debate revolves mainly around access to new and innovative life-saving treatments and while important, only affect a small proportion of clinical trials.³⁷⁸ But in countries such as Malaysia, a significant proportion of patients are unable to afford the high price of patented drugs and as such in many cases, exclusion from trial participation effectively means no treatment at all. This is especially true of the patients who attend the institutions that carry out the research. As pointed out earlier, clinical trials are only run in government hospitals and academic institutions, which as a general rule serve the less wealthy members of society. Despite the fact that Government-run institutions³⁷⁹ provide most medicines at highly subsidised rates or at no cost in some circumstances,³⁸⁰ this does not extend in many cases to

respect to the health of the subjects or the purpose of the research” and that the cost of inclusion is not a permissible consideration in determining whether inclusion is appropriate.

³⁷⁸ Menikoff and Richards, *What the Doctor Didn't Say : The Hidden Truth About Medical Research*. at 20

³⁷⁹ This is also true to a certain extent of the academic institutions.

³⁸⁰ For example, a patient may have to make a formal application to the Social Welfare Department and prove that he or she falls below the poverty line and is unable to cover any medical costs.

new³⁸¹ drugs. Additionally, a recent study³⁸² noted a low availability of medicines at government hospitals resulting in their patients having to purchase medicines from private pharmacies or dispensing clinics.³⁸³ Patients who have to purchase their medicines privately have to face the high costs of medicines in the country.³⁸⁴ For example, a popular anti-depressant, Fluoxetine, costs about 26 days' wages³⁸⁵ for one month's treatment.

Patients suffering from mental health problems are more likely than others to face these problems. Many of the effective treatments for psychiatric and neurological disorders are relatively new and most of the drugs are still very expensive. Added to this, patients who are not only just suffering from psychiatric or neurological disorders, but who are mentally incompetent as well, are even less likely to have the financial wherewithal to buy their own drugs, as most of them will probably be unemployed. The reality is that for a considerable number of mentally incompetent adult patients, their best chance of gaining access to any effective treatment will be by participating in clinical trials.³⁸⁶ It is important to recognise that the problem of patients in developing countries not having access to standard drugs is far more complex than is suggested here. Disputes about the use of placebo controls in trials where effective treatment for a disease exists, and post trial access to experimental therapy, also stem from the same root

³⁸¹ The word "new" refers to drugs that are registered for use by the Drug Control Authority and are protected by patents, as well as cutting-edge or innovative therapies that are only approved for clinical trials.

³⁸² Zaheer Ud Din Babar et al., "Evaluating Drug Prices, Availability, Affordability, and Price Components: Implications for Access to Drugs in Malaysia," *PLoS Medicine* 4, no. 3 (2007).

³⁸³ In Malaysia, in addition to pharmacists, doctors are also allowed to dispense medicines. Interestingly, this has regularly been a bone of contention between the two professions and the current tide is of opinion is moving towards restricting the dispensation of drugs to pharmacists.

³⁸⁴ See discussion on page about the high costs of medicines in Malaysia due to the "free market" system. Also see Babar et al., "Evaluating Drug Prices, Availability, Affordability, and Price Components: Implications for Access to Drugs in Malaysia."

³⁸⁵ The study calculated affordability using the daily wage of the lowest-paid unskilled government worker. *Ibid.*

³⁸⁶ There are a whole host of other ancillary problems that feed into this issue and I certainly don't mean to suggest that trial participation is a solution. In many ways, it raises as many problems as it seems to solve. However, the wider discussion of these issues is beyond the scope of this thesis.

problem, and this line of argument does not mean to suggest that ethics committees should always view participation as being in the best interests of patients or that the enrolment of patients into trials is the best solution. The discussion above is meant to draw attention to the practical realities on the ground, which ethics committees should both recognise and incorporate into their ethics discourse.

Trial Design – RCTs and mentally incompetent patients

Following from the previous argument that although scientifically valid, the design of a trial can be used to unfairly exclude mentally incompetent patients; scientifically valid trials that do land up enrolling mentally incompetent patients may also be ethically unsound. Therefore, when ethics committees review trials that might potentially enrol incompetent patients, they need to consider how the trial design might affect this population. This might seem like a rather surprising comment as the earlier discussion suggests that the current practice in Malaysia is to exclude mentally incompetent patients from participating in clinical research trials. However, there are two reasons why the issue of inclusion is also relevant. First, it is likely that once the Mental Health Act comes into force and there is a legislative basis for proxy consent, sponsors will no longer insist on excluding mentally incompetent adults. It is also interesting to note that it appears that ethics committee members are unaware of the general practice of excluding mentally incompetent patients, as all the ethics committee members who were interviewed, apart from a psychiatrist,³⁸⁷ accepted the fact that some of the protocols they reviewed would involve the participation of mentally incompetent adults. If ethics committees are working on this assumption, they should already be sensitive to the issues discussed below. The second and far more worrying reason is that given the problems with the

³⁸⁷ Interview with Psychiatrist/Investigator B, University A, 28 January 2008

assessment of capacity in Malaysia as discussed in Chapter 2, it is conceivable that some patients are being wrongly assessed as having the capacity to provide informed consent and are consequently being entered into clinical trials. If this is in fact happening, the subjects who are inappropriately deemed competent, will be assumed to have understood the information concerning the trial procedures, risks and benefits, and will not have had the benefit of any safeguard whatsoever – no relative or doctor required to act in their best interests. This makes scrutiny at the level of ethics committees that much more vital because the second level of safeguards that typically exist for mentally incompetent patients, i.e. proxy consent or doctors acting in the best interest of the subject, are absent. Also, it highlights the fact that ethics committees should pay close attention to methods of assessing capacity.

The type of clinical trial that is considered the gold standard in terms of scientific validity is the randomised placebo control trial (RCT). Ironically, the two key features that make RCTs scientifically important, randomisation and the use of placebo controls; are the very same features that render them ethically suspect. Randomisation and placebo controls are scientifically important because they enhance the quality of trial results, as they are highly effective methods of minimising bias. On the other hand, these concepts raise very real ethical problems. First, the concept of randomisation has been demonstrated to be incompatible with the ethical principle of acting in a patient's best interest. This argument, which is found in greater detail in chapter 5, provides one of the most compelling reasons why research should never be confused with therapy. Second, as described below, the use of placebo controls especially when effective treatments exist appears to violate the ethical principle of not harming patients.

There are two types of situations where placebo controls may be used. First where no current effective treatment exists for a condition and there is genuine uncertainty about the effectiveness of the experimental therapy. In such cases, the use of placebos is ethically justified as long as the concept of clinical equipoise is met. The concept of clinical equipoise³⁸⁸ was devised by Freedman who describes it as, "...a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial."³⁸⁹ Because the investigator does not know whether or not the treatment will help the patient at all and the only alternative is no treatment, having a placebo arm should not, theoretically place the patient in a riskier position just because he is enrolled in a trial.

The second type of situation, which is more ethically problematic, is where a placebo is used even though there is an existing effective treatment. The problem with using placebo controls when effective treatments exist, is that subjects who are randomised to the placebo arm are exposed to unacceptable levels of risk by being deprived of treatment. In an ordinary doctor-patient relationship, if a doctor knows that treatment A will relieve a patient of his symptoms, it is clearly unethical for him to offer his patient a placebo in place of treatment A. In fact, any doctor who does this is likely to face a negligence suit. In the context of research, there appear to be two broad conceptual frameworks³⁹⁰ that dominate the debate about whether or not these trials are ethically acceptable: one that sees the problem as being essentially a matter of weighing the risks and benefits of participation

³⁸⁸ This concept has been subject to a great deal of criticism from allegations that the standard is too easily met (Menikoff and Richards, *What the Doctor Didn't Say : The Hidden Truth About Medical Research.*) to allegations that true clinical equipoise is never possible because a trial drug has to demonstrate a certain level of effectiveness in the laboratory and in animal populations before it can be introduced to the human population, and therefore, there cannot be genuine uncertainty about its effectiveness as there will already be some evidence of this at the beginning of the trial.

³⁸⁹ B. Freedman, "Equipoise and the Ethics of Clinical Research," *N Engl J Med* 317, no. 3 (1987).

³⁹⁰ See Scott Kim, "Benefits and Burdens of Placebos in Psychiatric Research," *Psychopharmacology* 171, no. 1 (2003). at 13

and if the risks are acceptable, favour placebo trials; and the other that puts an ethical emphasis on the act on intentionally not providing a proven treatment, and are in general, not in favour of these types of trials. The current practice favours the former position and significantly, the Helsinki Declaration, which originally³⁹¹ prohibited placebo trials in the absence of clinical equipoise, retreated from this position in 2002 with the addition of note of clarification to paragraph 29, which allows for the use of placebos even when effective treatments exist if there are compelling and scientifically sound reasons to think the research is necessary to determine the efficacy or safety of a medical method, or where the medical method relates to a minor condition and the patients receiving placebos will not be subject to any additional risk or serious or irreversible harm.

The following discussion focuses on the use of RCTs when effective treatments exist in psychiatric research. This brings into sharp focus the complexities of ethics review in this area and the depth of understanding required of ethics committee members if they are to engage in meaningful discourses. Three accusations can be brought against the use of RCTs, the first two apply across the board to trials carried out in most jurisdictions and the last, specifically relates to the Malaysian context.³⁹² First, RCTs as noted above, are intrinsically ethically dubious because of their structure. Second, the current framework used by ethics committees to assess the risks and benefits of research, is inadequate. Finally, concerns regarding access to treatment and assessments of capacity in the Malaysian context exacerbate the first and second problems.

³⁹¹ Paragraph 29 World Medical Association, "Declaration of Helsinki: Ethical Principles Ofr Medical Research Involving Human Subjects."

³⁹² Having said this, it is more than likely that the concerns raised here would also apply to many other developing countries as well.

As mentioned earlier, current practice regarding the use of RCTs where effective treatments exist relies on weighing the risks and benefits of participation and allowing such trials to be conducted if risks are considered acceptable. This being the case, there are two questions that follow: what are acceptable levels of risk, and what does this have to do with ethics review of trials that might recruit mentally incompetent patients? As to acceptable levels of risk, the only guidance provided by the ICH-GCP regarding risk assessment is found in para 2.2, which states:³⁹³

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

The guideline merely suggests that as long as anticipated benefits justify the risk, a risk is deemed acceptable. Notably, benefits here are not only the benefits enjoyed by the subject, but also the benefits enjoyed by society as well. This is another instance where the guideline sets out a substantive duty, i.e. assessing risks and benefits of a trial, and fails to provide detailed guidance or a framework for assessment.

Para 2.2 fails to take into account the complexities of risk assessment. Take for example, a situation where a potentially deadly infectious disease, Flu A, has just been discovered. Out of all the people who receive the current antiviral therapy, AV1, only fifty percent are cured, while the rest die. Scientists have developed BV1, which they hope might be more effective than AV1 but are worried that the drug may cause blindness, as animal studies have indicated that this might be the case. They want to conduct a RCT using this drug and argue that because AV1 is more often than not ineffective, they are unsure if it

³⁹³ Para 2.2 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

has any therapeutic value and they need to run a placebo control trial to ensure that BV1 is actually effective. Although subjects risk blindness on the BV1 arm or death on the placebo arm, this is justified because the anticipated benefits to society are much greater owing to the fact that a great number of people will benefit from an effective cure as Flu A is an infectious disease and is easily spread. Also, the risk of blindness in some of the subjects is easily justified as a greater number of the general population may be saved from a graver type of harm, i.e. death. Some ethicists are concerned with the argument and contend that it is unethical to balance the rights and interests of an individual against society at large, it is wrong to expose a small number of people to harm for the benefit of others; moreover, the risk of blindness is too great a harm for any subject to be exposed to. Risk assessment as shown in this example can be based on several criteria, the interests of the subject alone (the risks borne by him – death, blindness; and the benefits he might obtain – an effective cure), this risk might be measured in terms of either the type of harm (blindness or death) or likelihood of harm (fifty percent). Or risk assessment can also be based on balancing the interests of the subject against the interest of the population. In this case, the number of subjects that might become blind or die against the number of people that might die if they contract Flu A. If ethics committees in Malaysia are to engage in proper risk assessments, they will need to be guided by more than para 2.2 of the ICH-GCP.

As demonstrated above, risk assessment is a vital part of ethics review of RCTs and because it is a complex exercise, ethics committees must be provided with adequate guidance and training. Ethics committees must also be able to recognise and engage in debate about emerging issues. In the case of risk assessment and RCTs in psychiatric research (which potentially might recruit incompetent patients), recent moves have been made to lower the bar for acceptable risks. While much of

the concern about risks in psychiatric research trials to date has revolved around the risk for suicide, where even proponents of placebo control trials would consider the risk of death or serious permanent harm unacceptable, Kim³⁹⁴ points out that recent moves have been made to advocate a lower barrier by adding two further categories: “reversible but serious harm” and “severe discomfort”. He flags the danger of considering these sorts of risks as ethically unimportant and demonstrates this by relying on studies that have demonstrated that suffering from major mental illness is a terrible state that causes immense suffering. Suicide is not the only terrible risk these patients face; any delay or deprivation of treatment is likely to be a very heavy burden on patients. An ethics committee reviewing an application to run a RCT on schizophrenic patients, for example, should be careful to note the level of risk attached to a schizophrenic subject receiving a placebo and be able to understand what that level of risk would mean to a schizophrenic patient.

Notwithstanding the worries about the ethical nature of RCTs and the role of ethics committees as risk assessors, there is an argument to be made that as long as subjects are provided with sufficient information, they are in the best position to decide for themselves whether or not to accept the risks inherent in the trial design.³⁹⁵ For this reason, as long as the design is scientifically valid, and the risks are not too disproportionate, it seems eminently reasonable to suggest that informed consent is a sufficient protection for competent adults, and as long as incompetent adults are provided with adequate safeguards, there really is no need to obsess about the issue of risk. However, given the situation in Malaysia, where assessments of capacity appear to be made in a rather arbitrary manner and that only the very profoundly incompetent seem to be excluded, it is submitted that there is a very

³⁹⁴ Kim, "Benefits and Burdens of Placebos in Psychiatric Research."

³⁹⁵ Note the very real problem of therapeutic misconception, which seems to suggest that this is not true.

real possibility that some incompetent persons are being enrolled as competent subjects. Persons, who in all probability are unable to provide real informed consent. If this is true, the risk/benefit assessment made by ethics committees is extremely important and should be conducted in as vigorous a manner as possible. Sadly, this does not seem to be the case in practice. In fact it appears that ethics committee members do not think very much about risk assessment at all. From interviews conducted with ethics committee members, the only person who raised the issue of risk assessment was a lay member, whose only concern was insurance coverage, who said,

‘... we always try to clarify the risk factor and to make sure that even if there is just using, there is very, very slim chance of some adverse effect you do have to have enough of er... insurance and all that to cover them’³⁹⁶

While it is clear that the duty of an IRB (as set out in the ICH-GCP guideline) to safeguard the rights, safety and well-being of all trial subjects, lies at the core of its responsibilities, it is also clear from the discussion above that ethics committees cannot merely rely on the ICH-GCP guideline alone if they are to achieve this objective. What more then does an IRB need in order to be able to safeguard the rights of subjects and in particular, mentally incompetent subjects? What needs to be put into place to ensure that ethics review is an effective safeguard? First, there is clearly a need for an ethical framework for decision-making and as proposed in Chapter 3 the starting point of any framework for decision-making should be the principle of respecting human dignity. Nonetheless, ethics committees need more than this in order to fulfil their responsibilities, i.e. they also need to be able to appreciate the context in which research is carried out and how the various aspects of a trial design, for example, might impact on the lives of subjects of human research. These considerations are not static and the needs and concerns of subjects will change with the flow of time. Accordingly, ethics committees must be able to keep up with the

³⁹⁶ Interview with Member A, Ethics Committee A, on 21 December 2007.

changing needs of trial subjects. Continuous training and collection of empirical evidence are necessary if ethics committees are to keep themselves current.

5 Chapter 5

Ethics Committee Review and Conflicts of Interest

One vital aspect of ethics committee review that is not covered in any detail by the ICH-GCP is the question of the independence of the ethics committee. Notably, the issue of independence of ethics review of research, which, as described below, was conceived primarily as independence from the individual investigator, has evolved over time into the larger notion of concern about conflicts of interest (CI). The purpose of this chapter is twofold. First, it is intended to demonstrate how the informed consent process is mired in an environment that is replete with conflicts of interests and that ethics committees must not only be made aware of this, but should also have at their disposals mechanisms which they can use to minimise the influence of conflicting interests where possible. Second, it is to show that ethics committees themselves operate in situations where they are faced with conflicting interests, which may affect the way in which they make their decisions.

Historical context of independent ethics review

Historically, the idea of instituting a system of independent review of research protocols can be traced back to the 1940s. Following the many disturbing exposés of research misconduct during and shortly after the Second World War, there was a growing realisation that the activities of providing medical care and running clinical research were based on very different goals. The provision of medical care was aimed at the welfare of the individual patient, whereas clinical research trials were primarily concerned with furthering scientific knowledge. “The bedrock principle of medical ethics – that the physician acted only to promote the well-being of the patient - did not hold in the laboratory.”³⁹⁷ More

³⁹⁷ Rothman, *Strangers at the Bedside : A History of How Law and Bioethics Transformed Medical Decision Making*. at 89

than this, the lessons of the past indicated that clinical researchers were not always able to objectively separate their functions as physician and researcher to make decisions that were ethically appropriate. Review committees (IRBs) were thus set up in order to be impartial reviewers of research protocols and to ensure the protection of human subjects.³⁹⁸ Traditionally, the main role of the ethics committee was to stand between the investigator and his potential human subjects, to ensure that the welfare of research subjects would be protected as investigators were seen as always operating from a position of potential conflict of interest. The centrality of the notion that ethics review should be independent of investigators was emphasised by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research in its report on IRBs where it stated, "Investigators should not have sole responsibility for determining whether research involving human subjects fulfils ethical standards. Others who are independent of the research must share this responsibility because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research."³⁹⁹

Clinical research has since developed into a sophisticated and complex enterprise involving extraordinarily large sums of money and connecting numerous institutions and players the world over.⁴⁰⁰ The players in modern clinical trials include sponsors, who are usually either pharmaceutical companies or government agencies;⁴⁰¹ clinical research organisations (CRO); institutions where research takes place; and investigators. There are far more parties and far more money

³⁹⁸ See Chapter 2 for a narrative of the history of ethics committees in the United States, and Malaysia.

³⁹⁹ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "Institutional Review Boards: Reports and Recommendations."

⁴⁰⁰ See Chapter 1 at 14-16

⁴⁰¹ In developing countries, such as Malaysia, national governments do not usually have the money to sponsor clinical trials, and multi-national pharmaceutical companies sponsor almost all clinical trials.

involved in clinical research today as compared to when ethics committees first came onto the scene and as result of this, there are many more areas of potential conflicts of interests. Therefore, ethics committee review today stands between not only the investigator and the subject; rather it stands between the entire machinery of the research enterprise and potential human subjects. The range and types of competing interests faced by parties participating in this modern research enterprise is considerable. Growing concern about the harmful consequences of these competing interests has resulted in a rising awareness of what is now commonly referred to as the notion of conflicts of interest (CIs). In this environment, the notion of independent ethics review is more vital than ever before.

The discussion in this chapter will focus on the two mechanisms that provide for human subject protection in clinical trials: ethics review and the informed consent process; and will demonstrate how the players (physician/investigators and caregivers) in the informed process are impossibly compromised. Consequently, the chapter will show this makes the need for as independent an ethics review as possible an urgent and compelling one.

To begin with, the chapter will examine the issue of CIs as a whole. In this regard, it is instructive to consider how much of the discussion on CIs to date, has over-emphasised the notion of economic interests and the chapter will show how this paints only a partial picture of the notion of CIs. Accordingly, if the idea of a CI is to be accurately described and understood, there must be a careful unwrapping of the concept and what it means to have a CI. Following from this, the next part of the chapter continues by identifying the main players in the clinical trial environment who are likely to be faced with situations involving CIs and demonstrates the prevalence and insidious reach of CIs in the clinical trial environment. Out of this discussion, it becomes

evident that meaningful ethics review, and more importantly, *independent* ethics review is vital to the protection of human subjects. The last part of this chapter considers the sources of CIs in ethics review committees.

Conflicts of Interest

History of Conflicts of Interest in the Research Environment

The concept of CIs as Krimsky notes,⁴⁰² is not a new one and has in the past, received a great deal of attention in areas of public ethics such as the legal community and government service but the attention given to CIs in the scientific and medical research community has been a relatively new development, dating back to the 1980s.⁴⁰³ The impetus for this was the injection of economic interests into the academic research environment. The 1980s saw a great deal of interest in the commercialisation of the research enterprise in America, as evidenced by among other things, the passing of the Bayh-Dole Act, which has been described as creating an environment where the “US government provides incentives for scientists to hold conflicts of interest”.⁴⁰⁴ Before the passing of this Act, the federal government owned the rights to the results of any research sponsored by it, and companies wanting to transfer these rights not only had to engage in tedious negotiations with federal agencies, but also were rarely, if ever, given exclusive rights to the patents. The result was that inventions and discoveries “sat in warehouses gathering dust”.⁴⁰⁵ In 1980, of the 28,000 patents owned by the American government, fewer than 5% had been licensed to industry and there were only a small number of patents produced by universities. One of the main reasons for the passing of the Bayh-Dole

⁴⁰² Sheldon Krimsky, "The Ethical and Legal Foundations of Scientific 'Conflict of Interest'," in *Law and Ethics in Biomedical Research*, ed. Trudo Lemmens and Duff R. Waring (Toronto: University of Toronto Press, 2006).63

⁴⁰³ Ibid. at 63, also see Dennis F. Thompson, "Understanding Financial Conflicts of Interest," *N Engl J Med* 329, no. 8 (1993), which cites Relman AS. The new medical-industrial complex. *N Engl J Med* 1980;303:963-970 and Relman AS. Dealing with conflicts of interest. *N Engl J Med* 1985;313:749-751.

⁴⁰⁴ Krimsky, "The Ethical and Legal Foundations of Scientific 'Conflict of Interest'." 67

⁴⁰⁵ The Economist, "Innovation's Golden Goose," *The Economist*, December 14, 2002 2002.

Act was to address this problem and to “promote the commercialization and public availability of inventions made in the United States by United States industry and labor”.⁴⁰⁶ This is achieved by allowing players, such as universities, the right to file for patents on the results of research funded fully or partially by federal funds.⁴⁰⁷ Moreover, when private companies supply monies, the statute requires that profits resulting from any inventions be shared with the universities.⁴⁰⁸ The enactment of the said Act resulted in a significant increase in industry relations with universities⁴⁰⁹ and by 2002, more than 3000 patents per year were awarded to universities with licensing revenues surpassing \$1.2 billion.⁴¹⁰ University biomedical research programmes in particular, have profited from this development and universities stand to make significant profits under this regime as evidenced by the \$20 million in gross royalties earned by Columbia University when in 2000, it licensed its patent on a novel way to treat glaucoma to Pharmacia, which went on to develop the blockbuster drug, latanoprost.⁴¹¹

An unfortunate offshoot of the Bayh-Dole Act, however, has been a change in the way academic research is now viewed as a result of the marriage of academia and private enterprise. Prior to its passage, the hallmark of the academic research environment was its independent pursuit of the advancement of scientific knowledge. The pharmaceutical industry on the other hand, has always had as its main concern, commercial interests such as the success and profitability of its products. The growing number of partnerships between these

⁴⁰⁶ *Patents and Trademarks Amendments Act 1980 (the Bayh-Dole Act)*. §200

⁴⁰⁷ For a more in-depth discussion of the historical background to the Bayh-Dole Act, see David C. Mowery et al., "The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980," *Research Policy* 30, no. 1 (2001).

