Changing Ethics – Changing Perceptions

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Abstract

The concept of ethics is something that all researchers must come to terms with every time they consider a study involving humans or animals. Since the Nuremberg Trials, the changing needs of the research community with regards to research design and the recruitment of participants has seen requirements for participation in studies change dramatically with respect to ethical guidelines. The aim of this thesis is to investigate, through well-documented long-term public health cohort studies, how changing perceptions of ethics have impacted on research design and outcomes. The research has been undertaken particularly from an epidemiological point of view as well as in terms of rates of participation.

In order to explore the evolution of ethical thinking and its potential effect on long-term longitudinal cohort studies with a public health bias, an iterative search process was employed to determine eligible studies and to extract relevant papers for the literature review. Examination of response rates in the context of the recruitment processes and ethical constructs in place at the time of recruitment was also undertaken. In addition to qualifying the nature of change in the ethical landscape, it is important to note that questions and changes resulting from ethics frameworks and committees may affect both the implementation and interpretation of the proposed work. By establishing this framework of change, the thesis explores and examines the impact of what can be coined as the "New Ethics Research Environment". A retrospective examination of landmark studies with respect to how they may be affected by contemporary guidelines was used to illustrate the influence of the New Ethics Research Environment on large scale cohort studies which impact on health research outcomes at both an international and local level.

The significance of this thesis is that it highlights the fact that ethics, as a construct in long-term research, generally has the most impact during recruitment and initial implementation of the study. Ethics, as an evolving concept, does not appear to affect long term studies which do not, themselves, change in scope – that is, those studies with only one cohort and no change in methodology. However, when cohorts are continually recruited, changing ethics and changing perceptions have significantly impacted on cohort selection and methodology both prospectively and retrospectively.

Dedication

This thesis is dedicated to the two people who wanted to see it finished but passed away before they could.

Associate Professor Christopher Newell

My original supervisor and mentor who helped me see the big picture from a small idea. It may not be exactly what we imagined but it's done.

Brian Leslie Doyle

My father, my biggest fan and most ardent supporter. I know you wanted me to finish this and you wanted so desperately to see me graduate. I will always regret that it took so long and you didn't get the chance. This thesis is yours Daddy.

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Abbreviations

Abbreviation	Full Name
AHEC	Australian Health Ethics Committee
AMA	American Medical Association
ARC	Australian Research Committee
AVCC	Australian Vice Chancellor Committee
CEC	Clinical Ethics Committee
CHD	Chronic Heart Disease
CIOMS	Council for International Organisations of Medical Sciences
COREC	Central Office of Research Ethics Committees
CVD	Cardio Vascular Disease
DHHS	Department of Health and Human Services
EU	European Union
HEC	Healthcare Ethics Committee
HoMER	Harmonisation of Medical Ethical Research
HREC	Human Research Ethics Committee
ICHT-GGCP	International Committee of Harmonisation Tripartite Guidelines of Good Clinical Practice
IEC	Institutional Ethics Committees
IRB	Institutional Review Board

Abbreviation	Full Name
LREC	Local Research Ethics Committee
MRC	Medical Research Council
MREC	Medical Research Ethics Committee
NEAF	National Ethics Application Form
NERE	New Ethics Research Environment
NHI	National Heart Institute
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NIH	National Institute of Health
NNHLI	National Heart Lung Institute
NRES	National Research Ethics Service
PRIVIREAL	Privacy in Research Ethics and Law
REC	Research Ethics Committee
UI	Urinary Iodine
WHO	World Health Organisation
WMA	World Medical Association

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Chapter One - Introduction

Ethical constructs as a concept is something that researchers contemplate every time they consider a study requiring human participation or use of laboratory animals. Changing legislation, best practice and even changing perceptions within a community can all influence how a research study is designed, implemented and analysed. In smaller public health studies the number of participants can impact on the decisions made from analysing the results. Evolving and changing ethical constructs, as well the way in which we monitor and interact with the ethical process can be assumed to have changed research. This thesis aims to investigate the effect of changing ethical constructs on the methodology in long-term studies with a public health focus.

Certain aspects of the study of bioethics have a basis in regulatory law and scientific literature. These areas, especially of late in genetics, end of life and reproductive technologies, have been legislated for and discussed due to the fact that they are areas which the general public has a perception that regulation and risk management is necessary [1-5]. While all experimentation has an ethical component that is