⁴⁰⁸ J. P. Kassirer, "Financial Conflict of Interest: An Unresolved Ethical Frontier," *American Journal of Law & Medicine* 27, no. 2-3 (2001). at 150

⁴⁰⁹ *Ibid.* pg 151

⁴¹⁰ Aaron S. Kesselheim and Jerry Avorn, "University-Based Science and Biotechnology Products: Defining the Boundaries of Intellectual Property," *JAMA* 293, no. 7 (2005). at 851

⁴¹¹ *Ibid.* at 851

players has raised worries that academic institutions and their researchers will no longer act independently in their research endeavours as concerns for monetary gain may unduly influence their behaviour. These concerns are not unfounded as a systematic review of studies on CIs concluded that a “comprehensive review of literature confirms that financial relationships among industry and scientific investigators and academic institutions are pervasive;”⁴¹² and that, “strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions.”⁴¹³

Current Emphasis – financial conflicts of interest

While economic concerns were the primary impetus for the development of CIs in biomedical research, economic concerns now provide much of the concern surrounding the area of ethics review and CIs. As such, much of the discussion on CIs to date continues to revolve around the issue of financial CIs. This is to a large extent due to the fact that clinical research has evolved into a billion dollar enterprise that is primarily led by for-profit organisations involved in complex relationships with governments, academic institutions and private individuals, and this has resulted in the creation of an environment where financial incentives offered to investigators and institutions are becoming increasingly lucrative. Stirred by worries that economic pressures and the use of clinical trials primarily as marketing tools were compromising the integrity, quality, and intellectual rigour of clinical trials, the editors of twelve of the world’s leading medical journals⁴¹⁴ issued a statement in 2001,⁴¹⁵ revising and strengthening

⁴¹² Justin E. Bekelman, Yan Li, and Cary P. Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review," *JAMA* 289, no. 4 (2003). at 463

⁴¹³ Ibid.

⁴¹⁴ Annals of Internal Medicine, Journal of the American Medical Association, The New England Journal of Medicine, The New Zealand Medical Journal, Canadian Medical Association Journal, Journal of the Danish Medical Association, The Lancet, MEDLINE/Index Medicus, Journal of the Norwegian Medical Association, Dutch Journal of Medicine, The Medical Journal of Australia, Western Journal of Medicine

the rules on publication ethics found in the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications”.⁴¹⁶ The revisions require authors to disclose details of their own and the sponsor’s role in the study particularly in respect of potential financial conflicts of interest. This indicates the increased awareness in this area of the pressing need to address the area of potential financial conflicts of interest in the biomedical field

Another worrying feature of contemporary financial CIs is that they involve complex relationships that are not easily discoverable by the general public. A good example of this is the highly publicised case of Jesse Gelsinger in America. Jesse Gelsinger, a young man who suffered from a mild form of a very rare metabolic disorder, OTC,⁴¹⁷ died while participating in a gene transfer clinical trial conducted at the University of Pennsylvania. Following his death, his father Paul, filed a lawsuit against the three principal investigators, their institutions, and their review boards.⁴¹⁸ Among the many accusations levelled at the defendants was the accusation that Jesse had not been fully advised of the conflicting interests of the parties involved in the research. The head investigator and director of the University of Pennsylvania’s Institute for Human Gene Therapy, Dr James Wilson, was also the founder of Genevo Inc, a company in which he and the University of Pennsylvania had equal stakes in and which had invested in the genetically altered virus used in the trial. Genevo had also at that time contributed a fifth of the \$25 million annual budget of the University’s gene therapy institute and in return had exclusive rights over any

⁴¹⁵ Frank Davidoff et al., "Sponsorship, Authorship, and Accountability," *N Engl J Med* 345, no. 11 (2001).

⁴¹⁶ A document developed by the International Committee of Medical Journal Editors (ICMJE) and widely used by individual journals as the basis for editorial policy

⁴¹⁷ Ornithine transcarbamylase deficiency syndrome

⁴¹⁸ Paul L. Gelsinger, "Uninformed Consent: The Case of Jesse Gelsinger," in *Law and Ethics in Biomedical Research: Regulation, Conflict of Interest, and Liability*, ed. Trudo Lemmens and Duff R. Waring (Toronto: University of Toronto Press Incorporated, 2006). at 30

commercial product. Moreover, Wilson and another colleague had also been awarded patents on certain aspects of the procedure contained in the trial. After Jesse's death, his father, Paul, brought a lawsuit against all the parties involved in the trial intimating among other things that the actions of some players were tainted by their financial entanglements, none of which were patently obvious and were never revealed to Jesse in the informed consent document.⁴¹⁹ Although the case never went to court as the Gelsingers were offered and accepted an undisclosed amount in settlement, the claims made by Paul Gelsinger regarding the tangled financial relationships of the investigators and institutions drew added attention to the problem of economic gains in CIs.

Finally, whilst the focus on economic gain in CIs is vital, it is submitted that the notion of a CI is far more complex than the linear notion of undue economic influence and has not been explored sufficiently. This is attributed to the fact that focusing on economic gain in CIs is more objective and fungible and therefore also easier to regulate by impartial rules.⁴²⁰ However, this is inadequate and Horton⁴²¹ rightfully points out that to put financial conflict to the fore is to "provide a smokescreen for more covert and possibly more influential commitments". The following section will demonstrate how some conflicting interests exist at a far more fundamental level and are in fact much more relevant in the Malaysian context. Moreover, if the avoidance or eradication of CIs, as claimed earlier, is essential to the issue of independence of ethics committees and the integrity of the informed consent process, it is necessary to unwrap the notion of CIs so as to be able to recognise its different manifestations in different situations.

⁴¹⁹ For a fuller account of Jesse Gelsinger's story and issues of conflicts of interest, see *Ibid.* and Krimsky, "The Ethical and Legal Foundations of Scientific 'Conflict of Interest'." at 70-71

⁴²⁰ Thompson, "Understanding Financial Conflicts of Interest."

⁴²¹ Richard Horton, "Conflicts of Interest in Clinical Research: Opprobrium or Obsession?," *The Lancet* 349, no. 9059 (1997).

What are Conflicts of Interest?

As noted by Lemmens and Freedman,⁴²² it is hard to find a clear definition of what constitutes a conflict of interest (CI). In the health care setting, CIs have been defined broadly as situations in which legal obligations or widely recognised professional norms are likely to be compromised by a person's other interests.⁴²³ They have also been construed more narrowly as occurring when discrepancies exist between the personal interests and professional responsibilities of a person in a position of trust.⁴²⁴ The favoured definition in the current literature appears to be that of Thompson, where he describes CIs as "set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."⁴²⁵ In seeking to draw up a unitary account of CIs, these definitions fail in one way or another to capture the rich and complex nature of what it is to have a CI. A useful counterpoint to these definitions is provided by Erde who engages in a much more insightful and thoughtful reflection of the notion of CIs. He states at the outset that CIs are so "pervasive and varied that they defy unitary definition" and that attempts to provide unified accounts merely lead to artificially narrow notions of CI".⁴²⁶ He contends that CIs are in fact a "family, resemblance of cases and criteria rather than a strictly defined uniform idea"⁴²⁷ and that persons dealing with CIs must "develop a "moral sense" of what is

⁴²² Trudo Lemmens and Benjamin Freedman, "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards," *The Milbank Quarterly* 78, no. 4 (2000). at 554

⁴²³ A.C. Shipp, "How to Control Conflict of Interest," in *Biomedical Research Collaboration and Conflict of Interest*, ed. R.J. Porter and T.E. Malone (Baltimore: John Hopkins University Press, 1992).

⁴²⁴ J. P. Orlowski and L. Wateska, "The Effects of Pharmaceutical Firm Enticements on Physician Prescribing Patterns. There's No Such Thing as a Free Lunch," *Chest* 102, no. 1 (1992). at 273

⁴²⁵ Thompson, "Understanding Financial Conflicts of Interest."

⁴²⁶ Edmund L Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology," in *Conflicts of Interest in Clinical Practice and Research*, ed. Roy G Spece, David S Shimm, and Allen E Buchanan (New York: Oxford University Press, 1996). at 12

⁴²⁷ *Ibid* at 12

acceptable akin to the “clinical judgment” that guides practitioners in their daily practice.”⁴²⁸ Regrettably, Erde’s final conclusion is less than helpful in that firstly, if CIs are to be managed or monitored on any sort of practical level, there needs to be, if not a unitary definition, at least a workable framework for identifying situations involving CIs. Second, the very reason why CIs are undesirable is because they are apt to skew an individual’s moral compass - therefore, leaving such an individual to his or her own “moral sense” will not go any way towards relieving the problems surrounding CIs.

Notwithstanding this, Erde’s analysis takes a journey that is well worth examining in some detail as it provides a thoughtful and insightful picture of CIs. In order to put together a meaningful and workable notion of CIs, the following section begins by using Thompson’s definition as a foundation and builds on it by adding relevant aspects of Erde’s analyses to finally construct a viable framework of CIs which can be applied to the different parties engaging in clinical research trials.

Conflicts of Interest as the Clash Between Primary and Secondary Interests

As mentioned above, Thompson defines a CI as a situation where a primary interest tends to be unduly influenced by a secondary interest.⁴²⁹ A primary interest is determined by the professional duties of the role-holder and although at times these may be controversial or conflicting, Thompson argues that there is normally agreement that they should be the primary consideration in any professional decision made by the role-holder.

While Thompson’s idea of primary interests being unduly influenced by secondary interests is a useful starting point for further exploration of

⁴²⁸ Ibid. at 12

⁴²⁹ Thompson, "Understanding Financial Conflicts of Interest."

the notion of CIs, his analysis fails to provide satisfactory answers to the following questions:

First, what sorts of relationships give rise to primary interests as understood in CIs?

Second, how are primary interests to be discovered, or in other words, what are the primary interests of the parties involved? Thompson's suggestion that these interests although controversial are normally discoverable by agreement, is unsatisfactory. He does not stipulate who should be party to this agreement and if there is no single body that sets the interests by agreement, primary interests are likely to be subjectively determined; and if, as he admits, there are conflicting and controversial interpretations of primary interests, there will undoubtedly be various depictions of primary interests depending on the wishes of different role holders. This in turn, would result in great confusion.

Lastly, when can it be said that interests (other than primary interests) amount to secondary interests? Are they determined by the subject matter of the interest, the creation of a dilemma, the fact that self-regard is involved? Thompson merely talks about the existence of undue influence but does not examine what this concept of undue influence actually entails.

The next section examines and answers each of the questions raised above.

(1) What sorts of relationships give rise to primary interests? – Erde's social role

In presenting the case for primary interests, Thompson fails to take into account an importance of primary interests; he fails to identify the features of the relationships or social roles that lead to the creation of

Formatted: Bullets and Numbering

primary interests. Not all types of relationships can be said to involve CIs. Erde⁴³⁰ provides an example in the case of Aeschylus' *Agamemnon*, where the only way Agamemnon could save his expedition was by sacrificing his daughter Iphigenia to the gods. Erde changes the case to one where Agamemnon is given a choice of saving either his daughter or the bulk of the crew and points out that while the crew might worry that Agamemnon might have a CI as their leader, it would be very odd to suggest that Iphigenia could frame her concerns in terms of a CI.

In describing the relationship that could lead to a CI, Thompson only seems to go so far as to imply that there should be some sort of professional relationship and makes reference to physicians, scholars or teachers. It is submitted that this is a far too narrow interpretation of the type of situation in which a CI might arise. Neither ethics committees nor caregivers for example, can be said to be in professional relationships with human research subjects. Erde on the other hand, presents the relationships that might involve CIs as ones where role-holders have a particular **social role** to play and lists four features of such relationships:⁴³¹

1. They are socially designed and elected, in contrast to those that seem natural and unavoidable.
2. They exist to serve the welfare or vital interests of others.
3. They involve discretion and judgment as part of the role holder's function.
4. Either the beneficiaries of the role holder's work or society in general must be able to trust the role holder simply because he holds the role. In other words, beneficiary must be in position of reliance on the role-holder because of the position he holds.

⁴³⁰ Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." at 24

⁴³¹ Ibid.

While there is much to recommend Erde's social role, he fails to explicitly point out one of the more important features of the social role, which is that the role holder holds some form of power that is used for the benefit of another and is in some way, akin to the idea of a fiduciary.⁴³² A more accurate formulation of the social role would involve amending the second feature to state: They hold some form of power or special knowledge that is used to serve the welfare or vital interests of others.

With the abovementioned criteria in mind, return to the example of Agamemnon. Erde points out that while Agamemnon could have declined to lead the expedition, he could not have declined to be his daughter's father and that while Iphigenia was not compelled to trust in her father's leadership, the members of his crew were committed to trust and follow their leader who was in a position of power. This depiction of a certain type of social role paints a truer reflection of what it means to have a primary interest as opposed to merely stating that it is based on having a professional duty.

Which relationships in the research environment fulfil Erde's social role?

Social roles that fulfil Erde's criteria and therefore attract the notion of primary versus secondary interests are as submitted above, those that exist for the benefit of third parties. This then begs the question as to which parties in the clinical trial context, and in particular, clinical trials that potentially enrol mentally incompetent adults, hold this social role? Which parties are potentially in positions of CI? The answer to this question must surely be the parties who are entrusted with ensuring the protection of the rights of human subjects in clinical trials; they would be participants in the mechanisms for safeguarding

⁴³² Morin et al., "Managing Conflicts of Interest in the Conduct of Clinical Trials." at 79

the rights of human research subjects. As stated in chapter 1,⁴³³ the two main safeguards provided to human participants in clinical research trials are (i) ethics committee review and (ii) the informed consent process. The below discussion examines these two main safeguards in greater detail. A greater part of the initial discussion focuses on the informed consent process and the role of the physician/researcher in this process. This is because as noted earlier in this chapter as well as in the chapter before, the remit of ethics review is clearly to protect the interests of people who take part in clinical trials and therefore the role and primary interests of ethics committees as far as CIs are concerned, are easily discoverable. However, scrutiny of the current literature and practice suggest that the roles of the parties involved in the informed consent process, and particularly, the role of the informed consent facilitator has been largely misconstrued, resulting in not only a misconception of the notion of CIs in relation to informed consent but also in a weakened informed consent process.

(i) Parties involved in ethics review

People who are deciding whether or not to enrol into a trial need to be able to trust that ethics committees have properly reviewed the trial protocol. Ethics committees take it upon themselves to carry out this task knowing that the beneficiaries are the potential human participants (as the ICH-GCP clearly states that the responsibility of the ethics review committee is to “safeguard the rights, safety and well-being of all trial subjects”).⁴³⁴ When these participants might include mentally incompetent adults, the role of the ethics committee becomes even more vital. The role played by ethics committees clearly fulfils the criteria set out by Erde as being a role that potentially involves CIs.

⁴³³ Section 1.1.2

⁴³⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Guideline 3.1.1

(ii) Parties Involved in the Informed Consent/Proxy Consent Process

The second tier of protection of human participants, the informed consent process, relies on the premise that the physician/researcher will present the necessary information to a potential subject in an impartial manner and engage him or her in a meaningful discourse, which will provide the subject with sufficient information that allows him or her to make a free and informed decision.

It is important at this juncture to digress briefly and make two observations, *i.e.* first, the importance of the informed consent process in the protection of human subjects in clinical trials; and second, the misguided notion that the role of informed consent facilitator (this term is used to indicate the role of the physician/researcher when he is engaged in the informed consent process) is somehow subsumed into the larger role of the physician/researcher.

The informed consent process and roles of physician/researcher/informed consent facilitator

As mentioned above, the first observation to be made is in relation to the importance of the informed consent process in the protection of human subjects in clinical trials. The informed consent process is a vital safeguard in protecting the rights of human subjects and heavily informs both national and international declarations on research using human subjects. A former Secretary of Health and Human Services in the United States⁴³⁵ when considering the principles that guide biomedical research remarked that, “none of these principles is more important than the protection of research subjects by informed consent based on full disclosure of potential risks and benefits.”⁴³⁶ The level of disclosure expected of an informed consent facilitator in the research

⁴³⁵ Donna Shalala, Secretary for Health and Human Services, United States of America, 1993-2001.

⁴³⁶ Donna Shalala, "Protecting Research Subjects -- What Must Be Done," *N Engl J Med* 343, no. 11 (2000).

environment is notably higher than that of a physician in a therapeutic context. The duty in the research context is to inform subjects of all the potential risks and benefits of a clinical trial. Full disclosure is a necessary precondition to free choice, whereas in the therapeutic context, physicians are able to rely to some extent on the idea of clinical judgment when offering information about treatment choices to patients.

The second observation to be made (again, as mentioned above), is in relation to the misguided notion that the role of informed consent facilitator is somehow subsumed into the larger role of the physician/researcher. In the current clinical trial environment, physicians/researchers play three separate tasks: they take informed consent, carry out the research, and manage patients' medical conditions. These involve three very different roles but almost all the literature has only focused on the latter two. Much has been written about the tension between the roles of the researcher and physician and how they might or might not be at odds with each other. In contrast, very little has been said about the role and duties of the informed consent facilitator. Most of the literature does not even recognise a third role of the informed consent facilitator and the informed consent process is subsumed into the larger physician/researcher debate. It is submitted that this approach is flawed as it fails to appreciate that in the research environment, the informed consent process is a vital mechanism for protecting human subjects. The purpose of informed consent is to ensure that subjects fully understand and accept the risks of participating in clinical trials. In cases that involve proxy consent, facilitators and proxy decision-makers work together to make decisions in the best interest of the incompetent adult. This means that when the facilitator is going through the process of informed consent, his primary duty is to protect the interests of the potential subject by ensuring that the subject is

able to make a full, free and informed decision about the research. As the discussion below demonstrates, the primary interests of physicians and researchers are both incompatible with the primary interests of an informed consent facilitator and that as long as the same person carries out these functions, the informed consent facilitator remains impossibly compromised. The discussion below also demonstrates how physician/investigators as well as subject/patients find it very hard to separate the roles of physician and researcher, and both tend to over-emphasise the therapeutic role in the context of research. This in turn tends to contribute to an undermining of the informed consent process because the facilitator is functioning with some very fundamental opposing primary interests that, as evidence suggests, are still very much unresolved.

Informed Consent Facilitator and Erde's Social Role

Having established these preliminary observations about the role of the informed consent facilitator, the question that arises now is whether the role is one that invokes Erde's social role? The informed consent facilitator's role clearly fulfils the first two criteria of Erde's social role, it is socially designed and exists to serve the welfare of the person providing the consent. It is however disputable that this role involves any discretion and judgment as part of its function. A closer look at how the informed consent process works in practice today reveals that, in fact, discretion and judgment do form part of the process. This is clarified and elaborated on below.

The dispute (i.e. whether or not the role of an informed consent facilitator involves any discretion or judgment) arises from the fact that the informed consent model in the research environment, as opposed to a paternalistic model, places the autonomous patient/subject at the centre of the decision-making process with the physician/researcher playing a peripheral role in supplying the

necessary information. This model envisages that both parties operate from positions of equal strength. As long as the physician/researcher provides the patient/subject with the information, he has fulfilled his duty and the latter is free to choose whether or not to enrol in the trial. It is also important to remember that the process of taking informed consent prior to enrolment in a clinical trial is very different from obtaining consent for medical treatment. The patient/subject is provided with a patient information sheet that has received the prior approval of an ethics committee, which should contain all the relevant information set out in a way that is easily understood.⁴³⁷ Theoretically, the physician/researcher is not a position to hold back any information or data from the patient/subject. If this is true, the physician/researcher cannot be said to hold a social role that might involve a CI as envisioned by Erde as the physician/researcher does not act with any discretion or judgment and makes no decision about the patient's best interest. He merely offers him pre-approved information. Consequently, the patient/subject is not placed in a position of reliance on the physician/researcher. Moreover, given that the informed consent is obtained for the purposes of a clinical trial, the physician/researcher can be said to be operating primarily as a researcher and as recognised by Brody and Miller, the researcher cannot be seen as having a fiduciary relationship with research subjects, including those who have a prior patient-physician relationship, as the researchers "cannot in good faith promise fidelity to doing what is best medically for the patient-subject".⁴³⁸ Given these arguments, it seems plausible to suggest that the question of CIs should not be raised in relation to taking informed consent for clinical trials.

⁴³⁷ There is some doubt as to the readability of the patient information sheet. See Christopher et al., "Consent Form Readability and Educational Levels of Potential Participants in Mental Health Research."

⁴³⁸ Howard Brody and Franklin G. Miller, "The Clinician-Investigator: Unavoidable but Manageable Tension," *Kennedy Institute of Ethics Journal* 13, no. 4 (2004). at 336

This however is not true for two reasons. First, even in the best of circumstances, the parties enter into this process from very different positions of power and knowledge, and if patients/subjects are to be informed, they must to some extent rely on the physicians/researchers to provide them with the information they need. Second, physicians/researchers cannot abrogate their positions as physicians when taking informed consent, as patients are generally unable to separate these roles and are likely to defer to or be influenced by the views of their physicians when making treatment decisions. The informed consent process relies on the idea that if a patient is supplied with sufficient relevant information, he will be in a position to make a choice that best reflects his values and interests. Most of time though, patients/subjects are unlikely to have any prior medical and scientific knowledge and because of this are provided with patient information sheets, which provide a brief account of the trial process, its benefits and risks in lay terms. They are never presented with the full complement of scientific and medical information available in the trial protocol and in all fairness, much of it is likely to be beyond the comprehension of a patient/subject. In fact, evidence suggests that many patients are unable to understand the information as set out in the information sheets notwithstanding the fact that the sheets have received prior ethics committee approval. This is particularly true of mental health research, where poor readability of informed consent forms have been a persistent problem. A study conducted at the Massachusetts Department of Mental Health suggests that even by the most conservative estimate, approximately 35% of patients would be found to lack the educational level required to read the average informed consent form.⁴³⁹

⁴³⁹ Christopher et al., "Consent Form Readability and Educational Levels of Potential Participants in Mental Health Research." at 230

Although ethics committees scrutinise patient information sheets to ensure that the language is non-technical and easily understandable, this does not necessarily produce the desired result. Most of the time ethics committees rely on their lay members to carry out this task and if committees are reviewing large numbers of trial protocols, lay members are likely to become familiar with medical terms and expressions very quickly, and are likely to be reading information sheets with levels of understanding far beyond the ordinary patient/subject. In fact, when asked about reading patient information sheets, one lay member of an ethics committee remarked very quickly

‘That is the danger because now I don’t query them as much as before because I have been exposed to all the jargon and I kind of could understand even though not perfectly I could figure out most of it.’⁴⁴⁰

If a patient/subject is unable to understand the information provided in the sheets, he would need to rely on the explanation provided by the physician/researcher and any subsequent discussion between them. How this explanation is provided to the patient/subject and the shape of the discussion that ensues is left to the discretion and judgment of the physician/researcher. Depending on how the physician/researcher presents the information, he may significantly influence the decision of the patient/subject as there is some evidence that word choice, can introduce framing biases that might influence the way in which a patient/subject makes a choice.⁴⁴¹

The other reason why the physician/researcher cannot escape Erde’s social role is that when patients decide whether or not to participate in research, they rely heavily on their physicians to guide their choice. This is rooted in the belief held by many subjects that participating in research will advance their individual best interests. This mistaken

⁴⁴⁰ Interview with Ethics Committee B, Institution A, 21 Dec 2007

⁴⁴¹ R. M. Epstein, B. S. Alper, and T. E. Quill, *Communicating Evidence for Participatory Decision Making*, vol. 291 (Am Med Assoc, 2004). at 2362

belief is known as the therapeutic misconception⁴⁴² and was first observed by Appelbaum and colleagues when they interviewed participants in several psychiatric trials.⁴⁴³ Their data indicated that many subjects entering psychiatric trials, despite being given comprehensive disclosure, believed that they would personally benefit from the trials. Numerous subsequent studies have supported this observation in other types of therapeutic trials. The therapeutic misconception is so prevalent that it has been noted among patients/subjects enrolled in Phase I chemotherapy trials. Phase I trials are carried out with the sole purpose of establishing safe dosage levels, but one third of patients interviewed by researchers from the University of Chicago said that their main reason for participating was to seek a cure or remission and nearly 90 percent said their goals in joining the Phase I study were the same as if undergoing established treatments.⁴⁴⁴ One of the offshoots of the therapeutic misconception is that because patients/subjects view participation in research as the same as conventional treatment, they are more likely to be influenced by the opinions of physicians/researchers because they believe that their physician have their best interests in mind.⁴⁴⁵ The Subject Interview Study carried out by the Advisory Committee on Human Radiation Experiments, which enrolled almost 1,900 outpatients to determine their experiences with research, found that recommendations of physicians were powerful factors influencing patients' choice.⁴⁴⁶ One subject was recorded as saying "there is not a

⁴⁴² Also, see the discussion on the role of the therapeutic misconception at 187

⁴⁴³ Paul S. Appelbaum, Loren H. Roth, and Charles Lidz, "The Therapeutic Misconception: Informed Consent in Psychiatric Research," *International Journal of Law and Psychiatry* 5, no. 3-4 (1982).

⁴⁴⁴ R. Dresser, "The Ubiquity and Utility of the Therapeutic Misconception " *Social Philosophy and Policy* 19, no. 02 (2002). at 275

⁴⁴⁵ Many studies have looked at the relationship between patients and physicians and how patients make decisions about conventional treatment. Although many of the studies indicate that patients have a strong desire for more information, the same patients rely heavily on their doctors when making their decisions. See L. M. L. Ong et al., "Doctor-Patient Communication: A Review of the Literature," *Social Science & Medicine* 40, no. 7 (1995).

⁴⁴⁶ N. E. Kass et al., "The Fragile Foundation of Contemporary Biomedical Research," *Hastings Cent Rep* 26 (1996). at 26

lot you can control when you are sick, so you have to rely on your doctors ... if he suggests that you should go into a research project, I think you should take his advice or her advice ... because if you take the time to get yourself a good doctor and they're involved in research, they would never steer you wrong."⁴⁴⁷ What is more, consent forms appeared to have little influence on the choices made by subjects as patients either assumed that they did not need to pay attention to the information in the consent form; or that if they could not understand the information, it did not matter because they had already made up their minds.⁴⁴⁸

In addition to this, in the Malaysian context, mentally ill patients are likely to be at the end of their tether. This is because there is still a perceived social stigma surrounding mental illness and recourse to Western medicine is more often than not a last resort after traditional remedies have been exhausted. Patients suffering from psychiatric conditions are described as having tried,

'... the bomoh⁴⁴⁹ first, the ustaz⁴⁵⁰ first, before they come to you, and probably after they can't really control the patient. They are really aggressive and violent and then only they come back you. "Okay doctor, now I am ready, I have depleted all my resources. ... and they are desperate. They will try anything."⁴⁵¹

Patients and their families are thus even more likely to be influenced or led by the advice of their physicians.

The informed consent/proxy consent process and the incompetent patient

It is therefore clear that, in reality, the role of the physician/researcher as an informed consent facilitator fulfils the criteria of the social role as described by Erde, which is potentially subject to CIs. However, the

⁴⁴⁷ Ibid. at 28

⁴⁴⁸ Ibid. at 28

⁴⁴⁹ This is the term used for a shaman in Malaysia.

⁴⁵⁰ Ustaz is a term used for a teacher of Islam.

⁴⁵¹ Interview with Psychiatrist/Investigator B, Institution A, 28 January 2008

above argument has relied on the idea that the patient/subject is a competent adult. In the event that the patient/subject is an incompetent adult, informed consent cannot be obtained from him. There are two common approaches to such a situation. The first is to obtain advanced informed consent from the subject before he becomes incompetent. This can be achieved by getting consent at an early stage of a degenerative disease (such as Alzheimer's disease) before the loss of cognitive function; or during a period of remission from a disease or disorder (for example, schizophrenia); or by allowing a competent subject to appoint a research agent to carry out his will through the execution of a written advance directive. At present, there is no provision for any sort of advanced decision-making in the Malaysian context and it is unlikely to change in the near future, as there is no mention of it in the new Mental Health Act.⁴⁵² Also, while advanced informed consent raises a number of serious concerns,⁴⁵³ as far as CIs are concerned, the players involved in the process and the social roles they occupy are similar to the informed consent process.

The second approach is to provide for some form of proxy decision-making.⁴⁵⁴ In England for example, the Medicines for Human Use (Clinical Trials) Regulations 2004, provides that if an adult is unable by virtue of physical or mental incapacity to give informed consent, consent can be obtained from a "legal representative" if certain conditions are met. As discussed in Chapter 2, there is currently in Malaysia, no clear legal authority for adult proxy decision-making in health care matters. Because of this legal uncertainty and the unwillingness of sponsors to enrol mentally incompetent adult

⁴⁵² *Mental Health Act 2001 (Act 615), Malaysia.*

⁴⁵³ For a good analysis of advance directives, see R. Dresser, "Advance Directives in Dementia Research," *IRB: Ethics and Human Research* 23, no. 1 (2001).

⁴⁵⁴ An in-depth discussion of the different types of advanced proxy consent models and their respective merits and perils is beyond the scope of this thesis. For a good discussion of the different models of proxy decision-making see Advisory Work Group on Human Subject Research Involving the Protected Classes, "Recommendations on the Oversight of Human Subject Research Involving the Protected Classes," (New York (State) Dept of Health, 2002).

patients, the present policy is one of exclusion of all mentally incompetent adults.⁴⁵⁵ This will, however, change when the Mental Health Act 2001 comes into force as it allows for consent by a relative⁴⁵⁶ or if there is no relative available or traceable, by two psychiatrists, one of who shall be the attending psychiatrist.⁴⁵⁷ Therefore, at some point in the future, mentally incompetent adults are likely to be enrolled in clinical trials via proxy consent. The next section considers the informed consent process and the role played by relatives of patients who are invited to enrol into clinical trials that might potentially involve mentally incompetent patients, and demonstrates that the role played by relatives also fulfils the criteria set out in Erde's social role.

Relatives & Proxy Consent and Erde's Social Role

Relatives of patients and proxy consent – after the Mental Health Act 2001 comes into force

When the Mental Health Act comes into force, relatives will be permitted to provide proxy consent for mentally incompetent adults to enter in clinical trials. The consent process in such cases involves three parties – the patient/subject, the physician/researcher and the proxy decision-maker. In these cases, the role of the physicians/researchers in the proxy consent process remains much the same as in the informed consent process: to facilitate the decision-making process in a manner that serves the vital interests of the incompetent subjects by ensuring that the proxy decision-makers are fully informed about the benefits and risks of the trial. The same arguments that have been raised above

⁴⁵⁵ The lack of certainty surrounding determinations of capacity would suggest that this might not always be the case. (See discussion on page...) If this is true and patients are being erroneously treated as competent adults, the fact that the physician/researcher is also the informed consent facilitator cannot bode well for the interests of the subject as there is little hope of the informed consent process achieving its aim of protecting the autonomy of the subject if he does not have the capacity to provide an informed consent, as even in circumstances where assessments of capacity are not called into question, physicians have been known to claim that they can get their patients to "consent to virtually anything" (R Macklin, "Some Problems in Gaining Informed Consent from Psychiatric Patients," *Emory L. J.* 31 (1982), at 353)

⁴⁵⁶ Section 77(1)(b) *Mental Health Act 2001 (Act 615), Malaysia.*

⁴⁵⁷ *Ibid.* Section 77(1)(c)

regarding provision of information and the therapeutic misconception hold true in relation to proxy decision-making. The physician/researcher holds the same social role.

The role played by the relatives as proxy decision-makers falls squarely within the conditions laid out by Erde.⁴⁵⁸ First, even though as relatives they will be in natural relationships with the incompetent adults, they are unlikely to be in unavoidable⁴⁵⁹ ones and as such would have elected to undertake their social roles. Second, the Mental Health Act confers on relatives the power to make decisions on behalf of the mentally incompetent subjects in order to serve the welfare of the subjects who are deemed incapable of protecting their own vital interests. Third, their role involves using their discretion in making judgments about whether or not to allow their mentally incompetent relatives to participate in research trials and finally, mentally incompetent subjects must trust their relatives to make decisions that are in their best interest.

Relatives of patients enrolled into psychiatric clinical trials - the current situation

As noted earlier, the current practice in Malaysia is to exclude all mentally incompetent patients from clinical trials. Assuming that determinations of capacity are correctly made, all competent subjects should be capable of providing informed consent, that is to say they should be able to understand the information provided to them and make their own decisions based on their personal values and interests. This being the case, there would be no reason to involve any third party and relatives would not have any significant role to play in the consent process. This is however, not the case at all. The current policy of the Ministry of Health is that all competent psychiatric patients who

⁴⁵⁸ See section 5.4.1

⁴⁵⁹ While it may be seen as a moral failing, people are not required by law to take care of or maintain adult relatives who are incompetent or incapacitated in any way.

participate in clinical trials can only do so with the added consent of their relatives or caregivers.⁴⁶⁰ This is also true of academic research centres in Malaysia as noted by a senior psychiatrist/researcher who pointed out that, “if the patient don’t sign and only the relative sign, the consent is not accepted. The patient must sign and the relatives must sign.”⁴⁶¹ The current practice is that even if a competent patient is willing to participate but his family is not keen, the patient is not enrolled in the trial. The justification provided is that in an Asian context, the role of family members is seen as being very important, particularly in Phase II and Phase III trials with a placebo arm. An interesting point to note is that Phase IV clinical trials that do not employ the use of placebos are exempt from this rule, because these trials are equated with the provision of treatment.⁴⁶²

There are many troubling aspects of requiring consent from a relative of a competent patient (relative’s consent) and although a full discussion of the concerns raised by this practice is beyond the scope of this thesis, the following points are worth noting. First and foremost, it undermines the patient’s fundamental right to autonomy and renders the entire informed consent process a meaningless formality. It strips the patient of his human dignity by undervaluing him as an individual by dismissing his personal values as expressed by his decision.⁴⁶³ This practice is also discriminatory and undervalues the human dignity of psychiatric patients as a whole. It is clearly based on the assumption that the cohort of patients suffering from psychiatric illnesses is incapable of making decisions; that decisions made by this group are in some way inferior to decisions made by patients suffering from other disorders. Relatives’ consent cannot be justified by claiming that

⁴⁶⁰ Telephone interview with Dr Suaran Singh, Director, Hospital Bahagia, Ulu Kinta – Chief Psychiatrist Malaysia. Wednesday, 2 January 2008, 9:30am

⁴⁶¹ Interview with Psychiatrist/Investigator B at University A, 28 January 2008

⁴⁶² The fact that post-marketing Phase IV trials are equated with treatment adds to the notion of the therapeutic misconception.

⁴⁶³ See the discussion on undervaluation of the individual human life in Chapter 3 section 3.2.2.1

families play a more important role in the Asian context. This line of reasoning might perhaps be relevant to the manner in which the informed consent process is carried out. It might be a good reason for allowing family members to participate in the decision-making process, and even then, only when a competent patient desires such participation. It cannot serve as a justification for vetoing a patient's choice. If a patient is competent, his decision should be allowed to stand.

There appear to be two other reasons for requiring relative's consent for competent patients: first, because of the uncertainty in the law, researchers are concerned about their potential liabilities. A psychiatrist when asked why relatives of competent patients were asked for their consent remarked,

'Because ... there is no law on this, so we are not sure what happened in the future. At least we, we get some of the [family] members to be around and we try to explain to them as well.'⁴⁶⁴

The second reason seems to be linked to the issue of compliance as another researcher pointed out that co-operation from relatives was necessary to allay worries such as,

'How often are these patients going to come for follow up? Are they going to come regularly as required? Number one, number two – if they are so of unsound mind, they are not going to last the trial. Especially if they have the placebo or the lower dose arm of the multi-arm study. So, we also want to take into concern the sustainability of the trial.'⁴⁶⁵

Neither of these reasons warrants denying a competent patient the right to make an informed decision about whether or not to participate in a clinical trial. Both of these reasons are self-serving; the first is

⁴⁶⁴ Interview with Psychiatrist/Investigator B, University A, 28 January 2008

⁴⁶⁵ Interview with Psychiatrist/Investigator A, Institution A, 30 June 2008

aimed at protecting researchers from lawsuits and the second, to protect the sustainability of the trial.⁴⁶⁶

Regardless of whether or not obtaining a relative's consent is ethical, the fact is that this type of consent is routinely obtained, which then raises the question of the role of the relative in such a situation. Accepting the justification provided by the Malaysian Chief Psychiatrist that this consent is based on the importance of the role played by relatives of mentally ill patients, and that it is limited to trials involving a placebo arm, it is possible to infer that because Phase II and III trials, especially those with placebo arms are riskier than Phase IV trials, that the role of the relative providing relative's consent must be to protect the rights and interests of the patient/subject. This in turn must be based on the belief, even if mistaken, that all mentally ill patients are unable to assess the added risks associated with Phase II and Phase III trials that have placebo arms. In other words, patients suffering from mental illness are presumed to be incapable of providing informed consent and what is obtained from them is merely assent and that in reality, relatives are providing some form of proxy consent. If this is the case, then the role played by the relatives would fulfil the criteria of Erde's social role for the same reasons as relatives who are proxy decision makers.

From the above discussion, three groups of players, ethics review committees, informed consent facilitators (physicians/researchers), and relatives, are in relationships with patients/subjects that fulfil the criteria of Erde's social role, and are therefore potentially subject to CIs.

⁴⁶⁶ Interestingly, both these are examples of secondary interests that might or in this case; actually do unduly interfere with primary interests.

The next step is to consider the nature of the primary interests of each group and whether or not there exists at the same time, secondary interests that might unduly influence these primary interests.

(2) How are primary interests to be discovered?

The physician/researcher

In determining the primary interests of the physician/researcher, an important point to note is the difference between role holders that only play a single social role as opposed to role holders who might play a number of different social roles. This difference is clearly demonstrated by comparing the roles played by ethics committees and physician/researchers. Ethics committees are set up for one single purpose: to review research protocols to ensure the protection of the rights and safety of trial subjects. Regardless of the different roles played by individual members in their personal or professional capacities, when they sit as an ethics committee, the remit of their review is human subject protection. The primary interest of an ethics committee is solely to protect the welfare of human research subjects. Similarly, when relatives act as proxy decision-makers, they have a clear singular purpose: that is to ensure that the interests of the patient/subject are protected. On the other hand, the physician/researcher wears a number of hats simultaneously and it is very difficult, if not impossible for the physician/researcher to separate these roles. As a physician, he is entrusted with the role of providing the best care and treatment for his patient. As a researcher, he is called upon to serve the interests of furthering scientific and medical knowledge to benefit society at large, and as an informed consent facilitator he must ensure that the patient/subject/relative is able to make an informed decision.

Given the fact that the physician/researcher is called to play a number of roles simultaneously, there are two approaches that can be taken in determining the primary interests of the physician/researcher in the informed consent process.⁴⁶⁷ The first and most common approach is to focus on the roles of physician and researcher, to compare and contrast the different primary interests of each role and determine how best to reconcile the differences in order to come up with an agreed primary interest. In this approach, the third role mentioned above, the role of the informed consent facilitator is not seen as a separate role with any special attributes. It is contended, that [this](#) is the wrong approach. To begin with, as described below, the primary interests of the roles of physician and researcher are impossibly conflicted and it is not possible to reconcile the roles. What is more, this approach fails to recognise the importance of the informed consent process as a tool for human subject protection. As long as this remains the dominant approach, the informed consent process is unlikely to achieve its purpose. The second approach proposed in this thesis is to view the role of the informed consent facilitator as a separate role, i.e. a role with a clear and uncompromised primary interest: the protection of the rights and interests of patients/subjects. Any other interest must therefore be seen as a secondary interest and should not be allowed to unduly influence the primary interest. However, given the manner in which informed consent is currently obtained and the fact that the therapeutic and research roles are so closely enmeshed, it is hard to see how it is achievable in the current context. While unravelling this dilemma and proposing a solution is beyond the scope of this thesis, it does highlight the importance of the notion of an independent ethics

⁴⁶⁷ Resnick offers the 'contextual approach' as an alternative to the two traditional approaches, where he describes the extent of investigators' obligations as varying from situation to situation. This approach is rejected at the outset as it creates even more uncertainty about the role played by the physician/researcher and opens the door to a relativistic approach to moral duties. See Resnik, David. "The Clinical Investigator-Subject Relationship: A Contextual Approach." *Philosophy, Ethics, and Humanities in Medicine* 4, no. 1 (2009): 16.

review, seeing that in the present climate, the informed consent process is riddled with CIs.

The first approach - reconciling the roles of the physician and the researcher

The conflict of roles between the physician and researcher seem irreconcilable⁴⁶⁸ and much debate has centred on this. In general there are two lines of argument that have been forwarded regarding this intersection of roles: the similarity position and the difference position.

According to the similarity position, the ethics of clinical research is just a simple application of the ethics of clinical medicine and the ethics of the physician-patient relationship is assumed also to govern the investigator-subject relationship. Brody and Miller⁴⁶⁹ contend that the adoption of this position has resulted in what they see as incoherence in the research ethics literature. This position, as they rightly argue, is an intractable one. Attempts at subsuming the role of the researcher into the larger role of the physician have only resulted in logical incoherence. Take for example the principle of clinical equipoise⁴⁷⁰ used by proponents of the similarity position to rationalise the use of randomisation in clinical research. The argument is that although the practice of randomisation is clearly inconsistent with the physician's duty to act in the best interests of an individual patient, it is permissible in cases where there is clinical equipoise, where there is genuine uncertainty about which of the two treatments is better. The principle is aptly described as placing two different treatments on two ends of a seesaw and if somehow magically weighed, their respective net benefits and risks would result in a seesaw that is perfectly

⁴⁶⁸ DuBois provides a number of vignettes that illustrate the types of conflicts that can arise as a result of the conflicting roles, see James M. DuBois, *Ethics in Mental Health Research, Principles, Guidance, and Cases* (New York: Oxford University Press, 2008). at 207-208

⁴⁶⁹ Brody and Miller, "The Clinician-Investigator: Unavoidable but Manageable Tension."

⁴⁷⁰ For a more detailed discussion on clinical equipoise and randomisation in clinical trials, see Chapter 5 section 5.4.3.1

balanced.⁴⁷¹ If a physician/researcher is in a position of clinical equipoise, he is said not to violate his primary role as a physician. This argument is flawed. Even if a physician might view the two arms of a trial as being in perfect balance, an individual patient with specific ideas about risks and benefits may not feel the same way. If a physician/researcher is to fulfil his role as a physician, he must be in a position to take into account the individual preferences of his patient. Menikoff⁴⁷² offers the example of the landmark studies where women with breast cancer were randomised to either mastectomies or breast-sparing surgeries. Even though doctors were in true clinical equipoise about the effectiveness of the treatments; women were generally unwilling to participate in the study as the differences between the treatments mattered a great deal to most women regardless of the fact that there was genuine uncertainty in the medical profession regarding the effectiveness of the procedures in eliminating the cancer. The problem with the principle of clinical equipoise is that it proceeds from the assumption that the risks and benefits of a clinical trial apply equally to all subjects across the board but this is simply not true because every patient/subject is an individual with distinct preferences and notions of acceptable risks. The two ideas are incompatible as are the roles of physician and researcher.

The difference position on the other hand claims to provide a sounder basis for research ethics as it recognises that research and clinical practice are “distinct activities with very different goals”⁴⁷³ and one “should not expect that the same ethical principles would necessarily apply in both of these distinct settings”.⁴⁷⁴ The only duty owed to a subject, they argue, is non-exploitation and four measures are suggested as being necessary to manage the ethical tension. The first

⁴⁷¹ Menikoff and Richards, *What the Doctor Didn't Say : The Hidden Truth About Medical Research*. at 32

⁴⁷² Ibid.

⁴⁷³ Brody and Miller, "The Clinician-Investigator: Unavoidable but Manageable Tension." at 330

⁴⁷⁴ Ibid. at 330

and perhaps most important measure being that physician/researchers must face the inherent ethical tension and recognise it for what it is; followed by the need for the physician/researcher to work especially hard to educate the patient/subject on how the research context differs from the patient context. This approach is one that assumes that naming the beast for what it is, will take away its bite. While the difference position is undoubtedly more honest and transparent than the similarity position, it does not offer any realistic or practical solutions to the problem. Realistically, evidence suggests strongly that physicians/researchers do not or are unable to separate their roles as researchers and physicians and in fact, believe that their patients benefit directly from participating in clinical trials. Results of an investigation⁴⁷⁵ carried out by researchers from Harvard University into the informed consent process for clinical research of cancer therapies demonstrated that physician/researchers often “deal with moral tensions inherent in their role by adopting the perspective of the pure clinician”⁴⁷⁶ and that physicians often recommend that patients with cancer enrol in trials because they feel that trials represent the best therapeutic option. Similarly, Miller contends that researchers may also be subject to a form of therapeutic misconception. Using an example of an article⁴⁷⁷ where three psychiatrists rationalise the ethics of using a washout period⁴⁷⁸ in schizophrenia research by conflating the language of medical care with that of research, he demonstrates how they not only reinforce the therapeutic misconceptions of patients but also fall prey themselves to this idea.⁴⁷⁹ This attitude appears to hold true of Malaysian physicians as well; a psychiatrist at an

⁴⁷⁵ Steven Joffe et al., “Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey,” *The Lancet* 358, no. 9295 (2001).

⁴⁷⁶ *Ibid.* at 1776

⁴⁷⁷ W. T. Carpenter, Jr., N. R. Schooler, and J. M. Kane, “The Rationale and Ethics of Medication-Free Research in Schizophrenia,” *Arch Gen Psychiatry* 54, no. 5 (1997).

⁴⁷⁸ Washout periods are when patients are taken off an existing drug for a period of time before starting a clinical trial. This is to ensure that the effects of the prior medication do not contaminate the results of the trial. The use of “washout periods” in mental health research is especially contentious.

⁴⁷⁹ Franklin G. Miller, Donald L. Rosenstein, and Evan G. DeRenzo, “Professional Integrity in Clinical Research,” *JAMA* 280, no. 16 (1998) at 1451

academic medical centre considered the benefits of participation as being -

“...just different aspects of total treatment. Because when a person enrolls in a study, they also tend to benefit from different aspects. More time spent on them, lesser waiting time, easier medication dispensing, closer monitoring, whereas if you were to sit in the government clinic, it is just not physically possible to spend half an hour on each patient, because you have fifteen to twenty patients to see in three hours. So there is a benefit for patients.”⁴⁸⁰

In fact, in a telephone interview with the Chief Psychiatrist of Malaysia, he noted that Phase IV trials were regarded as a form of treatment.⁴⁸¹

Miller ascribes this phenomenon to the “deep socialisation of investigators as clinicians and the blurring of clinical medicine and clinical research in the academic medical center”.⁴⁸² It is hard to see how the socialisation of the investigator as clinician can be reversed as most physicians/researchers will have received their primary training as physicians and in practice, will function primarily as physicians. The only true solution to this problem is to completely separate the role of the physician from the researcher.

It is obvious that the position of the physician/researcher is an uncomfortable one where primary interests themselves appear to conflict. It is thus ironic that the duty to obtain informed consent, which is a vital part of human subject protection, is entrusted to the very person who is in such a conflicted position. More than this, it is surprising that the role played by the physician/researcher as an informed consent facilitator in the informed consent process in

⁴⁸⁰ Interview with Psychiatrist/Investigator A, University A, 30 June 2008

⁴⁸¹ Telephone interview with Dr Suaran Singh, Director, Hospital Bahagia, Ulu Kinta – Chief Psychiatrist Malaysia. 2 January 2008, 9:30am

⁴⁸² Miller, Rosenstein, and DeRenzo, "Professional Integrity in Clinical Research." at 1450

therapeutic clinical trials has received so little attention.⁴⁸³ Much of the literature, as noted above, has only concentrated on the physician-researcher dichotomy. Approaching the issue in this way is to fail to recognise the singular importance of the informed consent process in the research environment as a means of protecting human subjects. And as long as the debate continues to revolve around the physician/researcher dichotomy, the informed consent process will not be an effective protection for human subjects.

Second Approach – Informed consent facilitator as a separate role

What is needed is a different approach where the informed consent process is viewed as separate from therapy and research, and where the role of the informed consent facilitator is distinct from physician and researcher. Informed consent is not consent for therapy and is not part of the treatment process. Neither is it part of the research trial itself. It is a process that is taken prior to the initiation of a research trial in respect of an individual patient. In many ways it is the same sort of creature as the ethics review process; it exists to protect human subjects and it is taken prior to the trial. The difference between the two is that ethics review is carried out to protect the interests of all potential research subjects who might enrol in a particular clinical

⁴⁸³ Habiba and Evans (Marwan Habiba and Martyn Evans, "The Inter-Role Confidentiality Conflict in Recruitment for Clinical Research," *Journal of Medicine and Philosophy* 27, no. 5 (2002).) provide a novel approach to the physician-researcher role conflict and its relationship to the issue of informed consent by claiming that it results in an inter-role breach of confidentiality. This occurs when a physician utilises confidential information obtained within the therapeutic relationship beyond its primary object. They offer the concept of preliminary consent, which is obtained prior to being treatment, where patients are asked if they would ever be willing to be approached about the possibility of treatment. While this approach is an interesting one, it fails to appreciate that the real danger of the conflict is that it undermines the fundamental purpose of the informed consent process, the protection of human dignity. An excellent critique of their approach and the problems with the notion of preliminary consent is provided by Iltis in Iltis, A. S. "Timing Invitations to Participate in Clinical Research: Preliminary Versus Informed Consent." *Journal of Medicine & Philosophy* 30, no. 1 (2005): 89.

trial; whereas the informed consent process exists to protect the interests of each individual potential subject. As such they are both taken *prior* to the trial itself and are distinct from treatment or trial.

The centrality of informed consent as a means of human subject protection can be traced back to what is now generally accepted as the point of conception of a discourse on research ethics; the World War II experiments on human subjects carried out by the Germans and the articulation of the Nuremberg Code. The very first principle of the Code states that⁴⁸⁴

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

Beginning with the Nuremberg Code; every subsequent articulation of the ethical and legal standards required of research involving human participants has included the notion of requiring the informed consent of subjects. Significantly, the development of the doctrine of informed consent in the research setting has been driven by incidences of research misconduct.⁴⁸⁵ Misconduct in this context includes instances where human subjects were enrolled into trials where there were not fully informed of the risks of the procedures; where they were lied to regarding the treatment they were receiving; and in some instances

⁴⁸⁴At <http://ohsr.od.nih.gov/guidelines/nuremberg.html> accessed 15 September 2008.

⁴⁸⁵ For an overview of the history of research misconduct and the articulation of research ethics guidelines, see the discussion in Chapter 3, section 3.1

where they were completely unaware that they were taking part in clinical research.⁴⁸⁶ Moreover, the trials were never intended to benefit the subjects, they were intended at best, to serve the greater good of society. The subjects in these trials were given inadequate information, misleading information, false information, and some were never informed of anything at all. These persons were treated inequitably and deprived of their human dignity because they were treated as means to an end and were never given the choice or opportunity to decide whether or not to bear the risks of the research trials they were subjected to. The doctrine of informed consent addressed these issues directly. Potential subjects would be provided with full disclosure of the trial methods, risks, benefits and any other pertinent information, which would allow them to make decisions that would serve their individual interests. Ethics review is only able to consider the question of the interests of potential subjects at a more general level. Ethics committees scrutinise patient information sheets and informed consent sheets to assess accuracy and sufficiency of information, as well as lay readability. They do not and cannot be expected to have each individual patient in their contemplation. The test of whether a subject's consent is in fact informed will depend on the exchange between the subject and the informed consent facilitator. It is a vital mechanism for human subject protection and for reasons stated earlier; patients/subjects/relatives rely very heavily on informed consent facilitators. For this reason, the role of the informed consent facilitator should never be seen as a role that is subsumed into the larger role of the physician or researcher. The informed consent process must have at its heart, the interests of the subject/patient. Therefore, notwithstanding the dichotomy of the physician role and the researcher role, when taking informed consent, the physician/researcher is acting

⁴⁸⁶ For an excellent overview of the history of human research trials and the many ways in which misconduct has occurred see, J. Goodman, A. McElligott, and L. Marks, *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century* (Baltimore Johns Hopkins University Press, 2003).

as an informed consent facilitator and his primary interest must be in accordance with Erde's second criteria: to serve the welfare or vital interest of the patient/subject. All other interests and roles are secondary to this and to the extent that they are in conflict with this interest, place physician/researchers in positions of CIs.

A more detailed consideration of the conflict of roles of the physician/researcher/informed consent facilitator in the informed consent process is beyond the scope of this thesis but the conflict above raises two very important points. First, as long as the role of the informed consent facilitator is inextricably tied into the roles of physician and researcher, the informed consent process will remain compromised as very the primary interests of the physician, researcher, and informed consent facilitator are at odds with each other. And this in turn this highlights the importance of the role of ethics review: that it must not only be independent, but that ethics committees must also be aware of and seek to minimise this conflict whenever possible.

Relatives

This section is concerned with exploring the role and primary interests of third parties that are involved in the enrolment of mentally incapacitated subjects into research projects. Although the following discussion is concerned primarily with the relative/carer/legal representative taking on the role of the third party, it is recognised that there are other players that might be drawn into this process as third parties.⁴⁸⁷ As noted earlier, the role played by relatives fall squarely within Erde's social role, as incapacitated adults must rely on these proxies to make decisions or act on behalf of them. Also, unlike the physician/researcher, a person who acts as a proxy decision maker

⁴⁸⁷ For example – independent MCA advocates, independent third party assessors, etc ...

takes on a single social role, that of acting on behalf of the incapacitated adult. This being the case, it would seem logically obvious to conclude that in such cases the proxy decision maker is required to serve the welfare of the incapacitated adult and that there should be no difficulty in locating the primary interests of the relative or proxy decision maker and all that is required is a straightforward application of Thompson's notion of primary interests. Thompson, as described earlier, asserts that primary interests are determined by the professional duties of the role-holder and that there is normally agreement that they should be the primary consideration in any professional decision made by the role holder. Because the inclusion of third parties into the process of enrolling incapacitated adults into clinical trials in both Malaysia and England are governed by statutes, the primary interests of such parties should be discoverable by looking at the statutes. If Thompson is correct, there should be some agreement in the law regarding the primary considerations that should guide the actions of proxy decision makers.

The discussion below reveals that it is not the case and that while legislation is silent in Malaysia, the English legislation prescribes very different duties for third parties involved in the enrolment of mentally incapacitated adults in research projects. In fact, a perusal of the English statutes that provide for enrolment of incapacitated adults into research projects,⁴⁸⁸ provides a surprising picture with the Mental Capacity Act 2005 (MCA) found wanting and the Medicines for Human Use (Clinical Trials) Regulations 2004 (MHUR) providing a more satisfactory basis for proxy decision making.⁴⁸⁹

⁴⁸⁸ *Mental Capacity Act 2005*. and *The Medicines for Human Use (Clinical Trials) Regulations 2004 (as Amended by S.I 2006/1928 & 2984)*.

⁴⁸⁹ The result is surprising given the general ethos of the MCA, which is based on a set of laudable principles articulated in Section 1 of the Act. This is compared to the MHUR, which is based on GCP principles that are often more concerned with scientific accuracy and administrative efficiency rather than the protection of human subjects. For a more in-depth discussion of the relevant legislative provisions governing research with adults who lack capacity, see Biggs, Hazel.

This leads to two possible conclusions, first, that the primary interests of relatives are simply different depending on the different rules that apply to different research projects. This position is as demonstrated below, untenable given the absence of any rational justification for the different rules. The second conclusion is that it is not sufficient to look to either standards prescribed by law or professional bodies to determine the scope of primary interests of role holders, particularly when there is disagreement. The fact that certain role holders hold social roles as described by Erde, places these parties in special positions where certain obligations are placed upon them and these are normative obligations that are described in terms of their primary interests. Therefore in order to determine the proper remit of primary interests, it is necessary to examine the underlying basis for the creation of that particular social role.

Role of relatives in the Malaysian Context

As discussed in Chapter 2, there is no legislation in Malaysia that allows for any sort of proxy health care decision making for incompetent adult patients. There is also no law that regulates the running of clinical trials. It would thus seem that relatives have little or no role to play in the consent taking process, but this, as evidenced by interviews with psychiatrist/investigators, is not the case. Relatives do in fact play a significant role in the enrolment process of mentally incompetent patients. What then are the duties and responsibilities of relatives in such situations? While there is no guidance to be found in the existing law, there are two possible sources that may of some use. First, the Mental Health Act 2001(MMHA), which will, when it comes into force, allow relatives to provide consent on behalf of incompetent

Healthcare Research Ethics and Law: Regulation, Review and Responsibility. London: Routledge-Cavendish, 2010 at 129-139

adult patients to enrol into clinical trials;⁴⁹⁰ and the ICH-GCP, which recognises that 'legally acceptable representatives' may provide consent on behalf of mentally incapacitated adults.⁴⁹¹

The term relative is used to represent the role of the third party involved in decision-making in the rest of this section, as it is the term used in the MMHA to identify the person with proxy decision-making powers in relation to a mentally incompetent adult patient. The terms relative, carer, proxy decision-maker and legally acceptable representative are used interchangeably in the proceeding discussion.

Unfortunately, there is little help to be found in either the MMHA or the ICH-GCPs about the duties or responsibilities of relatives. The MMHA is silent as to the duties and responsibilities of relatives of mentally disordered persons and only provides for remedies where the mentally disordered person is either not under proper care and control;⁴⁹² or is being neglected or treated cruelly by a relative or any other person having charge of him.⁴⁹³ The ICH-GCP guideline⁴⁹⁴ makes no mention as to the duties or responsibilities of proxy decision-makers.⁴⁹⁵ In the absence of any guidance either in the Malaysian context or the ICH-GCP, it is instructive to consider the duties of such role-holders in the English context.

Role of relatives in the English context

⁴⁹⁰ Section 77(1)(b) *Mental Health Act 2001 (Act 615), Malaysia*.

⁴⁹¹ para 1.37 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

⁴⁹² *Mental Health Act 2001 (Act 615), Malaysia*. section 13(1)(a)

⁴⁹³ *Ibid.* section 13(1)(b)

⁴⁹⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Good Clinical Practice: Consolidated Guideline E6 (R1)."

⁴⁹⁵ The guideline refers to a proxy decision-maker as a 'legally acceptable representative', defined in para 1.37 as "an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial."

There are two pieces of legislation that provide for the participation of mentally incapacitated adults in research trials in England: the Mental Capacity Act 2005 (MCA) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (MHUR). Although clinical trials that enrol incapacitated adults fall under the remit of the MHUR and not the MCA, it is instructive to also consider the provisions of the MCA relating to research and the roles of relatives/carers. This is because even though both these Acts provide for some sort of proxy decision making role, the primary interests of the carer under the MCA differ significantly from the primary interests of the legal representative under the MHUR.⁴⁹⁶ This in turn reveals the difficulty with Thompson's assertion that primary interests are normally discoverable by agreement, or in this case, by reference to statutory requirements; and as will be argued re-enforces the notion that the nature of the social role played by a party should inform the determination of the primary interests of the role holder.

Primary Interests and the Mental Capacity Act 2005 (MCA)

Under the MCA, there is oddly enough no provision for proxy decision-making in relation to research involving mentally incapacitated adults. Such research is permitted provided certain requirements are met. The responsibility for meeting these requirements falls on the researcher carrying out the research.⁴⁹⁷ Prior to enrolment, researchers are required to do two things. First, obtain approval of 'the appropriate body';⁴⁹⁸ and second, consult persons who are caring for or are interested in the subjects' welfare (carers).⁴⁹⁹ When consulting the

⁴⁹⁶ For a good discussion on the reform of English law in relation to adults lacking capacity who participate in clinical trials, see McHale, Jean. "Law Reform, Clinical Research and Adults without Mental Capacity - Much Needed Clarification of a Recipe for Further Uncertainty?" In *First Do No Harm: Law, Ethics and Healthcare*, edited by Sheila Mc Lean. Aldershot: Ashgate Publishing Ltd, 2006.

⁴⁹⁷ Section 32 *Mental Capacity Act.*, para 11.8 *Code of Practice Mental Capacity Act 2005.*

⁴⁹⁸ Section 31 *Mental Capacity Act.* The 'appropriate body' in England is a research ethics committee recognised by the Secretary of State, para 11.10

⁴⁹⁹ *Ibid.* Section 32. These persons cannot be working in a professional capacity.

carer, the researcher is required to provide the carer with information about the project and ask for advice as to whether the subject should take part in the research; and for the carer's opinion as to the likely wishes and feelings of the subject about taking part in the research.⁵⁰⁰ This requirement can be likened in some ways to the proxy decision-making process in that the carer is asked to represent the likely wishes and feelings of the subject. However, unlike typical proxy decision-making processes where the role of the proxy is an active one, in that he provides the consent on behalf of the subject; the role of the carer/proxy under the MCA is passive as the carer/proxy only possesses a form of veto power in that if he advises that the subject would be likely to decline to take part in the process, the researcher is barred from enrolling the subject.⁵⁰¹

More importantly, the section does not impose any duties or responsibilities on the carer. Moreover, given the passive nature of the role played by the carer in this regard; that he is merely consulted on his opinion as opposed to the active role placed on the researcher to seek out the consultation and act upon it, it is contended that the carer cannot be said to be 'acting for or making a decision on behalf of a person who lacks capacity', and therefore he should not be subject to the duty to act in the best interests of the subject.⁵⁰² As far as participation in research is concerned, the parties who appear to be making decisions on behalf of and acting for incapacitated subjects are research ethics committees⁵⁰³ and the researchers.⁵⁰⁴ Because research ethics committees are only able to consider the interests of potential subjects as a group, they are unable to act in the in best of individual subjects, therefore the burden for ensuring the protection of the best interests of subjects must fall on the shoulders of the researcher. This

⁵⁰⁰ Ibid. Section 32(4)

⁵⁰¹ Ibid. Section 32(5)

⁵⁰² Ibid. Section 1(5)

⁵⁰³ Ibid. Section 31

⁵⁰⁴ Ibid. Sections 32-33

as discussed earlier, is an unsatisfactory position as the researcher is placed in an impossibly compromised situation. The absence of any duty placed on a third party to act in the best interests of a person who lacks capacity, leaves the person who lacks capacity in a most vulnerable position.⁵⁰⁵ Moreover, under the MCA, researchers are only required to act upon a carer's opinion regarding the possible reluctance of a subject to take part in research. If, as argued in Chapter 3, the true basis of human subject protection is the respect for human dignity, and that in respect of incapacitated adults, this embraces more than just a negative duty to not harm them, the role carved out for carers under the MCA leaves a great deal to be desired.

Primary Interests and the Medicines for Human Use (Clinical Trials) Regulations 2004 (MHUR)

The second piece of legislation, the MHUR, incorporates GCP principles and as such recognises the notion of proxy consent which is provided by a 'legal representative'. It also spells out the principles that apply to proxy decision-making in relation to an incapacitated adult.⁵⁰⁶ Two of these principles relate to the role of the 'legal representative', they are:

- 1) The consent provided by a legal representative shall represent the adult's presumed will;⁵⁰⁷ and
- 2) The interests of the patient always prevail over those of science and society.⁵⁰⁸

Under the MHUR, the primary interests of the legal representative appear to be twofold. First, to discover as far as is possible, the will of the incapacitated adult and second, to ensure that the adult's interests prevail over the interests of science and society.

⁵⁰⁵ While the MCA does not provide specific insight into the primary duties of carers or proxy decision makers, there is much to recommend it as a guide to making decisions for people who lack capacity.

⁵⁰⁶ Paras 12 – 15, , Part 5, Schedule 1 *The Medicines for Human Use (Clinical Trials) Regulations 2004 (as Amended by S.I 2006/1928 & 2984)*.

⁵⁰⁷ Ibid. Para 12, Part 5, Schedule 1

⁵⁰⁸ Ibid. Para 15, Part 5, Schedule 1

The MHUR provides a very different conception of the role and primary interests of the relative⁵⁰⁹ as compared to the MCA, which does not provide for any proxy decision making process and places the burden of recruiting incapacitated adults on the researchers, who are only required to act on the opinion of relatives about possible objections of subjects. In contrast to this, the MHUR provides for proxy decision-makers and prescribes the principles that they should be guided by. Notably, there is no rational reason why the primary interests of relatives under the MCA should be any different from those under the MHUR. They both provide mechanisms, which allow people who lack decisional capacity to participate in medical research projects. The only difference between the research projects carried out under the MCA and the MHUR is that research projects under the MHUR involve testing medicinal products.⁵¹⁰ Take for example a situation where two research projects are being conducted at Hospital X: Project A, which involves investigating the therapeutic potential of deep brain stimulation (by implanting electrodes into targeted locations of the brain) as a treatment for patients with moderate to severe Alzheimer's disease; and Project B, which entails investigating the therapeutic effects of Memantine⁵¹¹ on patients suffering from moderate to severe Alzheimer's disease. Mr M, who is suffering from severe Alzheimer's disease and is a patient at hospital A is approached by Doctors A and B from Projects A and B respectively, about participating in their research projects. He can only choose to enter into one research project. Both investigators conclude that Mr M lacks the capacity to decide for himself. Mr M's wife, Mrs M, has been dutifully taking care of him throughout his illness and by all accounts they seem to share a loving

⁵⁰⁹ As stated earlier, the term relative is used to represent any party who has some sort of proxy decision-making power and here would include the role of carer as well as legal representative.

⁵¹⁰ Medicinal products are defined by reference to Article 1 of Directive 2001/83/EC or S 130 of the Medicines Act 1968, see regulation 2, *The Medicines for Human Use (Clinical Trials) Regulations 2004 (as Amended by S.I 2006/1928 & 2984)*.

⁵¹¹ Memantine is a new drug that is showing promising results in reducing the clinical deterioration of patients suffering from moderate to severe Alzheimer's disease. See Barry Reisberg et al., "Memantine in Moderate-to-Severe Alzheimer's Disease," *N Engl J Med* 348, no. 14 (2003).

relationship. Doctor A, whose project falls under the MCA, has a chat with Mrs M. and asks for her opinion as to her husband's wishes and specifically whether she thinks that her husband would have objected to participating in the trial. Doctor B, however, whose project falls under the MHUR, tells Mrs M that she must decide whether or not to enter her husband into the trial based on what she thinks he would have wanted and that she must consider his interests above that of society in general (she mustn't make a decision based on 'the right thing to do' because it would benefit other patients at a later date) and that she will be required to sign a consent form on behalf of her husband. Mrs M is uneasy about providing consent for Project B, as she is unsure about where her husband's best interests might lie and she is also uncomfortable about the responsibility of signing a consent form. Mr M is eventually entered into Project A by Dr A, as Mrs M could not think of any specific objections that Mr M might have had about taking part in the project, and she was in fact relieved that the final decision to enrol her husband would be taken by his doctor, who would surely act in her husband's best interest. It is difficult to see any reason why Mrs M's role should be any different depending on whether her husband enrolls in project A or B. Both projects involve giving her husband some form of treatment; they both have the potential to confer some benefit on her husband; and both will involve subjecting her husband to certain levels of risk.

Discussion

The fact is that under English law, the responsibilities (and as Thompson would argue, the primary interests) of relatives differ greatly depending on whether a research project falls under the MCA or the MHUR. Therefore, Thompson's assertion that primary interests can be discovered by looking to practice or agreement cannot stand. The better approach to determining the primary interests of relatives is to consider the underlying basis of requiring some sort of input from

a third party (in this case, relatives) in the consent taking process involving adults who lack capacity.

As noted earlier, the informed consent process is a vital component of human subject protection. A person needs to be able to understand the nature of the research trial and the attendant risks and benefits thereof, if he is to make an informed choice whether or not to participate. To deny him that choice is to treat him as a means to an end, and thereby fail to respect his human dignity. When a potential subject lacks the capacity to understand the information provided, someone else must make the decision for him and in a normal consent process; the only other person involved is the investigator/physician. This is by no means ideal as the investigator is already working from a position where his interests as physician and investigator are in conflict.⁵¹² This being the case, the function of admitting a third party into the decision making process must be to ensure that the informed consent process achieves its goal of human subject protection. How exactly this should be achieved and what the precise role of the third party/relative should be is beyond the scope of this thesis but the relevant idea that emerges from this discussion is that the primary interest of the relative should be the protection of the subject who lacks capacity, and that the guiding principle that relatives should be led by is that of respecting the human dignity of the subject.⁵¹³

Research Ethics Committees

The determination of the primary interests of research ethics committees is a much less contentious issue, as there appears to be

⁵¹² See the discussion in section 5.4.3.1

⁵¹³ See the discussion in Chapter 3, section 3.3.2 and 3.3.3

general agreement on the responsibility of the committees. The ICH-GCP⁵¹⁴ notes that

“...the primary responsibility of the committees is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.”

Similarly, Directive 2001/20/EC relating to the implementation of GCP in the conduct of clinical trials in European Member States, states that ethics committees have a responsibility “to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection...”⁵¹⁵ This has been implemented in the United Kingdom by the MHUR. This view is also echoed by the US Food and Drug Administration’s Rules and Regulations which state that the primary purpose of ethics review is to “assure the protection of the rights and welfare of the human subjects.”⁵¹⁶

(3) When can it be said that interests other than primary interests amount to secondary interests?

Not all interests other than primary interests will amount to secondary interests. A secondary interest is an interest that unduly influences the judgment of a role holder concerning a primary interest, resulting in a CI. ⁵¹⁷ Because one of the features of the social role held by the role holder is that the beneficiary is required to rely on the role holder to

⁵¹⁴ Para 1.37 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

⁵¹⁵ Article 2(k) *Directive 2001/20/EC*, (4 April 2001).

⁵¹⁶ 21 CFR 56

⁵¹⁷ Thompson, Dennis F. "Understanding Financial Conflicts of Interest." *N Engl J Med* 329, no. 8 (1993): 573-76.

use his powers in a way that serves the welfare of the beneficiary, the beneficiary must be able to trust the person or the position associated with the role. The existence of unrecognised and unchecked secondary interests is detrimental to this relationship. Secondary interests are therefore undesirable even though they may not cause any harm to specific beneficiaries, because the harm that inevitably eventuates is to the integrity of the social role. Thus it is important to be able to recognise and name secondary interests for what they are and to endeavour to minimise their impact on the role holder.

When then can it be said that an interest is a secondary interest? The following section explores this question beginning with Thompson's account of secondary interests, which while insightful in some respects, is on the whole, rather simplistic as it fails to recognise the multidimensional nature of secondary interests. This multidimensional nature is explored using Erde's analysis, which considers how secondary interests may be drawn from both individual motives and social structures that may operate on their own or simultaneously. This account of secondary interests provides a sounder basis for management of CIs.

Thompson's discussion

Thompson's discussion on secondary interests focuses on what they are not. He identifies two characteristics of secondary interests in this way; first, that they are not usually illegitimate and in fact may be necessary and desirable (for example, the preference for family and friends).⁵¹⁸ Second, he points out that CIs are not just another choice between competing values and that regarding secondary interests as just another set of competing values, dilutes the conception of CIs and gives the impression that the conflict is inevitable and cannot be

⁵¹⁸ Ibid.

avoided. The highly charged abortion debate, in which entrenched pro-life and pro-choice values are locked in an unavoidable and seemingly irresolvable tussle is an example of a situation involving conflicting values, but not conflicting interests. The problem in a CI situation, he states, is that “both claims have a presumptive claim to priority and the problem is to ensure that the [secondary] interest does not dominate”.⁵¹⁹ He locates the distinctive nature of CIs as being the asymmetry between interests.

Although Thompson makes some important observations regarding the characteristics of secondary interests, he fails to provide a satisfactory answer to the question of when interests other than primary interests amount to secondary interests. First, when he points out the fact that secondary interests are not usually illegitimate but necessary and desirable, he does not carry on to supply the necessary tools that will enable accurate identification of secondary interests. Second, his assertion that the existence of an asymmetry between interests lies at the crux of CIs, while insightful, fails to explore the basis of the asymmetry. What is it about the nature of an interest that transforms it from being just a competing interest into a conflicting (secondary) interest? Erde’s analysis of secondary interests provides a more three dimensional picture of secondary interests.

Erde’s analysis

It is worthwhile to note at this juncture that Erde never talks about the notion of primary and secondary interests and that the definition of CIs he puts forward (albeit reluctantly) is that “[CIs] are either motives that caregivers have and/or situations in which we could reasonably think caregivers’ responsibilities ... are or will be compromised to an

⁵¹⁹ Ibid.

unacceptable degree.”⁵²⁰ This tentative definition provided by Erde when read as a whole is not very different from Thompson’s. However, instead of the notion of secondary interests that unduly influence primary interests, Erde offers up the idea of personal motives and social structures that operate to compromise primary interests.⁵²¹ By exploring and incorporating Erde’s language of personal motives and social structures into the larger more general notion of secondary interests, it is possible to develop not only a richer understanding of secondary interests, but also a sounder basis for designing tools to identify these interests.

Motives

Motives according to Erde are either universal to the human condition or personal to individuals. CIs are not concerned with universal motives because they would apply to all people in all circumstances with equal force and as they would always apply regardless of circumstances, it would be pointless to include them. CIs are therefore concerned with personal motives. He puts forward the argument that personal motives arise from (1) ideals, (2) practical interests, and (3) gut instincts or predilections.⁵²² Ideals are “the values that provide a person with a sense of calling or meaning”; they are intrinsic rather than instrumental; and derive from religious, professional or personal values.⁵²³ Practical interests on the other hand, are instrumental in nature and represent a person’s sense of the worth of material elements. Examples of practical interests are concern for personal safety, emotional resources, financial well-being. Predilections are dispositions to value something positively or negatively and might be justified or prejudicial; rational or irrational. They include among other things, hobbies, animosity, and the bonds of friendship.

⁵²⁰ Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." at 33

⁵²¹ Erde does not, as stated earlier speak of primary or secondary interests.

⁵²² Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." at 23

⁵²³ Ibid. at 20

The benefit of adopting Erde's discourse on personal motives into the determination of secondary interests is twofold. First, it allows the discussion to move beyond the previously discussed, often held narrow view that CIs are only concerned with economic gain. In this model, economic gain, which is a personal motive based on practical interests, represents only one of the many possible sources of secondary interests. More importantly, by breaking down and describing different types of possible motives, it provides a starting point for constructing a practically useful framework for identifying the sources of secondary interests.

Not all personal motives, however, will amount to secondary interests. What transforms a motive into a secondary interest⁵²⁴ is dependent on whether or not that motive unduly influences the primary interests of a person holding a particular social role. The fact that secondary interests are said to 'unduly influence' primary interests must mean that there is some level of influence that is considered legitimate and only undue influence is to be rejected. The responsibilities of a role holder do not "mandate forsaking all self-regard",⁵²⁵ and that some cases of self-regarding actions are tolerable. Erde offers the example of a physician who because she has an incidental wound of her own, refuses to put her ungloved hands into a patient's blood for fear of contracting HIV; and suggests that her refusal would not invite moral censure. The problem with accepting this notion of tolerable self-regard is that not all people are made up of the same moral fibre. What is harmless to the heroic is great peril to the faint-hearted. Tolerability must therefore be an objective standard set by the standard of a person of normal fortitude; neither hero nor coward. The question then to be asked is whether a person has a personal motive to act in a way that is

⁵²⁴ That is an interest that unduly influences a primary interest, or as Thompson would say, is asymmetrical to the primary interest.

⁵²⁵ Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." at 30

unacceptable and inconsistent with the primary interests of the social role he has undertaken? Does he have any ideals, practical interests or predilections that might unduly conflict with his social role?

Erde makes a perceptive observation about the nature of the conflict in this sort of situation when he points out that a conflict can exist in a situation where observers might objectively question the objectivity of a person even without the person feeling or knowing that he is in a CI situation.⁵²⁶ Take for example, ethics committee member, Dr Q, who is on a panel reviewing a protocol submitted by his best friend, Dr T. Prior to the ethics committee meeting, Dr Q and Dr T have several private discussions about the merits of the trial, during the course of which, Dr T manages to persuade a sceptical Dr Q about the merits of the research trial. At the ethics review committee, Dr Q has no problems supporting the protocol because he now honestly believes in the soundness of the trial. He does not experience any sense of dilemma. However, an observer might feel that Dr Q's close friendship with Dr T has influenced his decision and whether or not he realises it, Dr Q is in a CI situation. More importantly, regardless of whether or not Dr Q's judgment has been influenced by a personal motive (in this case based on a predilection – friendship), an existing close friendship between an ethics committee member and an investigator submitting a protocol for review presents the appearance of a CI.

Social Structures

This leads to the second feature of secondary interests - that they arise not only from personal interests, but can also be created by situational or social structures. In the abovementioned example, the situational structure where Dr Q and Dr T share a friendship, regardless of the

⁵²⁶ Ibid. at 25.

influence of the friendship on the personal motives of Dr Q, results in the creation of a secondary interest. Similarly, as discussed in greater detail in later in the chapter, the appointments of senior faculty members as chairpersons of academic ethics committees constitute CIs, whether or not chairpersons themselves experience a sense of dilemma.⁵²⁷

Secondary interests may thus operate at two levels: first, at an individual level depending on the personal motives that drive individuals; and second at a structural level, where the duties and responsibilities attached to certain social positions infect their role holders with secondary interests (regardless of whether or not they have any personal motives or experience any dilemma). Accepting that secondary interests are engaged at both these levels is to recognise the importance of not only protecting against CIs that actually occur, but also against the appearance of CIs. Erde maintains and rightfully so, that the “distinction between *having a* [CI] and *having the appearance of a* [CI] is most likely bogus, radically overdrawn or misused...”⁵²⁸ His reasons, however, for making this assertion, which are based on his claim that having a CI is not dependent on the existence of conflict, and the general misconception that only individuals can have CIs, fail to take into account a much more compelling reason, that is that the social role upon which the CI operates is a relationship that is based on trust. Beneficiaries, in this case, mentally incapacitated subjects, have no choice but to place their trust in the social roles that have been created to safeguard their interests. They must rely on the parties that engage in the enrolment/consent process and ethics committees to act in their best interests, to respect their human dignity. The mere

⁵²⁷ An interesting counterpoint to this is that the experience of a dilemma alone does not necessarily point toward a COI. Erde uses the example of a physician struggling to decide whether or not to feed an anencephalic baby who lacks a sucking reflex. In this case, there is no asymmetry between the interests and this example would fall under Thompson’s description of competing interests and not conflicting interests.

⁵²⁸ Erde, "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." at 8

appearance of bias or undue influence compromises the integrity of these social structures and diminishes trust. The importance of the social role of human subject protection requires that there is no distinction between actual and perceived CIs. Consequently, this realisation necessitates taking Thompson's definition one step further to say that secondary interests are not only those that unduly influence primary interests, but also those that appear to unduly influence primary interests.

Therefore, secondary interests are defined as motives and social structures that unduly influence or might appear to unduly influence the primary interests of a person holding a particular social role.

Secondary Interests and the Informed Consent Process

As the focus of this thesis is the role of ethics committee review as a vehicle of human subject protection, a detailed discussion of the issue of secondary interests that bedevil the participants in the informed consent process is beyond the scope of this paper. It is however, important to point out some of the types of secondary interests that impact on physicians/researchers and relatives who participate in this process as it serves as a strong reminder that the informed consent process, as a mechanism for human subject protection is at best, unsafe. There are two lessons that should be learned from this. First, that ethics review is that much more vital given the CIs inherent in the informed consent process and second, that ethics committees need to be able to recognise the pervasive nature of CIs in the consent taking process.

Secondary interests and the physician/researcher

As noted earlier, the role of informed consent facilitator in therapeutic clinical trials is taken up by the physician/researcher, which results in

an untenable position of clashing primary interests. Closely tied with this issue is the prevalence of secondary interests that bedevil the informed consent process. Significantly, these secondary interests are generally present as a direct result of the multiple roles held by the informed consent facilitator. Because the informed consent facilitator is at the same time a physician and a researcher, the traditional areas of conflict of interest associated with roles of physician and researcher inevitably become attached to the role of the informed consent facilitator. The section below describes some of the secondary interests that are commonly associated with the physician/researcher in clinical trials. The discussion considers secondary interests that arise from motives as described by Erde and focuses on two types of motives, ideals and practical interests.

Motive as a secondary interest

Ideals

As noted earlier, physicians/researchers are also subject to a form of therapeutic misconception, arising from an “intensive and protracted process of professional socialisation as clinicians”.⁵²⁹ Their propensity to equate clinical trials with medical care, presents the danger of undermining the informed consent process as they are no longer functioning as impartial informed consent facilitators (their primary interest), but as clinicians promoting a particular course of treatment.

Another secondary interest that arises from the ideals of a physician/researcher, which has the potential to undermine the primary interests of an informed consent facilitator, is the research imperative. This has been noted by Levinsky,⁵³⁰ who notes that in some cases, investigator zeal, namely the desire to advance knowledge can also operate as a secondary interest. The physician/researcher in such cases arrives at the informed consent process stage convinced of the

⁵²⁹ Miller, Rosenstein, and DeRenzo, "Professional Integrity in Clinical Research." at 1450

⁵³⁰ Norman G. Levinsky, "Nonfinancial Conflicts of Interest in Research," *N Engl J Med* 347, no. 10 (2002). at 759

vital need for a particular type of research and this strong conviction is likely to colour the discussion he will have with potential trial subjects.

Practical interests

Economic gain, unlike investigator zeal and the therapeutic misconception, is instrumental in nature, and as such is a practical interest. As noted in the earlier part of the chapter, CIs have been traditionally associated with economic interests and as such, these interests are often viewed as raising the greatest concern in the research environment.⁵³¹

There are two routes by which economic interests are injected into the physician/researcher role. The first and the most common, is by way of interactions with the pharmaceutical industry.⁵³² Gifts, payment for meals, attendance at lectures and conferences, scholarships, payment for speakers, provision of ghost writing services, provision of pharmaceutical supplies, grants for research projects and payments for consulting relationships are cited as typical examples of interactions with industry.⁵³³ Direct economic incentives are also commonly offered to researchers by way of recruitment incentives.⁵³⁴ Because of the high stakes involved in drug development, pharmaceutical companies are constantly under a great deal of pressure to produce new drugs as

⁵³¹ The International Committee of Medical Journal Editors has identified this as the most important conflict of interest. Sheldon Krimsky and L. S. Rothenberg, "Financial Interest and Its Disclosure in Scientific Publications," *JAMA* 280, no. 3 (1998). at 225

⁵³² An excellent article that examines the relationships between physicians and drug companies at the turn of the 21st century, which portrays how it begins in medical school and continues throughout the physicians' careers is David Blumenthal, "Doctors and Drug Companies," *N Engl J Med* 351, no. 18 (2004).. Also see Kassirer, "Financial Conflict of Interest: An Unresolved Ethical Frontier."

⁵³³ Troyen A. Brennan et al., "Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers," *JAMA* 295, no. 4 (2006). at 430. The pharmaceutical industry is estimated to spend approximately \$12 billion annually on gifts and payments to physicians. D Katz, AL Caplan, and JF Merz, "All Gifts Large and Small: Towards an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving," *American Journal of Bioethics* 3, no. 3 (2003).

⁵³⁴ J Bryant and J Powell, "Payment to Healthcare Professionals for Patient Recruitment to Trials: A Systematic Review," *BMJ* 331, no. 7529 (2005). at 1377.

quickly as possible and as such are willing to pay researchers for the rapid recruitment of sufficient numbers of patients into trials.⁵³⁵

Evidence⁵³⁶ suggests that industry focuses more attention on certain groups of physicians, notably, academic researchers. An Australian survey⁵³⁷ of medical specialists found a significant correlation between research collaboration and an increasing number of ties⁵³⁸ with industry. One of the reasons forwarded for this phenomenon is that academic researchers are perceived to be opinion leaders who are likely to influence the behaviour of other physicians. Their opinions are also more likely to be positively received by medical students they have come into contact with and in addition to this, prescribing patterns practiced by academic physicians/researchers are likely to be mimicked by students as there is some evidence that physicians establish their prescribing patterns while still at university. Therefore, researchers in general, and academic researchers in particular are more likely than not to have had substantial interactions with industry that involve economic interests. The extent to which these interactions exist is well illustrated by an article on psychotropic drugs in the *New England Journal of Medicine*, where declarations of financial conflicts of interests of the authors consumed nearly three single-spaced typewritten pages.⁵³⁹

The question to be asked then is whether interactions with industry have any effect on physician/researcher behaviour? An oft cited article notes that physicians who interacted with pharmaceutical companies

⁵³⁵ Manufacturers are said to offer investigators US\$2000 to \$5000 per patient in certain cases. Morin et al., "Managing Conflicts of Interest in the Conduct of Clinical Trials." at 81

⁵³⁶ Eric G. Campbell et al., "A National Survey of Physician-Industry Relationships," *N Engl J Med* 356, no. 17 (2007).

⁵³⁷ David Henry et al., "Ties That Bind: Multiple Relationships between Clinical Researchers and the Pharmaceutical Industry," *Arch Intern Med* 165, no. 21 (2005).

⁵³⁸ Ties were defined as specific interactions that were likely to involve a degree of reciprocity. Ibid. at 2943

⁵³⁹ Kassirer, "Financial Conflict of Interest: An Unresolved Ethical Frontier." at 154 referring to the article

were nine to twenty one times more likely than other doctors to have requested a drug made by the company.⁵⁴⁰ In the research arena, a review of the literature on financial relationships between industry, scientific investigators and academic institutions carried out in 2003,⁵⁴¹ found that not only were these relationships pervasive; but that where such relationships existed, research results tended to be pro-industry and were likely to be subject to publication delays and withholding of data.

Admittedly, not all interactions between physician/researchers and industry involved large gifts or sums of money and some physicians contend that small gifts fail to influence their behaviour.⁵⁴² However, a number of compelling research findings demonstrate that this is a fallacy.⁵⁴³ Social science research has demonstrated that even small gifts can exert powerful influences on recipients to reciprocate whether or not they are conscious of it.⁵⁴⁴

There is clear and compelling evidence that interactions between industry and physicians/researchers have the potential to distort and disrupt the scientific validity of clinical trials. How then does this translate into a CI in the informed consent process? Apart from the direct financial interest in receiving recruitment incentives, the impact

⁵⁴⁰ MM Chren and CS Landefeld, "Physicians'behavior and Their Interactions with Drug Companies: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary," *Obstetrical & Gynecological Survey* 49, no. 8 (1994).

⁵⁴¹ Bekelman, Li, and Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review." 463, also see Joel Lexchin et al., "Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review," *BMJ* 326, no. 7400 (2003). who confirmed and extended the study by adding another 16 studies to the 5 studies identified by Bekelman et al.

⁵⁴² Anita Damle, "Build Rather Than Burn Bridges," *BMJ* 338, no. feb24_1 (2009).

⁵⁴³ Blumenthal, "Doctors and Drug Companies.", Katz, Caplan, and Merz, "All Gifts Large and Small: Towards an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving.", M Chren, "Interactions between Physicians and Drug Company Representatives," *The American Journal of Medicine* 107, no. 2 (1999).

⁵⁴⁴ Katz, Caplan, and Merz, "All Gifts Large and Small: Towards an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving." The article describes how the success secret of the world's record holder for car sales was to send mass-produced greeting cards to his customers every month printed with the phrase "I like you" (at 41)

of industry interactions with physicians/researchers on the informed consent process is that it affects the ability of physicians/researchers to be objective in relation to clinical trials that are sponsored by industry. Regardless of whether the interactions involve large or small sums of money, physicians/researchers are drawn into relationships of reciprocity within which they are likely to view participation in clinical trials as something that is to be encouraged.

The second route by which economic interests might operate as secondary interests is when physicians/researchers have equity interests in either the pharmaceutical companies sponsoring the trials, or the trial drugs. In practice, this is not really an issue in Malaysia, as almost all patents for trial drugs are held by researchers or companies in developed countries.

Apart from economic interests, another type of practical interest that has been described as “potent” is the desire for career advancement. Publications of research results and maintaining grant support are viewed as “academic currency that buys prestige and promotion”.⁵⁴⁵ A report published by the Forum for Institutional Review Boards in Canada and the United States (FOCUS) pursuant to its 2004 International Conference on Conflicts of Interest, noted that the “largest conflict in universities has to do with the process of promotion in tenure”.⁵⁴⁶ For many physicians/researchers in Malaysia, running pharmaceutical sponsored trials will provide them with the best opportunities to publish in peer reviewed journals, which in turn will enhance their prospects for promotion and as such, they may be very keen to show sponsors how efficient they are at among other things, recruiting the subjects needed for the trials. The prospect of career

⁵⁴⁵ Levinsky, "Nonfinancial Conflicts of Interest in Research." at 759

⁵⁴⁶ (Forum for Research Ethics Boards (REBs)/Institutional Review Boards (IRBs) in Canada and the United States FOCUS, "Report on an International Conference on Conflict of Interest," in *FOCUS International Conference on Conflict of Interest* (Washington DC, USA: National Council on Ethics in Human Research, 2004). pg 15

advancement and professional prestige is potentially a greater inducement for researchers from countries such as Malaysia, where significant financial gain through equity holdings is unlikely.

Secondary interests and caregivers/relatives

Caregivers/relatives of mentally incompetent adults may also be subject to the influence of secondary interests. Like physicians/researchers, the secondary interests that are likely to affect caregivers will in all probability arise from motives rather than social structures. However, unlike physicians/researchers, the secondary interests of caregivers/relatives are more complex in nature and harder to define as the interests of carers are so closely intertwined with the interests of the incompetent adults, to the point that it is sometimes almost impossible to separate them. Take for example a situation where an elderly Muslim man suffering from severe dementia is considered for recruitment into a clinical trial studying a new and promising drug for the treatment of dementia. Because he is certified as incompetent to provide consent, his daughter, who is his caregiver and closest relative, is asked to provide consent on his behalf. When reading the patient information sheet, the daughter notes that the drug contains porcine material. Although the daughter is aware that her father, if competent, would have been vigorously opposed on religious grounds to taking such a drug, she herself does not feel strongly about the Muslim religion and feels that it is far more important that her father participate in the trial because it might improve his condition. In this case, the secondary interests that operate on the daughter stem from first, her personal ideals about the importance of Islam, which are very different from her father's personal ideals.

In addition to this, she has practical interests in the possibility that the treatment might improve her father's condition. (In fact, research has shown that when proxies are asked the reasons for enrolling incompetent adults into clinical trials, they almost always include hope for direct benefit or a sense of desperation in finding some way of relieving the patients' conditions.⁵⁴⁷) An improvement in her father's condition would be likely to relieve her of some of the stresses of caring for him. Individuals that care for others suffering from diseases and conditions that affect cognitive function, are recognised as being in danger of suffering what is called 'caregiver strain'. Caregivers such as the daughter in the abovementioned example are likely to suffer from significant financial, social and economic strains.⁵⁴⁸ Research⁵⁴⁹ has demonstrated that where patients suffer from chronic disorders such as Parkinson's Disease,⁵⁵⁰ the level of strain experienced by caregivers increases significantly as the disease advances and patients are less able to care for themselves. In addition to this, caregivers themselves are also at risk of developing mental health problems⁵⁵¹ and suffering from general poor health.⁵⁵² Therefore in the example given above, secondary interests in being relieved of her 'caregiver strain' and

⁵⁴⁷ See Jeremy Sugarman et al., "How Proxies Make Decisions About Research for Patients with Alzheimer's Disease," *Journal of the American Geriatrics Society* 49, no. 8 (2001)., Jason H.T. Karlawish et al., "How Do Ad Patients and Their Caregivers Decide Whether to Enroll in a Clinical Trial?," *Neurology* 56, no. 6 (2001)., P. Elad et al., "Demented Patients' Participation in a Clinical Trial: Factors Affecting the Caregivers' Decision," *International Journal of Geriatric Psychiatry* 15, no. 4 (2000).

⁵⁴⁸ See Frank D. Gianfrancesco, Ruey-hua Wang, and Elaine Yu, "Effects of Patients with Bipolar, Schizophrenic, and Major Depressive Disorders on the Mental and Other Healthcare Expenses of Family Members," *Social Science & Medicine* 61, no. 2 (2005). This article provides an overview of the literature that demonstrates the effect of care giving.

⁵⁴⁹ J. H. Carter, B. J. Stewart, P. G. Archbold, I. Inoue, J. Jaglin, M. Lannon, E. Rost-Ruffner, M. Tennis, M. P. McDermott, D. Amyot, R. Barter, L. Cornelius, C. Demong, J. Dobson, J. Duff, J. Erickson, N. Gardiner, L. Gauger, P. Gray, B. Kanigan, B. Kiryluk, P. Lewis, K. Mistura, T. Malapira, M. Pay, C. Sheldon, L. Winfield, K. Wolfington-Shallow and K. Zoog, "Living with a person who has parkinson's disease: The Spouse's perspective by stage of disease" (1998) 13 *Movement Disorders* 20-28.

⁵⁵⁰ This account holds true for most mental health and neurological conditions that result in cognitive dysfunction

⁵⁵¹ In particular, depression and anxiety - estimates of the prevalence of depression in caregivers range from as high as twenty-five to fifty percent. Jason H. T. Karlawish and David Casarett, "Addressing the Ethical Challenges of Clinical Trials That Involve Patients with Dementia," *J Geriatr Psychiatry Neurol* 14, no. 4 (2001). at 224

⁵⁵² Gianfrancesco, Wang, and Yu, "Effects of Patients with Bipolar, Schizophrenic, and Major Depressive Disorders on the Mental and Other Healthcare Expenses of Family Members."

prudential concerns may influence the daughter's decision to enrol her father in the trial. However, given the manner in which their interests are linked, it may very well be the case that the furtherance of the daughter's practical interests are linked to the best interests of the father as "there is no way to detach the lives of patients from the lives of those who are close to them"⁵⁵³. There will undoubtedly be a direct correlation between the levels of strain experienced by the daughter and the standard of care offered to her father. So it is not so easy to declare these interests as forming secondary interests that must be excluded from the decision making process.

While it is beyond the scope of this thesis to delve into the intricacies of the interests of caregivers and their wards, what is evident from the discussion above is that caregivers who act as proxy decision makers are potentially acting from positions where they might have secondary interests that conflict with their primary interests. As the above discussion has demonstrated, both parties to the informed consent process: the physician and the caregiver, are likely to be in positions of conflicts of interest. Therefore, it is clear that the consent process as it stands cannot be considered an effective way of protecting the interests of a mentally incompetent adult. There needs to be a radical rethinking of the way in which the informed consent process is carried out in relation to clinical research. The question that needs to be answered now is whether anything can be done to improve the level of protection provided by the informed consent process given the systems and the mechanisms that are currently in place? The arrow then must surely point to the ethics review process, as it is the only other mechanism for protecting the rights of human subjects. If the ethics review process is to provide some level of redress, two things must be present. First and foremost, ethics committee members must be cognisant of these matters, and this goes to the issue of how members are trained and

⁵⁵³ John Hardwig, "What About the Family?," *The Hastings Center Report* 20, no. 2 (1990). at 5

whether or not they are able to engage in meaningful discussions about the ethics of human subject research.⁵⁵⁴ In addition to this, there must also be a spirit of independence and engagement whereby committees are willing and able to impose obligations on researchers such as requiring independent third party assessors to be present during the informed consent process.

Secondary Interests and Research Ethics Committees

The final portion of this chapter considers whether research ethics committees themselves are subject to secondary interests, which compromise their independence. The importance of having an independent research ethics committee cannot be overstated. First, as pointed out at the outset of this chapter, the *raison d'être* of establishing a system of ethics review was to inject an independent evaluation of proposed research projects, as investigators were no longer trusted with the sole responsibility for protecting human subjects. If ethics committees are not independent, they lose the very reason for their existence. Also, having recognised that the informed consent process is mired in an environment replete with conflicts, the burden of recognising and acting against these conflicts must lie with ethics committees and to fulfil this task, they must in turn be independent themselves.

The following section will describe the types of secondary interests that ethics committee members are likely to have. Secondary interests as far as ethics committees are concerned are likely to arise from both personal motives as well as social structures.⁵⁵⁵ The first part of this section will consider the types of secondary interests that originate

⁵⁵⁴ This goes to the argument that at present, ethics committees are engaged not in meaningful ethics discourses, but rather in administrative 'ticking of boxes'. One reason for this being the inaccessibility of current ethical guidelines and principles. This is then remedied by applying the notion of respecting human dignity. See discussion in Chapters 3 and 4.

⁵⁵⁵ For a discussion of the types and sources of secondary interests, see section 5.4.4

from personal motives and the second part will discuss the social and institutional structures which create these secondary interests.

Secondary Interests based on personal motives

As noted earlier, personal motives can arise from three sources: ideals, practical interests and predilections.

Ideals as personal motives

Ideals are among other things, formed by the values that individuals hold to be important. People may learn or come to adopt certain values depending on the societies they live in, the religions they believe in, the experiences they share and in this instance, perhaps most vitally, the education and training they receive both prior to becoming ethics committee members as well as after their appointments. While ethics committee members are expected to act impartially when making their decisions, it is impossible to imagine that their ideals will not in some way influence their deliberations. Given that the task of ethics review is to consider the interests of subjects, and that subjects are likely to be drawn from many different cultural, religious and educational backgrounds; it stands to reason that ethics committees should also be made up of people from different walks of life, who are able to bring their different experiences and values to the discussion. It is important to bear in mind that the different ideals that different people bring into the ethics review process are not necessarily sources of secondary interests.⁵⁵⁶ Just because a situation may involve competing values,

⁵⁵⁶ However, Eckenwiler makes a valuable observation that IRB members are as a whole, likely to be drawn from more privileged social groups as compared to subjects and as such, their imaginings with respect to subjects interests are likely to be 'faint depictions'. Lisa Eckenwiler, "Moral Reasoning and the Review of Research Involving Human Subjects," *Kennedy Institute of Ethics Journal* 00011, no. 00001 (2001). at 46-47. Also see Department of Health, "Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees," (Department of

does not mean that the situation involves a CI. For a secondary interest to exist, it must be shown that it unduly influences or might appear to unduly influence the primary interests of a person holding a particular social role.⁵⁵⁷ Therefore the ideals or values held by ethics committee members will only constitute secondary interests insofar as they unduly influence the primary interest of ethics committee members, which is the protection of human subjects. In the situation above, this is not necessarily the case as an ethics committee that is made up of a good balance of people who hold different values, where competing ideals are discussed and debated, is likely to provide better protection to human subjects and consequently, these different ideals cannot be said to be secondary interests.⁵⁵⁸

What is however, a potential source of secondary interests in this respect is the fact that the membership of ethics committees in Malaysia is heavily skewed in favour of scientific/clinically-trained persons.⁵⁵⁹ The Medical Research Ethics Committee that oversees all clinical research trials carried out under the aegis of the Ministry of Health has a membership of 18 people, 17 of which are either clinicians or scientists and a single lay person. The research ethics committees at academic medical centres are of much the same ilk. At the University of Malaya, seven out of ten members are scientists or clinicians; at the National University of Malaya (UKM),⁵⁶⁰ sixteen out of eighteen members are scientists or clinicians; at University Putra

Health, 2005). 10, which points out that in the UK, RECs are not sufficiently representative of community diversity

⁵⁵⁷ For a fuller discussion of secondary interests and the notion of competing interests, see the discussion section 5.4.4

⁵⁵⁸ This is in fact recognised in American federal regulation, 45 CFR 46. 107, which requires that “each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution”

⁵⁵⁹ The ICH-GCP regulation provides very basic guidance on the constitution of ethics committees it merely requires that the committee should consist of at least five members and that only one member should have a non-scientific primary area of interest. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)." Para 3.2.1

⁵⁶⁰ <http://www.ppukm.ukm.my/index.php?menuid+MN09050066> accessed 21 January 2010

Malaysia (UPM),⁵⁶¹ eleven out of twelve members are scientifically or clinically trained; and at University Science Malaysia (USM),⁵⁶² eleven out of thirteen members are clinicians or scientists.

This is significant for two reasons. First, the high proportion of scientifically trained members reduces diversity in the board, which is important (as discussed above). Second, scientific study relies to a large extent on establishing or extending the frontiers of knowledge by the experimental testing of hypotheses. Scientists are trained to place a high value on the research process and as such are likely to view the research agenda as being primarily a good thing.⁵⁶³ This being the case, they are likely to approach the review process with a bias towards the benefits of research and unlikely to be able to assume the subjects' point of view and understand the vulnerabilities of subjects.⁵⁶⁴

It is also worth considering the primary reason for establishing ethics review in the first place: that review was necessary because individual researchers were believed to be unable to impartially assess the risks to human subjects as they were too committed to their research projects. Similarly, scientists may also be unable to impartially assess the risks to human subjects as they may be committed to idea of the advancement of useful knowledge by way of observation and experimental testing. However, just because some people may come to the table with certain biased views, (as pointed out earlier) this does not render the entire review process illegitimate. In fact, the review

⁵⁶¹

http://www.medic/upm.edu.my/index.php?option=com_content&task=view&id=819&item=437
accessed 21 January 2010

⁵⁶² http://research.kk.usm.my/borang/jepem_ethical_members_09.pdf accessed 21 January 2010

⁵⁶³ Daniel D. Federman, Kathi E. Hanna, and Laura Lyman Rodriguez, eds., *Responsible Research : A Systems Approach to Protecting Research Participants* (Washington, D.C. ; [Great Britain]: National Academies Press, 2003). 84, C. A. Schuppli and D. Fraser, "Factors Influencing the Effectiveness of Research Ethics Committees," *J Med Ethics* 33, no. 5 (2007). at 297, Eckenwiler, "Moral Reasoning and the Review of Research Involving Human Subjects." at 47

⁵⁶⁴ Emily E. Anderson, "A Qualitative Study of Non-Affiliated, Non-Scientist Institutional Review Board Members," *Accountability in Research: Policies and Quality Assurance* 13, no. 2 (2006).at 136

process is enhanced by the injection of competing values.⁵⁶⁵ What does, in this case create a situation of potential CIs is that on average, 86% of ethics committee members are scientifically trained persons.⁵⁶⁶

Moreover, there is some evidence that scientist members tend to dominate the discussions and are not always receptive to the opinions of lay members. A study carried out in 2000⁵⁶⁷ where lay members of IRBs were asked open ended questions about their interactions with scientific members, 88% reported having negative experiences that were associated with feeling that “scientists disrespected their opinions, did not understand them, or did not take them seriously.”⁵⁶⁸ Similarly, a 2005 study carried out on the effectiveness of research ethics committees in Canada⁵⁶⁹ found that the preponderance of scientist members was a source of concern to lay members who felt that their views carried little weight in discussions as the scientists outnumbered them. In Malaysia, there also appears to be a culture of deference to medical opinion in ethics committees. In an interview with the immediate past chair of the MREC, he noted “... in our country, ...doctors tend to hold sway sometimes over the discussions. ... we have one or two PhDs [who] are well versed in research... but there are others who are too frozen, who don’t speak up.”⁵⁷⁰

The review process is thus tainted with bias at the outset, given that the majority of ethics committee members bring to the table a

⁵⁶⁵ This was recognised by a UK Department of Health Report which stated that RECs should be broadly representative of the community. (Department of Health, "Report of the Ad Hoc Advisory Group on the Operation of Nhs Research Ethics Committees." at 10

⁵⁶⁶ The American National Bioethics Advisory Commission recommended that non-scientific members should represent at least 25% of the membership of IRBs. See United States. National Bioethics Advisory Commission., "Ethical and Policy Issues in Research Involving Human Participants," (Bethesda, Md. (6705 Rockledge Drive, Suite 700, Bethesda, 20892-7979): The Commission, 2001). at xvi

⁵⁶⁷ Sohini PhD M. P. H. Sengupta and Bernard M. D. Lo, "The Roles and Experiences of Nonaffiliated and Non-Scientist Members of Institutional Review Boards," *Academic Medicine* February 78, no. 2 (2003).

⁵⁶⁸ Ibid. at 215.

⁵⁶⁹ Schuppli and Fraser, "Factors Influencing the Effectiveness of Research Ethics Committees."

⁵⁷⁰ Interview with Ethics Committee Member A, MREC, 25 November 2008

scientifically value-laden discourse. This bias is not adequately addressed by appointing lay members because first, there are too few lay members; and second, evidence seems to suggest that the few lay voices that are present are either dismissed or stifled by scientifically trained members.

Practical Interests as Personal Motives

Practical interests include personal financial interests and interests in the prospects of personal career advancement. While much has been said about the financial interests of investigators, it is also important to recognise that ethics committee members are just as likely to have financial ties with industry as well. A survey of 893 IRB members at 100 academic institutions in the US⁵⁷¹ concluded that ethics committee members sometimes participate in decisions about protocols sponsored by companies that they have financial relationships with. Given that almost all clinical trials that are run in Malaysia are sponsored by industry, it is more than likely that committee members who are investigators will at some point have to make decisions on protocols sponsored by companies with whom they have worked with.

In addition to this, given the current climate of the research imperative, committee members who are also researchers will be under some pressure to carry out their own research projects. The career advancement prospects of these individuals will to a large extent be dependent on their research work and publications. In Malaysia, where almost all clinical trials are sponsored by the industry, it is not unreasonable to imagine that researchers may want to keep industry sponsors happy and interested in investing their time and money in the local clinical trial industry, which will in turn afford these researchers opportunities to take part in clinical trials. Moreover,

⁵⁷¹ Eric G. Campbell et al., "Financial Relationships between Institutional Review Board Members and Industry," *N Engl J Med* 355, no. 22 (2006).

because many committee members are likely to want to run research trials in their own institutions as well, they have a personal interest in the standards that are being set by their review process. Therefore, there is a danger that committee members may be influenced by these practical considerations when making their decisions.⁵⁷²

It is important to point out at this juncture that the problem of conflict that arises here, while often associated with the fact that these individuals have institutional affiliations, is not necessarily linked to the institutional structure. This is not an issue of institutional conflicts of interests. The argument is that individual committee members who are also researchers are likely to have personal reasons first, for not wanting to discourage sponsors from running trials and as such, these reasons may influence their decisions; and second, because committee members are also likely to be researchers within the institution who will themselves at some point need to submit protocols for review, they may not want to set precedents that they may impede their own research.

Predilections as Personal Motives

Predilections as described above, are dispositions to value something positively or negatively and might be justified or prejudicial; rational or irrational. They include among other things, hobbies, animosity, and the bonds of friendship. There is some evidence⁵⁷³ that suggests that ethics committee members with institutional affiliations s may view favourably the research protocols submitted by their colleagues, as they “must live with any disappointed applicants whose protocols they have rejected”.⁵⁷⁴ When interviewed, one of the members of the MREC

⁵⁷² See also Adil E. Shamoo and Felix A. Khin-Maung-Gyi, *Ethics of the Use of Human Subjects in Research : Practical Guide* (London: Garland Science Pub, 2002). at 67

⁵⁷³ See Federman, Hanna, and Rodriguez, eds., *Responsible Research : A Systems Approach to Protecting Research Participants*. at 84, Lester Francis, "Irbs and Conflicts of Interest," in *Conflicts of Interest in Clinical Practice*, ed. Roy G Spece, David S Shimm, and Allen E Buchanan (New York: Oxford University Press, 1996). at 425,

⁵⁷⁴ Harold Edgar and David J. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation," *The Milbank Quarterly* 73, no. 4 (1995).

remarked, "... there are many other institutes having their own projects coming in for review and approval, and we basically joke about it. Come on, this is your fellow sister's project; take it easy, man, you know? ... I think we do take it easy."

Moreover, as far as the appointment of lay persons are concerned, a systematic study in the US⁵⁷⁵ showed that lay members tend to be appointed by relatively high-level institutional officials often through friendship with "little or no effort ... to recruit outside members from community or patient advocacy groups". There is some evidence that this also holds true in the Malaysian context as a lay member of Institution A, a retired science teacher, remarked that she had been appointed by the chair of the committee because "her mother knows me personally and she was looking out for a member of the public and her mother mentioned my name to her and so she approached me".⁵⁷⁶ Also, the immediate past chair of the MREC noted that it was very difficult to find lay members and "quite often we fall back on our ex staff members or hospital staff who are not doctors".⁵⁷⁷ The selection of lay members drawn from a rather selected pool of either retired employees or people from the same social circles as other ethics committee members (mid to high-level employees) makes it likely that these lay members will be sympathetic to the interests of researchers and the institutions. More than this, the appointment of members in this way makes it highly unlikely that lay members are likely to represent the research subject population.⁵⁷⁸

at 492, Lemmens and Freedman, "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards." at 576

⁵⁷⁵ See Francis, "IRBs and Conflicts of Interest." at 429. Similar results were reported in Anderson, "A Qualitative Study of Non-Affiliated, Non-Scientist Institutional Review Board Members." at 141

⁵⁷⁶ Interview with Ethics Committee Member B, Institution A, 21 December 2007

⁵⁷⁷ Interview with Ethics Committee Member A, MREC, 25 November 2008

⁵⁷⁸ See D. Evans and Evans M, *A Decent Proposal, Ethical Review of Clinical Research* (Chichester: John Wiley & Sons, 1997). at 110

Secondary Interests based on Social and Institutional Structures

As noted earlier, secondary interests may also arise at a structural level, that is, the duties and responsibilities attached to certain social positions infect their role holders with secondary interests regardless of whether or not they have any personal motives or experience any dilemma. Because the role holders themselves may not necessarily experience any dilemma in situations where secondary interests arise from institutional structures, the question is not necessarily whether CIs are present, but rather whether the institutional or social structure creates an appearance of a CI. Two main areas of concern are discussed below in relation to secondary interests based on institutional structures: the appointment of institutionally affiliated chairpersons, and the fact that many members of ethics committees are also mid-level or senior employees of the institution.

Chairpersons of ethics committees

The chairperson of the ethics committee plays a very important role. Generally, members see the chairperson as being particularly important in maintaining an atmosphere where all views are accepted, and playing a neutral role in participating in the discussion and helping the committee reach a consensus.⁵⁷⁹ All the chairpersons of academic ethics research committees in Malaysia are appointed from senior faculty members of the institutions, and the chairperson of the MREC is the Director General of Health of the Ministry of Health. These individuals are not only affiliated to the institutions where the research is to be carried out, they are senior members of the institutions and often hold senior administrative posts in their institutions in addition to being chairs of their respective ethics committees.

⁵⁷⁹ Schuppli and Fraser, "Factors Influencing the Effectiveness of Research Ethics Committees." at 295

As discussed in chapter 2, the clinical trial industry in Malaysia is viewed by the government as an important source of revenue and job creation and various institutions and programmes have been put into place to encourage sponsors to run their trials in this country. Almost all of these institutions and programmes fall under the purview of the Director General of the Ministry of Health. His position as Director General requires him to actively promote the clinical trial industry in the country. However, as the chairperson of the MREC (which reviews all trial protocols from Ministry of Health institutions), his primary interest must be the protection of human subjects, which may be in conflict with the interests of the industry. The fact that the chairperson of the MREC is also the Director General of the Ministry of Health, creates at the minimum an appearance of a CI.

In a similar vein, academic institutions in Malaysia are keen to present themselves as research centres and actively promote their institutions as being ideal centres for running clinical trials. Clinical trials are important to universities as they represent sources of revenue, new equipment and training opportunities for staff. Universities also have an interest in acquiring reputations for bringing in large amount of research money, as this attracts more students and top researchers.⁵⁸⁰ Chairpersons appointed from senior faculty members who also hold institutional administrative positions (most of the chairpersons are either heads of departments or hold administrative positions in relation to research activities in their universities.), inevitably appear to face CIs. Their positions as senior administrative officers with interests in furthering institutional policies that favour research projects (secondary interests) clearly appear to be potentially in conflict with their roles as chairpersons of ethics committees.

⁵⁸⁰FOCUS, "Report on an International Conference on Conflict of Interest." at 3

Ethics Committee Membership

All the ethics committees in Malaysia are affiliated to the institutions that carry out the clinical trials being presented for review. The majority, if not all of their members are drawn from mid-level to senior employees of the institution. The members of the ethics committee of the University of Malaya,⁵⁸¹ for example, include the Dean of the Faculty of Medicine, the Deputy Director of the hospital; and the Heads of the departments of medicine, psychological medicine, surgery, pharmacology and pharmacy.

As heads of departments, they will be aware that the research monies that come into their departments are likely to improve the facilities and prestige of their departments. Because they have a vested interest in the success of the departments they lead, there is a danger that when members of their departments present protocols for review, their interests in seeing these protocols approved may unduly influence them.⁵⁸²

The membership of the MREC on the other hand, includes the directors of the Institute for Medical Research, the Institute for Public Health and the Network of Clinical Research Centres (CRC). As in the case of heads of departments in academic institutions, directors of institutes are able to understand and appreciate the value of research to their institutions and these secondary interests may very well alter their judgments. A member of the MREC pointed out that because individuals are appointed to the committee based on their posts, "they might be interested in managing research but not interested in ethical issues".⁵⁸³ Moreover, the conflicts faced by these individuals was readily admitted by the Director of the Network of Clinical Research Centres, who very honestly pointed out that

⁵⁸¹ http://www.ummc.edu.my/index.php?option=com_content&task=view&id=842&Itemid=1430
accessed on 7 Feb 2008

⁵⁸² There is some evidence for this, see Lemmens and Freedman, "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards." at 576

⁵⁸³ Interview with Ethics Committee Member A, MREC, 25 November 2008

“To a larger extent, my role is conflicted. ... as Director of CRC I have many responsibilities... and many of these responsibilities actually conflict. On the one hand, I am supposed to promote clinical research, right? Then on the other hand, I am supposed to promote Malaysia as a research hub ... I go out there and rub shoulders with all the key decision-makers and key stakeholders and say “Come on bring your trials to Malaysia.” ... The CRC also allocates funding, so there are some accountability issues there... then finally, there is of course, human subject involvement.

... So me sitting in the ethics committee on one hand I say – hey, I have a job to protect the human research subject. But on the other hand I say - hey, I have to take it easy on this guy if this project is to be done in Malaysia. And on the other hand I say - hey, I have just allocated a millions bucks in this research project, don't screw it up for me mate, just pass the research so we can carry on with this project. You can imagine the several conflicting interests, and we just have to deal with that.”⁵⁸⁴

⁵⁸⁴ Interview with Ethics Committee Member B, MREC, 26 November 2008

6 Chapter 6

Conclusion

It is clear that there are problems with the way in which ethics review is conducted in Malaysia, especially with regard to clinical trials involving mentally incapacitated adults. The thesis focuses on two main areas that are essential to meaningful ethics review: first, the process by which decisions are made; and second, the issue of the independence of ethics committees. This by no means suggests that these are the only issues relating to ethics review worth exploring, but it is suggested that these issues strike at the heart of the ethics review process, which is to provide independent review of trial protocols to ensure that the rights and interests of human subjects are protected.

While it would be unfair to make sweeping generalisations about the nature of the clinical trial industry in Malaysia, some general points may be drawn out from the discussions in Chapter 2. The one single factor that has had the largest impact on the size of and the way in which clinical trials are run in developing countries such as Malaysia is the ICH process. This project has brought together the regulatory authorities of the United States, Europe and Japan; and has changed the face of drug development by opening the clinical trial industry to a global market. This in turn has created an environment where countries like Malaysia compete against other developing countries for a piece of the market. To this end, the government of Malaysia has instituted a number of policies and set up several institutions to attract sponsors to its shores. The danger created by this is that the government in bending over backwards to attract foreign investment might be less vigilant about providing adequate systems of human subject protection. This is evidenced by the absence of any statutory measures aimed at protecting human subjects.

This is, however, not to say that there are no mechanisms for protecting human subjects. Because trials need to be compliant with the ICH process, which includes the ICH-GCP⁵⁸⁵, all clinical trials that are conducted in Malaysia have to be subject to prior ethics review as stated in the ICH-GCP guideline. Whether ethics committees acting under the ICH-GCP guideline are providing meaningful protection to trial subjects, however, is another issue, and this was dealt with in Chapter 4.

As far as the issue of the treatment of mentally incapacitated adults who participate in clinical research is concerned, the outlook is gloomy. There is no legislation that provides for proxy decision-making. As a result of this, the official position taken by sponsors and investigators is that mentally incapacitated adults are not permitted to participate in trials even if trials provide the only opportunity for some patients to receive drugs that they would otherwise not have access to because of the high costs of those drugs. Ethics committee members, on the other hand, seem unaware of this practice, and routinely consider trial protocols that they believe might involve the participation of mentally incapacitated adults. However, a more troubling observation is that even patients who are judged to be competent are not permitted to enrol in clinical trials without the consent of relatives.⁵⁸⁶ This is a clear violation of patient autonomy. It is evident that the practice that has emerged in relation to the enrolment of mentally incapacitated adults is highly unsatisfactory.

This is therefore the context in which ethics committees must operate and bearing in mind these matters, a number of conclusions can be drawn from the preceding chapters as to whether ethics committees provide meaningful protection to mentally incompetent adults who enrol in clinical trials. There are, as mentioned earlier, two broad areas

⁵⁸⁵ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Good Clinical Practice: Consolidated Guideline E6 (R1)."

⁵⁸⁶ See Chapter 5 at 179

of enquiry: the process by which ethics committees make decisions – whether they engage in meaningful ethics discourse, and whether ethics committees are independent.

Are ethics committees independent?

The importance of independent ethics review cannot be overstated. Conflicts of interests abound in the modern clinical trial industry and if ethics committees are to function as protectors of human subjects, they must stand apart from the other players who have vested interests. More so, because as demonstrated in chapter 5,⁵⁸⁷ the only other vehicle for human subject protection in the research arena; the informed consent process, is riddled with conflicts of interest.

The main sources of secondary interests as far as ethics committees are concerned are the social and institutional structures of these committees. Because these committees are made up primarily of scientists and investigators, they inevitably bring to the discussion values and personal interests that may influence their decisions. What is needed is an injection of more lay members drawn from a larger and more diverse pool of society. The fact that chairpersons are appointed from senior members of staff who hold high positions in the institutions create a danger that the committees might be led to make decisions that favour the interests of the institutions. The institutions that carry out the research under review should not at the same time be the employers of chairpersons of ethics committees. Also, all members of the committees save for the few lay members are employees of the institutions carrying out the research. This again, creates a potential situation of conflicts of interests where employees may feel inclined to make decisions that favour the interests of the institution. To remedy this, employees of the institution carrying out

⁵⁸⁷ At 169-176

the research should comprise of less than half of the entire membership of the committee.

Significantly, while examining the issue of the independence of ethics committees and conflicts of interests (CIs), it became clear that the notion of CIs in the field of bioethics has not been well defined in the past, and that most commentators have focused on matters concerning financial gain.⁵⁸⁸ It was therefore, important to attempt to construct a meaningful and workable notion of CIs that could then be applied to the parties engaged in clinical trials. This was achieved by combining Thompson's⁵⁸⁹ definition of CIs as a foundation and building on it by adding relevant aspects of Erde's⁵⁹⁰ analyses resulting in a viable framework of CIs.⁵⁹¹

Do ethics committees engage in meaningful ethical discourse?

The question of whether ethics committees engage in meaningful discourse encompasses several subsidiary questions. Do ethics committees understand the role they are expected to play? What principles if any do ethics committees use in their discussions? Do these principles facilitate meaningful ethics discourse? What rules and regulations must ethics committees adhere to? The answers to the subsidiary questions help answer the ultimate question: does the ethics review process provide meaningful protection to mentally incapacitated adults?

The first three subsidiary questions were considered in Chapter 3. First, while most ethics committee members appear to know that the

⁵⁸⁸ See Chapter 5, section 5.2.2

⁵⁸⁹ Thompson, Dennis F. "Understanding Financial Conflicts of Interest." *N Engl J Med* 329, no. 8 (1993): 573-76.

⁵⁹⁰ Erde, Edmund L. "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." In *Conflicts of Interest in Clinical Practice and Research*, edited by Roy G Spece, David S Shimm and Allen E Buchanan, 12-42. New York: Oxford University Press, 1996.

⁵⁹¹ See Chapter 5, sections 5.3, 5.4, 5.4.1, 5.4.2, 5.4.3

function of ethics review is to protect human subjects, they appeared to have a very narrow view of what this protection should encompass, and most of them seemed to think that they should focus on ensuring that subjects were not made to pay for additional tests or drugs. Further, when asked about the ethical principles or guidelines they use or think that they should know, most ethics committee members could not name any of the guidelines or declarations; and the few who named the Helsinki Declaration were unable to list any of the principles contained within it.⁵⁹² In fact, none of the ethics committee members were provided with any sort of formal training prior to their appointments. Significantly, all the ethics committee members who were interviewed appeared to recognise that they needed training because when asked what would improve the ethics review process, they all expressed a need for more training. Unless ethics committee members understand what is required of them, and unless they are provided with the tools that they need to engage in meaningful ethics discourse, the ethics review process is not an effective means for protecting human subjects.

Because it was clear from the interviews that most ethics committee members were not relying on any specific set of principles when making decisions, the question that then needs to be asked is not whether the principles they use facilitate meaningful ethics discourse, but rather whether the guidelines and principles that *are on offer* facilitate meaningful ethics discourse? An examination of three of the most influential sets of guidelines: the Nuremberg Code, the Helsinki Declaration and the Belmont Report, revealed a number of flaws that render these documents confusing and ineffective at best; and at worst, subject to manipulation. Consequently, little would be gained by using these guidelines to train ethics committees. Because ethics committee members come from a variety of backgrounds (scientists, clinicians, investigators, lawyers and lay persons) they need to be provided with a

⁵⁹² See Chapter 3 at 67 - 68

common discourse in a language that is both coherent and easily accessible to every member. But at the same time, this discourse must be rich enough to reflect the complex nature of the issues raised by medical research. The last part of chapter 3 is the first step in this direction. A framework for ethics discourse based on the single principle of respecting human dignity, and how this might work in relation to mentally incapacitate adults is offered as an alternative to the existing guidelines. While much more work remains to be done in constructing a framework that applies across the board; this is an important first step.

Chapter 4 continues with the enquiry into the decision-making process of ethics committees by examining the ICH-GCP guideline. Several conclusions may be drawn from this part of the enquiry. First, the guideline itself provides very little specific guidance to ethics committees as to how they should protect human subjects. Second, the guideline is largely concerned not with substantive issues of whether the decisions reached by ethics committee protect human subjects, but focuses on the administrative processes that ethics committees should adhere to. Therefore, compliance with the guideline does not necessarily ensure the protection of human subjects. Third, in requiring that investigators disclose an exhaustive amount of data for every protocol they submit for ethics review, the guideline places a very heavy burden on ethics committees who have to plough through an average of 2,700 pages every month. Because of the volume of the data, there appears to be a tendency for ethics committee members to focus their attention on the aspects of clinical trials that they are most familiar with, or that they understand most easily. By approaching ethics review in this disjointed manner, ethics committees run the risk of glossing over certain aspects of clinical trials that raise serious ethical concerns. This is particularly true in respect of clinical trials that enrol mentally incapacitated adults. By offering the example of

how clinical trials are designed, what originally appear to be questions of scientific merit best understood and examined by scientists, turn out to raise very serious ethical concerns.⁵⁹³ If ethics review is to achieve its purpose, ethics committees need to address these issues during their review process. To do this, they need to understand the difference between scientific validity and scientific value, they need to understand certain scientific aspects of clinical trials, they need to appreciate the context in which specific trials are carried out, they need to be able to recognise the special needs of vulnerable populations and they need to keep up with the changing needs and concerns of trial subjects within their purview. Ethics committee members must therefore receive sufficient training that will allow them to meet these needs.

While it is beyond the scope of this thesis to offer any specific and detailed recommendations for reform of the ethics review process, it is clear from the findings in chapters 3 and 4 that there is an urgent need for formal training of ethics committee members. Training should be approached at two levels: initial and continuous training. Ethics members should have at the minimum in-depth knowledge of the history and principles of human subject protection. They should be familiar with the regulations and guidelines that govern clinical trials. They should be aware of the specific needs and interests of vulnerable populations such as mentally incapacitated subjects. And finally, ethics committees should have an understanding of the local context in which the research is being carried out; they should recognise the particular issues raised by conducting research in a developing country that is at the same time, multi-cultural and multi-religious.⁵⁹⁴ Without this, it

⁵⁹³ See Chapter 4 at 134 - 140

⁵⁹⁴ Given that there are examples of curricula for training research ethics committees that have been developed in countries such as the U.S, it is possible to use these templates as a basis for developing country specific training programmes. See Silverman, H., B. Ahmed, S. Ajeilet, S. Al-Fadil, S. Al-Amad, H. El-Dessouky, I. El-Gendy, M. El-Guindi, M. El-Nimeiri, R. Muzaffar, and A. Saleh. "Curriculum Guide for Research Ethics Workshops for Countries in the Middle East." *Developing World Bioethics* 10, no. 2 (2010): 70-77.

cannot be said that ethics committees are committed to protecting the rights of mentally incapacitated subjects.

Conclusion

Several conclusions can be drawn by looking at the evolution of the Malaysian clinical trial industry and the way in which ethics review is presently carried out. First, unlike the United States, which instituted ethics review in response to specific instances of research misconduct, and which has over time developed both legal regimes and institutional mechanisms with the primary aim of protecting human subjects;⁵⁹⁵ the Malaysian ethics review process was developed to bring the country's clinical trial industry within the rules of the ICH process. Because the main impetus for creating ethics review committees was not human subject protection, but rather economic gain, the ethics review processes is based solely on the ICH-GCP guideline. Given the fact that the ICH-GCP guideline was not drafted for the primary purpose of human subject protection, but rather as part of a larger project to standardise pharmaceutical development practices and procedures across the U.S, Europe and Japan, it does not provide sufficiently for human subject protection. If the ethics review process in Malaysia is to truly reflect the idea of human subject protection, authorities need to rethink the entire way in which the process is structured and the way in which ethics committees conduct their reviews.

Second, because of the growing influence of the ICH process across many countries, the issue of how far other countries rely on the ICH-GCP principle to develop ethics review processes becomes very important. It is very likely that other developing countries will also have built up their local clinical trial industries in the same way as Malaysia. If this is true, there is a danger that the ethics review

⁵⁹⁵ See the discussion in Chapter 2, section 2.4.2 about the U.S experience. The U.S regulations go far beyond the GCP principles

processes in many countries are similarly compromised. Very little research has been done on how the ICH process has affected human subject protection across developing countries and there is an urgent need for more research into this matter.

Human subject protection lies at the heart of the ethics review process, and unless ethics committee members in Malaysia understand what this means, and until they are provided with the tools they need to engage in meaningful ethics discourses, they will not be able to fulfil their duties to potential research participants in general and specifically to mentally incapacitated adults. The findings of this thesis demonstrate an urgent need for reform of both the law relating to mentally incapacitated adults as well as the way in which ethics review is conducted in Malaysia.

While this thesis focuses on the ethics review process in Malaysia; most of the discussions in the preceding chapters are also relevant to the ethics review process in other jurisdictions. This is particularly true of the discussions in chapter 4 that focus on the ICH-GCP guideline. Two important and new ideas put forward in this thesis that will merit further investigation and deliberation are: first, the idea that the undervaluation of human life lies at the heart of research misconduct and that this understanding is crucial to the construction of a rational and effective basis of ethical research because it invites the question of what is the appropriate value of human life, the answer to which is presented as the principle of respect for human dignity. Second, the idea that there needs to be a recognition of the role of the informed consent facilitator which is not subsumed into the larger role of the physician/researcher. Much has been written about the tension between the roles of physician and researcher, but almost nothing about the very important role of the informed consent facilitator.

BIBLIOGRAPHY

BOOKS

- Ackerknecht, Erwin Heinz. *Medicine at the Paris Hospital, 1794-1848*: Baltimore: Johns Hopkins Press, 1967.
- Berg, Jessica W. Appelbaum, Paul S. Lidz. Charles W. Parker, Lisa S. *Informed Consent: Legal Theory and Clinical Practice*. Second ed. New York: Oxford University Press, 2001.
- Bernard, Claude. *An Introduction to the Study of Experimental Medicine*. New York: Dover Publications, 1957.
- Beyleveld, Deryck, and Roger Brownsword. *Human Dignity in Bioethics and Biolaw*. Oxford: Oxford University Press, 2001.
- Biggs, Hazel. *Healthcare Research Ethics and Law: Regulation, Review and Responsibility*. London: Routledge-Cavendish, 2010.
- Callahan, Daniel. *What Price Better Health? : Hazards of the Research Imperative*, California/Milbank Series on Health and the Public; 9. Berkeley, Calif; London: University of California Press, 2003.
- Cunningham, Andrew, and Perry Williams. *The Laboratory Revolution in Medicine*. Cambridge: Cambridge University Press, 1992.
- Demaitre, Luke E., and Pontifical Institute of Mediaeval Studies. *Doctor Bernard De Gordon, Professor and Practitioner*. Toronto: Pontifical Institute of Mediaeval Studies, 1980.
- Doyal, L., and J. S. Tobias, eds. *Informed Consent in Medical Research*. London: BMJ Books, 2001.
- DuBois, James M. *Ethics in Mental Health Research, Principles, Guidance, and Cases*. New York: Oxford University Press, 2008.
- Dworkin, R. *Life's Dominion*: Harper Collins Publishers, 1993.
- Emanuel, Ezekiel J. Crouch, Robert A. Arras, John D. Moreno, Jonathan D. Grady C., ed. *Ethical and Regulatory Aspects of Clinical Research : Readings and Commentary*. Baltimore: Johns Hopkins University Press, 2003.
- Epstein, R. M., B. S. Alper, and T. E. Quill. *Communicating Evidence for Participatory Decision Making*. Vol. 291: Am Med Assoc, 2004.
- Evans, D. , and Evans M. *A Decent Proposal, Ethical Review of Clinical Research*. Chichester: John Wiley & Sons, 1997.
- Faden, Ruth R., Tom L. Beauchamp, and Nancy M. P. King. *A History and Theory of Informed Consent*. New York ; Oxford: Oxford University Press, 1986.
- Federman, Daniel D., Kathi E. Hanna, and Laura Lyman Rodriguez, eds. *Responsible Research : A Systems Approach to Protecting Research Participants*. Washington, D.C. ; [Great Britain]: National Academies Press, 2003.
- Freyhofer, Horst H. *The Nuremberg Medical Trial: The Holocaust and the Origin of the Nuremberg Medical Code*, Studies in Modern European History,. New York: P. Lang, 2004.

- Goldberg, David Theo. *Anatomy of Racism*. Minneapolis: University of Minnesota Press, 1990.
- Goodman, J., A. McElligott, and L. Marks. *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century*. Baltimore Johns Hopkins University Press, 2003.
- Hawkins, J S, and E. Emanuel, eds. *Exploitation and Developing Countries. The Ethics of Clinical Research*. Princeton: Princeton Universtiy Press, 2008.
- Jones, James H. *Bad Blood : The Tuskegee Syphilis Experiment*. New and expanded ed. ed. New York: Free Press ; Toronto : Maxwell Macmillan Canada ; New York : Maxwell McMillan International, 1993.
- Kaczor, Christopher. *The Edge of Life: Human Dignity and Contemporary Bioethics*. Dordrecht: Springer, 2005.
- Kass, Leon. *Life, Liberty, and the Defense of Dignity : The Challenge for Bioethics*: San Francisco ; Encounter Books, 2002.
- Kennedy, Ian, and Andrew Grubb. *Medical Law : Text with Materials*. 3rd ed. London: Butterworths, 2000.
- Lemmens, Trudo, and Duff R. Waring, eds. *Law and Ethics in Biomedical Research: Regulation, Conflict of Interest and Liability*. Toronto: University of Toronto Press, 2006.
- Levine, Robert J. *Ethics and Regulation of Clinical Research*. 2nd ed. Baltimore: Urban & Schwarzenberg, 1986.
- Macklin, R. *Double Standards in Medical Research in Developing Countries*: Cambridge University Press, 2004.
- Martin, Wayne. *Medical Heroes and Heretics*. Old Greenwich, Conn.: Devin-Adair Co., 1977.
- Menikoff, Jerry, and Edward P. Richards. *What the Doctor Didn't Say : The Hidden Truth About Medical Research*. New York ; Oxford: Oxford University Press, 2006.
- Murphy, Kevin M., and Robert H. Topel. *Measuring the Gains from Medical Research : An Economic Approach*. Chicago, Ill. ; London: University of Chicago Press, 2003.
- O'Neill, Onora. *Autonomy and Trust in Bioethics: The Gifford Lectures, University of Edinburgh, 2001*, Gifford Lectures 2001. Cambridge: Cambridge University Press, 2002.
- Pappworth, M H. *Human Guinea Pigs: Experimentation on Man*. Harmondsworth: Pelican Books, 1969.
- Pellegrino, Edmund D., Adam Schulman, and Thomas W. Merrill. *Human Dignity and Bioethics. Essays Commissioned by the President's Council on Bioethics*. Notre Dame, Ind.: University of Notre Dame Press, 2009.
- Pitt-Lewis, G., John Anthony Hawke, and Robert Percy M. D. Smith. *The Insane and the Law* London: J. & A. Churchill: London, 1895.
- Pincus, Harold Alan, Jeffrey A. Lieberman, and Sandy Ferris. *Ethics in Psychiatric Research : A Resource Manual for Human Subjects Protection*. Washington, DC: American Psychiatric Association,

- 1999.
- Porter, Roy. *The Cambridge Illustrated History of Medicine*. Cambridge: Cambridge University Press, 1996.
- Ramanathan, K., Winnie C. Cheah, and Timothy J. Dondero. *75 Years of Medical Research in Malaysia : 1901-1976*. Rev. ed. ed. Kuala Lumpur: Institute for Medical Research, 1976.
- Rothman, David J. *Strangers at the Bedside : A History of How Law and Bioethics Transformed Medical Decision Making*. New York, NY: Basic Books, 1991.
- Rubin, Herbert j., and Irene S. Rubin. *Qualitative Interviewing : The Art of Hearing Data*. Second ed. Thousand Oaks: Sage Publications, 2005.
- Schmidt, Ulf, and Andreas Frewer. *History and Theory of Human Experimentation : The Declaration of Helsinki and Modern Medical Ethics*. Stuttgart: Steiner, 2007.
- Shamoo, Adil E., and Felix A. Khin-Maung-Gyi. *Ethics of the Use of Human Subjects in Research : Practical Guide*. London: Garland Science Pub, 2002.
- Smart and Williams, *Utilitarianism For and Against* (Cambridge University Press 1990)
- Spicker, Stuart F. *The Use of Human Beings in Research : With Special Reference to Clinical Trials*, *Philosophy and Medicine* ; V. 28. Dordrecht ; London: Kluwer Academic, 1988.

BOOK SECTIONS

- Caplan, A L. "Is There an Obligation to Participate in Biomedical Research." In *The Use of Human Beings in Research with Special Reference to Clinical Trials*, edited by Stuart F. Spicker, 229-48. Dordrecht: Kluwer Academic, 1988.
- Erde, Edmund L. "Conflicts of Interests in Medicine: A Philosophical and Ethical Morphology." In *Conflicts of Interest in Clinical Practice and Research*, edited by Roy G Spece, David S Shimm and Allen E Buchanan, 12-42. New York: Oxford University Press, 1996.
- Francis, Lester. "IRBs and Conflicts of Interest." In *Conflicts of Interest in Clinical Practice*, edited by Roy G Spece, David S Shimm and Allen E Buchanan, 418 - 36. New York: Oxford University Press, 1996.
- Gelsinger, Paul L. "Uninformed Consent: The Case of Jesse Gelsinger." In *Law and Ethics in Biomedical Research: Regulation, Conflict of Interest, and Liability*, edited by Trudo Lemmens and Duff R. Waring, 12-34. Toronto: University of Toronto Press Incorporated, 2006.
- Harris, Sheldon H. "Japanese Biomedical Experimentation During the World-War II Era." In *Military Medical Ethics Volume 2*, edited by Thomas E Beam and Linette R Sparacino. Washington D.C.: Office of the Surgeon General, Department of the Army, United States of America, 2003.
- Huth, Edward J. "Conflicts of Interest in Industry-Funded Clinical Research." In *Conflicts of Interest in Clinical Practice and Research*, edited by Roy G Spece, David S Shimm and Allen E Buchanan, 389-406. New York: Oxford University Press, 1996.
- Kipnis, Kenneth. "Vulnerability in Research Subjects: A Bioethical Taxonomy." In *Ethical and Policy Issues in Research Involving Human Participants*, G1-G13. Bethesda MD: National Bioethics Advisory Commission, 2001.
- Krimsky, Sheldon. "The Ethical and Legal Foundations of Scientific 'Conflict of Interest'." In *Law and Ethics in Biomedical Research*, edited by Trudo Lemmens and Duff R. Waring, 63-81. Toronto: University of Toronto Press, 2006.
- Lederer, Susan E. "Research without Borders: The Origin of the Declaration of Helsinki." In *History and Theory of Human Experimentation: The Declaration of Helsinki and Modern Medical Ethics*, edited by Ulf Schmidt and Andreas Frewer. Stuttgart: Steiner, 2007.
- Macklin, R, and S Sherwin. "Experimenting on Human Subjects: Philosophical Perspectives." In *Human Experimentation and Research*, edited by G F Tomossy and D V Weisstub. Aldershot: Ashgate/Dartmouth, 2003.

- Marshall, P, B A Koenig, P Grifhorst, and M V Ewijk. "Ethical Issues in Immigrant Health Care and Clinical Research." In *Handbook of Immigrant Health*, edited by Loue, 208-09. New York: Plenum Press, 1998.
- McHale, Jean. "Law Reform, Clinical Research and Adults without Mental Capacity - Much Needed Clarification of a Recipe for Further Uncertainty?" In *First Do No Harm: Law, Ethics and Healthcare*, edited by Sheila Mc Lean. Aldershot: Ashgate Publishing Ltd, 2006.
- Neuhaus, R J. "Human Dignity and Public Discourse." In *Human Dignity and Bioethics. Essays Commissioned by the President's Council on Bioethics*, edited by President's Council on Bioethics: Government Printing Office, 2008.
- Schulman, Adam. "Bioethics and the Question of Human Dignity." In *Human Dignity and Bioethics: Essays Commissioned by the President's Council on Bioethics*, edited by President's Commission on Bioethics: US Independent Agencies and Commissions, 2008.
- Shipp, A.C. "How to Control Conflict of Interest." In *Biomedical Research Collaboration and Conflict of Interest*, edited by R.J. Porter and T.E. Malone, 163-84. Baltimore: John Hopkins University Press, 1992.

ARTICLES

- Anderson, Emily E. "A Qualitative Study of Non-Affiliated, Non-Scientist Institutional Review Board Members." *Accountability in Research: Policies and Quality Assurance* 13, no. 2 (2006): 135 - 55.
- Appelbaum, Paul S., and Thomas Grisso. "The Macarthur Treatment Competence Study. I." *Law and Human Behavior* 19, no. 2 (1995): 105-26.
- Appelbaum, Paul S., Loren H. Roth, and Charles Lidz. "The Therapeutic Misconception: Informed Consent in Psychiatric Research." *International Journal of Law and Psychiatry* 5, no. 3-4 (1982): 319-29.
- Ashcroft, Richard E. "Making Sense of Dignity." *J Med Ethics* 31, no. 11 (2005): 679-82.
- Asprey, D. "UK Government Asks Academy to Review Regulation of Research." *BMJ* 340 (2010): c1770.
- Babar, Zaheer Ud Din, Mohamed Izham Mohamed Ibrahim, Harpal Singh, Nadeem Irfan Bukahri, and Andrew Creese. "Evaluating Drug Prices, Availability, Affordability, and Price Components: Implications for Access to Drugs in Malaysia." *PLoS Medicine* 4, no. 3 (2007): e82.
- Babar, Z. Ibrahim, MIM. . "Affordability of Medicines in Malaysia - Consumer Perception." *Essential Drug Monitor, Vol 33* 33 (2003): 18-19.
- Barnes, M, and PS Florencio. "Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future." *Seton Hall Law Review* 32 (2001): 525.
- Beecher, H. K. "Ethics and Clinical Research." *New England Journal of Medicine* 274, no. 24 (1966)
- Bekelman, Justin E., Yan Li, and Cary P. Gross. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review." *JAMA* 289, no. 4 (2003): 454-65.
- Blumenthal, David. "Doctors and Drug Companies." *N Engl J Med* 351, no. 18 (2004): 1885-90.
- Brennan, Troyen A., David J. Rothman, Linda Blank, David Blumenthal, Susan C. Chimonas, Jordan J. Cohen, Janlori Goldman, Jerome P. Kassirer, Harry Kimball, James Naughton, and Neil Smelser. "Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers." *JAMA* 295, no. 4 (2006): 429-33.
- Brody, Howard, and Franklin G. Miller. "The Clinician-Investigator: Unavoidable but Manageable Tension." *Kennedy Institute of Ethics Journal* 13, no. 4 (2004): 329-47.

- Bryant, J, and J Powell. "Payment to Healthcare Professionals for Patient Recruitment to Trials: A Systematic Review." *BMJ* 331, no. 7529 (2005): 1377-78.
- Burke, D. "Laboratory Medicine in the 21st Century." *American Journal of Clinical Pathology* 114, no. 6 (2000): 841-46.
- Cahill, M., and A. Wichman. "Research Involving Persons with Cognitive Impairments: Results of a Survey of Alzheimer Disease Research Centers in the United States." *Alzheimer Disease & Associated Disorders* 14, no. 1 (2000): 20-27.
- Campbell, Eric G., Russell L. Gruen, James Mountford, Lawrence G. Miller, Paul D. Cleary, and David Blumenthal. "A National Survey of Physician-Industry Relationships." *N Engl J Med* 356, no. 17 (2007): 1742-50.
- Campbell, Eric G., Joel S. Weissman, Christine Vogeli, Brian R. Clarridge, Melissa Abraham, Jessica E. Marder, and Greg Koski. "Financial Relationships between Institutional Review Board Members and Industry." *N Engl J Med* 355, no. 22 (2006): 2321-29.
- Carpenter, W. T., J. M. Gold, A. C. Lahti, C. A. Queern, R. R. Conley, J. J. Bartko, J. Kovnick, and P. S. Appelbaum. "Decisional Capacity for Informed Consent in Schizophrenia Research." *Archives of General Psychiatry* 57, no. 6 (2000): 533-38.
- Carpenter, W. T., Jr., N. R. Schooler, and J. M. Kane. "The Rationale and Ethics of Medication-Free Research in Schizophrenia." *Arch Gen Psychiatry* 54, no. 5 (1997): 401-07.
- Cho, Mildred K., and Lisa A. Bero. "The Quality of Drug Studies Published in Symposium Proceedings." *Ann Intern Med* 124, no. 5 (1996): 485-89.
- Chopra, Sameer S. "Industry Funding of Clinical Trials: Benefit or Bias?" *JAMA* 290, no. 1 (2003): 113-14.
- Chren, M. "Interactions between Physicians and Drug Company Representatives." *The American Journal of Medicine* 107, no. 2 (1999): 182-83.
- Chren, MM, and CS Landefeld. "Physicians'behavior and Their Interactions with Drug Companies: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary." *Obstetrical & Gynecological Survey* 49, no. 8 (1994): 550.
- Christopher, P. P., M. E. Foti, K. Roy-Bujnowski, and P. S. Appelbaum. "Consent Form Readability and Educational Levels of Potential Participants in Mental Health Research." *Psychiatric Services* 58, no. 2 (2007): 227-32.
- Damle, Anita. "Build Rather Than Burn Bridges." *BMJ* 338, no. feb24_1 (2009): b765-.
- Davidoff, Frank, Catherine D. DeAngelis, Jeffrey M. Drazen, John Hoey, Liselotte Hojgaard, Richard Horton, Sheldon Kotzin, M. Gary Nicholls, Magne Nylenna, A. John P. M. Overbeke, Harold C. Sox, Martin B. Van Der Weyden, and Michael S. Wilkes.

- "Sponsorship, Authorship, and Accountability." *N Engl J Med* 345, no. 11 (2001): 825-27.
- Davidoff, Frank, Catherine D. DeAngelis, Jeffrey M. Drazen, Editors The, John Hoey, Liselotte Hojgaard, Richard Horton, Sheldon Kotzin, Magne Nylenna, A. John P. M. Overbeke, Harold C. Sox, Martin B. Van Der Weyden, and Michael S. Wilkes. "Sponsorship, Authorship, and Accountability." *Ann Intern Med* 135, no. 6 (2001): 463-66.
- Davidson, Richard. "Source of Funding and Outcome of Clinical Trials." *Journal of General Internal Medicine* 1, no. 3 (1986): 155-58.
- Djulbegovic, Benjamin, Mensura Lacevic, Alan Cantor, Karen K. Fields, Charles L. Bennett, Jared R. Adams, Nicole M. Kuderer, and Gary H. Lyman. "The Uncertainty Principle and Industry-Sponsored Research." *The Lancet* 356, no. 9230 (2000): 635-38.
- Drane, James F. "The Many Faces of Competency." *The Hastings Center Report* 15, no. 2 (1985): 17-21.
- Dresser, R. "Advance Directives in Dementia Research." *IRB: Ethics and Human Research* 23, no. 1 (2001): 1-6.
- . "The Ubiquity and Utility of the Therapeutic Misconception." *Social Philosophy and Policy* 19, no. 02 (2002): 271-94.
- Dunn, L. B., M. A. Nowrangi, B. W. Palmer, D. V. Jeste, and E. R. Saks. "Assessing Decisional Capacity for Clinical Research or Treatment: A Review of Instruments." *American Journal of Psychiatry* 163, no. 8 (2006): 1323-34.
- Eckenwiler, Lisa. "Moral Reasoning and the Review of Research Involving Human Subjects." *Kennedy Institute of Ethics Journal* 00011, no. 00001 (2001): 37-70.
- Edgar, Harold, and David J. Rothman. "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation." *The Milbank Quarterly* 73, no. 4 (1995): 489-506.
- Elad, P., T. A. Treves, M. Drory, R. Verchovsky, S. Klimovitsky, S. Ben-Laish, S. Yaron, K. Ginzburg, and A. D. Korczyn. "Demented Patients' Participation in a Clinical Trial: Factors Affecting the Caregivers' Decision." *International Journal of Geriatric Psychiatry* 15, no. 4 (2000): 325-30.
- Fletcher, W. "Rice and Beri-Beri: Preliminary Report on an Experiment Conducted in the Kuala Lumpur Insane Asylum." *Lancet* 1 (1907): 1776-79.
- Freedman, B. "Equipose and the Ethics of Clinical Research." *N Engl J Med* 317, no. 3 (1987): 141-45.
- Freedman, Benjamin. "Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication." *IRB: Ethics and Human Research* 9, no. 6 (1987): 7-10.
- Garrafa, V, JH Solbakk, S Vidal, and C Lorenzo. "Between the Needy and the Greedy: The Quest for a Just and Fair Ethics of Clinical Research." *Journal of Medical Ethics* 36, no. 8 (2010): 500.

- Gianfrancesco, Frank D., Ruey-hua Wang, and Elaine Yu. "Effects of Patients with Bipolar, Schizophrenic, and Major Depressive Disorders on the Mental and Other Healthcare Expenses of Family Members." *Social Science & Medicine* 61, no. 2 (2005): 305-11.
- Glasziou, Paul, and Iain Chalmers. "Ethics Review Roulette: What Can We Learn?" *BMJ* 328, no. 7432 (2004): 121-22.
- Glickman, Seth W., John G. McHutchison, Eric D. Peterson, Charles B. Cairns, Robert A. Harrington, Robert M. Califf, and Kevin A. Schulman. "Ethical and Scientific Implications of the Globalization of Clinical Research." *N Engl J Med* 360, no. 8 (2009): 816-23.
- Gupta, V.B., and D Mukherjee. "Conflicting Beliefs." *Hastings Cent Rep* 40, no. 4 (2010): 14-15.
- Habiba, Marwan, and Martyn Evans. "The Inter-Role Confidentiality Conflict in Recruitment for Clinical Research." *Journal of Medicine and Philosophy* 27, no. 5 (2002): 565 - 87.
- Haque, Amber. "Mental Health Concepts and Program Development in Malaysia." *Journal of Mental Health* 14, no. 2 (2005): 183-95.
- Hardwig, John. "What About the Family?" *The Hastings Center Report* 20, no. 2 (1990): 5-10.
- Hearnshaw, Hilary. "Comparison of Requirements of Research Ethics Committees in 11 European Countries for a Non-Invasive Interventional Study." *BMJ* 328, no. 7432 (2004): 140-41.
- Henry, David, Evan Doran, Ian Kerridge, Suzanne Hill, Paul M. McNeill, and Richard Day. "Ties That Bind: Multiple Relationships between Clinical Researchers and the Pharmaceutical Industry." *Arch Intern Med* 165, no. 21 (2005): 2493-96.
- Hoffmaster, B. "What Does Vulnerability Mean?" *Hastings Center Report* 36, no. 2 (2006): 38-45.
- Horton, Richard. "Conflicts of Interest in Clinical Research: Opprobrium or Obsession?" *The Lancet* 349, no. 9059 (1997): 1112-13.
- Hunter, David. "Efficiency and the Proposed Reforms to the NHS Research Ethics System." *J Med Ethics* 33, no. 11 (2007): 651-54.
- Joffe, Steven, E. Francis Cook, Paul D. Cleary, Jeffrey W. Clark, and Jane C. Weeks. "Quality of Informed Consent in Cancer Clinical Trials: A Cross-Sectional Survey." *The Lancet* 358, no. 9295 (2001): 1772-77.
- Jonas, Hans Philosophical Reflections on Experimenting with Human Subjects, *DAEDALUS* 98, (Spring, 1969), 219-247
- Jones, Alysun M., and Bryony Bamford. "The Other Face of Research Governance." *BMJ* 329, no. 7460 (2004): 280-81.
- Kaitin, K. I., N. R. Bryant, and L. Lasagna. "The Role of the Research-Based Pharmaceutical Industry in Medical Progress in the United States." *J Clin Pharmacol* 33, no. 5 (1993): 412-17.

- Karlawish, Jason H. T., and David Casarett. "Addressing the Ethical Challenges of Clinical Trials That Involve Patients with Dementia." *J Geriatr Psychiatry Neurol* 14, no. 4 (2001): 222-28.
- Karlawish, Jason H.T., David Casarett, Jennifer Klocinski, and Pamela Sankar. "How Do Ad Patients and Their Caregivers Decide Whether to Enroll in a Clinical Trial?" *Neurology* 56, no. 6 (2001): 789-92.
- Karlberg, J. "Development of Sponsored Clinical Trials in Asia." *Clinical Trial Magnifier* 1, no. 5 (2008): 77-99.
- Kass, N. E., J. Sugarman, R. Faden, and M. Schoch-Spana. "The Fragile Foundation of Contemporary Biomedical Research." *Hastings Cent Rep* 26 (1996): 25-29.
- Kassirer, J. P. "Financial Conflict of Interest: An Unresolved Ethical Frontier." *American Journal of Law & Medicine* 27, no. 2-3 (2001): 149-62.
- Katz, D, AL Caplan, and JF Merz. "All Gifts Large and Small: Towards an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving." *American Journal of Bioethics* 3, no. 3 (2003): 39-46.
- Kesselheim, Aaron S., and Jerry Avorn. "University-Based Science and Biotechnology Products: Defining the Boundaries of Intellectual Property." *JAMA* 293, no. 7 (2005): 850-54.
- Kim, Scott. "Benefits and Burdens of Placebos in Psychiatric Research." *Psychopharmacology* 171, no. 1 (2003): 13-18.
- Krimsky, Sheldon, and L. S. Rothenberg. "Financial Interest and Its Disclosure in Scientific Publications." *JAMA* 280, no. 3 (1998): 225-26.
- Lang, C.C. "The Current Status of Clinical Trials in Malaysia." *Drug Information Journal* 32, no. Oct-Dec 1998 (1998): 1243S-46S.
- Lemmens, Trudo, and Benjamin Freedman. "Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards." *The Milbank Quarterly* 78, no. 4 (2000): 547-84.
- Levine, Carol, Ruth Faden, Christine Grady, Dale Hammerschmidt, Lisa Eckenwiler, and Jeremy Sugarman. "The Limitations Of "Vulnerability" As a Protection for Human Research Participants." *The American Journal of Bioethics* 4, no. 3 (2004): 44 - 49.
- Levine, Robert J., and Louis Lasagna. "Demystifying Central Review Boards: Current Options and Future Directions: A Summary Report of Outcomes From "Central Irb Review of Multi-Site Trials," 27-28 October 1998." *IRB: Ethics and Human Research* 22, no. 6 (2000): 1-9.
- Levinsky, Norman G. "Nonfinancial Conflicts of Interest in Research." *N Engl J Med* 347, no. 10 (2002): 759-61.
- Lewis, Penney. "Procedures That Are against the Medical Interests of Incompetent Adults." *Oxford J Legal Studies* 22, no. 4 (2002): 575-618.
- Lexchin, Joel, Lisa A. Bero, Benjamin Djulbegovic, and Otavio Clark. "Pharmaceutical Industry Sponsorship and Research Outcome

- and Quality: Systematic Review." *BMJ* 326, no. 7400 (2003): 1167-70.
- Lott, Jason P. "Module Three: Vulnerable/Special Participant Populations." *Developing World Bioethics* 5, no. 1 (2005): 30-54.
- Macklin, R. "Some Problems in Gaining Informed Consent from Psychiatric Patients." *Emory L. J.* 31 (1982): 345 - 74.
- Macklin, Ruth. "Bioethics, Vulnerability, and Protection." *Bioethics* 17, no. 5-6 (2003): 472-86.
- . "Dignity Is a Useless Concept." *BMJ* 327, no. 7429 (2003): 1419-20.
- . "Personhood in the Bioethics Literature." *The Milbank Memorial Fund Quarterly. Health and Society* 61, no. 1 (1983): 35-57.
- Miller, Franklin G., and Howard Brody. "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials." *The Hastings Center Report* 33, no. 3 (2003): 19-28.
- Miller, Franklin G., Donald L. Rosenstein, and Evan G. DeRenzo. "Professional Integrity in Clinical Research." *JAMA* 280, no. 16 (1998): 1449-54.
- Montaner, Julio S. G., Michael V. O'Shaughnessy, and Martin T. Schechter. "Industry-Sponsored Clinical Research: A Double-Edged Sword." *The Lancet* 358, no. 9296 (2001): 1893-95.
- Morin, Karine, Herbert Rakatansky, Frank A. Riddick, Jr., Leonard J. Morse, John M. O'Bannon III, Michael S. Goldrich, Priscilla Ray, Matthew Weiss, Robert M. Sade, and Monique A. Spillman. "Managing Conflicts of Interest in the Conduct of Clinical Trials." *JAMA* 287, no. 1 (2002): 78-84.
- Mowery, David C., Richard R. Nelson, Bhaven N. Sampat, and Arvids A. Ziedonis. "The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980." *Research Policy* 30, no. 1 (2001): 99-119.
- Ong, L. M. L., J. C. J. M. de Haes, A. M. Hoos, and F. B. Lammes. "Doctor-Patient Communication: A Review of the Literature." *Social Science & Medicine* 40, no. 7 (1995): 903-18.
- Orlowski, J. P., and L. Wateska. "The Effects of Pharmaceutical Firm Enticements on Physician Prescribing Patterns. There's No Such Thing as a Free Lunch." *Chest* 102, no. 1 (1992): 270-73.
- Perlis, Roy H., Clifford S. Perlis, Yelena Wu, Cindy Hwang, Megan Joseph, and Andrew A. Nierenberg. "Industry Sponsorship and Financial Conflict of Interest in the Reporting of Clinical Trials in Psychiatry." *Am J Psychiatry* 162, no. 10 (2005): 1957-60.
- Perrey, C, D. Wassenaar, S Gilchrist, and B Ivanoff. "Ethical Issues in Medical Research in the Developing World: A Report on a Meeting Organised by Foundation Merieux." *Developing World Bioethics* 9, no. 2 (2009): 88-96.
- Procyshyn, R.M., A. Chau, P. Fortin, and W. Jenkins. "Prevalence and Outcomes of Pharmaceutical Industry-Sponsored Clinical Trials

- Involving Clozapine, Risperidone, or Olanzapine." *Can J Psychiatry* 49, no. 9 (2004): 601-06.
- Reilly, P. R. "Involuntary Sterilization in the United-States - a Surgical Solution." *Quarterly Review of Biology* 62, no. 2 (1987): 153-70.
- Reisberg, Barry, Rachele Doody, Albrecht Stoffler, Frederick Schmitt, Steven Ferris, Hans Jorg Mobius, and Group the Memantine Study. "Memantine in Moderate-to-Severe Alzheimer's Disease." *N Engl J Med* 348, no. 14 (2003): 1333-41.
- Resnik, David. "The Clinical Investigator-Subject Relationship: A Contextual Approach." *Philosophy, Ethics, and Humanities in Medicine* 4, no. 1 (2009): 16.
- Robertson, John A. "The Law of Institutional Review Boards." *UCLA L. Rev* 26 (1978-1979): 484-549.
- Rochon, P. A., J. H. Gurwitz, R. W. Simms, P. R. Fortin, D. T. Felson, K. L. Minaker, and T. C. Chalmers. "A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis." *Arch Intern Med* 154, no. 2 (1994): 157-63.
- Rochon, Paula A., Azad Mashari, Ariel Cohen, Anjali Misra, Dara Laxer, David L. Streiner, Julie M. Dergal, Jocalyn P. Clark, Jennifer Gold, and Malcolm A. Binns. "Relation between Randomized Controlled Trials Published in Leading General Medical Journals and the Global Burden of Disease." *CMAJ* 170, no. 11 (2004): 1673-77.
- Saxena, Shekhar, Guillermo Paraje, Pratap Sharan, Ghassan Karam, and Ritu Sadana. "The 10/90 Divide in Mental Health Research: Trends over a 10-Year Period." *Br J Psychiatry* 188, no. 1 (2006): 81-82.
- Schüklenk, U., and A. Pacholczyk. "Dignity's Woolly Uplift." *Bioethics* 24, no. 2 (2010)
- Schuppli, C. A., and D. Fraser. "Factors Influencing the Effectiveness of Research Ethics Committees." *J Med Ethics* 33, no. 5 (2007): 294-301.
- Secker, Barbara. "Labeling Patient (in)Competence: A Feminist Analysis of Medico-Legal Discourse." *Journal of Social Philosophy* 30 (1999): 295-314.
- Sengupta, Sohini PhD M. P. H., and Bernard M. D. Lo. "The Roles and Experiences of Nonaffiliated and Non-Scientist Members of Institutional Review Boards." *Academic Medicine February* 78, no. 2 (2003): 212-18.
- Shalala, Donna. "Protecting Research Subjects -- What Must Be Done." *N Engl J Med* 343, no. 11 (2000): 808-10.
- Shalowitz, D. I., E. Garrett-Mayer, and D. Wendler. "The Accuracy of Surrogate Decision Makers - a Systematic Review." *Archives of Internal Medicine* 166, no. 5 (2006): 493-97.
- Shapshay, S, and KD Pimple. "Participation in Biomedical Research Is an Imperfect Moral Duty: A Response to John Harris." *British Medical Journal* 33, no. 7 (2007): 414.
- Silverman, H., B. Ahmed, S. Ajeilet, S. Al-Fadil, S. Al-Amad, H. El-

- Dessouky, I. El-Gendy, M. El-Guindi, M. El-Nimeiri, R. Muzaffar, and A. Saleh. "Curriculum Guide for Research Ethics Workshops for Countries in the Middle East." *Developing World Bioethics* 10, no. 2 (2010): 70-77.
- Sugarman, Jeremy, Carole Cain, Roberta Wallace, and Kathleen A. Welsh-Bohmer. "How Proxies Make Decisions About Research for Patients with Alzheimer's Disease." *Journal of the American Geriatrics Society* 49, no. 8 (2001): 1110-19.
- Szasz, T. "'Idiots, Infants, and the Insane': Mental Illness and Legal Incompetence." *J Med Ethics* 31, no. 2 (2005): 78-81.
- Thompson, Dennis F. "Understanding Financial Conflicts of Interest." *N Engl J Med* 329, no. 8 (1993): 573-76.
- Tully, Joanna, Nelly Ninis, Robert Booy, and Russell Viner. "The New System of Review by Multicentre Research Ethics Committees: Prospective Study." *BMJ* 320, no. 7243 (2000): 1179-82.
- Unsworth, Clive. "Law and Lunacy in Psychiatry's 'Golden Age'." *Oxford Journal of Legal Studies* 13, no. 4 (1993): 479-507.
- Wald, David S. "Bureaucracy of Ethics Applications." *BMJ* 329, no. 7460 (2004): 282-84.
- Welie, Jos, and Sander Welie. "Patient Decision Making Competence: Outlines of a Conceptual Analysis." *Medicine, Health Care and Philosophy* 4, no. 2 (2001): 127-38.

GUIDELINES, PARLIAMENTARY REPORTS, COMMITTEE REPORTS AND OTHERS

International Guidelines and Reports

- Council for International Organizations of Medical Sciences, (CIOMS). "International Ethical Guidelines for Biomedical Research Involving Human Subjects." 2002.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Good Clinical Practice: Consolidated Guideline E6 (R1)." In *ICH Harmonised Tripartite Guideline*, 1996.
- . "Structure and Content of Clinical Study Reports E3." In *ICH Harmonised Tripartite Guideline*, 1995.
- World Medical Association. "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects." 2008.
- . "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects." 2004.
- FOCUS, (Forum for Research Ethics Boards (REBs)/Institutional Review Boards (IRBs) in Canada and the United States. "Report on an International Conference on Conflict of Interest." In *FOCUS International Conference on Conflict of Interest*. Washington DC, USA: National Council on Ethics in Human Research, 2004.
- World Health Organisation. "The World Health Report 2001: Mental Health: New Understanding. New Hope." World Health Organisation, 2001.
- World Health Organisation. "Operational Guidelines for Ethical Committees That Review Biomedical Research." Geneva: World Health Organisation, 2000.

Malaysia

- Malaysian Guidelines for Good Clinical Practice 2004, 2nd Edition.
- National Institutes of Health Guidelines for Conducting Research in the Ministry of Health Institutions and Facilities 2007.
- Guidelines for Application to Conduct Drug-Related Clinical Trials in Malaysia. 12 April 2007.
- Economic Planning Unit Prime Minister's Department Malaysia. "Ninth Malaysia Plan 2006-2010." edited by Prime Minister's Department: Economic Planning Unit Prime Minister's Department Malaysia, , 2006.
- Ministry of Science Technology and Innovation Malaysia. "Biootechnology for Wealth Creation and Social Well Being. The

- Way Forward." edited by Technology and Innovation (MOSTI) Ministry of Science: MOSTI, 2005.
- National Mental Health Registry Malaysia. *The Preliminary Report of the National Mental Health Registry, January to May 2003*. Edited by Nor Hayati Ali Salina Abdul Aziz, Safraz Manzoor Hussain, . Kuala Lumpur, Malaysia: National Mental Health Registry, 2003.

United States of America

- Advisory Work Group on Human Subject Research Involving the Protected Classes. "Recommendations on the Oversight of Human Subject Research Involving the Protected Classes." New York (State) Dept of Health, 2002.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. "Institutional Review Boards: Reports and Recommendations." edited by DHEW. Washington D.C.: U.S. Government Printing Office, 1978.
- . "The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects Research." Washington: Department of Health, Education and Welfare, 1979.
- Department of Health and Human Services. "Mental Health: A Report of the Surgeon General.". Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institutes of Mental Health, 1999.
- Department of Health and Human Services, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, Final Guidance Document." edited by United States Department of Health and Human Services, 2004.
- Department of Health and Human Services, "National Institutes of Health: Conflicts of Interest in Extramural Research." edited by Department of Health and Human Services Office of Inspector General, 2008.
- United States. National Bioethics Advisory Commission. "Ethical and Policy Issues in Research Involving Human Participants." Bethesda, Md. (6705 Rockledge Drive, Suite 700, Bethesda, 20892-7979): The Commission, 2001.
- . "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume I." Rockville, Md. (6100 Executive Blvd., Suite 5B01, Rockville 20892-7508): National Bioethics Advisory Commission, 1998.
- . "Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Volume Ii." 78. Rockville, Md.

(6100 Executive Blvd., Suite 5B01, Rockville 20892-7508):
National Bioethics Advisory Commission, 1998.

United Kingdom

- Commission on Intellectual Property, British. "Integrating Intellectual Property Rights and Development Policy." In *Report of the Commission of Intellectual Property*. London, 2002.
- Department of Health. "Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees." Department of Health, 2005.
- Joint Committee on the Draft Mental Incapacity Bill. "Draft Mental Incapacity Bill: Report with Formal Minutes." edited by House of Lords House of Commons: The Stationery Office, 2003.
- Law Commission. "Mentally Incapacitated Adults and Decision-Making: An Overview, Consultation Paper No 119." 1991.
- Law Commission. "Mental Incapacity, Law Commission Report No 231." In *Law Commission No 231*. London, 1995.
- Medicines and Healthcare Products Regulatory Agency. "Explanatory Memorandum to the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006." OPSI, 2006.

Miscellaneous

- Economist, The. "Billion Dollar Pills." *The Economist*, Jan 25 2007 2007.
- Economist, The. "Innovation's Golden Goose." *The Economist*, December 14, 2002 .
- Evans, D. Smith, M. and Wilen, D. "Big Pharma's Shameful Secret." <http://www.bloomberg.com/specialreport/pharma.pdf>.
- Jackson, D. "The Pharmaceutical Market Outlook to 2010." In *Reuters Business Insight - Healthcare*, edited by Reuters: Reuters, 2003.
- Ong, Y. M. "Role of CRC in Promoting Malaysia to Industry." In *National Conference for Clinical Research, Malaysia*. Kuala Lumpur, 2009.
- PRA International. "Clinical Research in Taiwan, South Korea and Malaysia." PRA International, www.prainternational.com
- Star Online. "Clinical Trials in Malaysia." *The Star Online*, April 22 2007 2007.
- Zakaria, ZH. "Regulatory Aspects of Clinical Trials in Malaysia." edited by Ministry of Health National Pharmaceutical Control Bureau.

Statutes

Malaysia

Civil Law Act 1956

Guardianship of Infants Act 1961 (Act 351).

Mental Disorders Ordinance 1952, Federation of Malaya.

Mental Health Act 2001 (Act 615), Malaysia.

Official Secrets Act 1972

United Kingdom

Code of Practice Mental Capacity Act 2005.

Mental Capacity Act 2005.

Mental Health Act 1983

The Medicines for Human Use (Clinical Trials) Regulations 2004 (as Amended by S.I 2006/1928 & 2984).

United States of America

Patents and Trademarks Amendments Act 1980 (the Bayh-Dole Act).

The National Research Act (1974)

21 CFR 50, 56

45 CFR 46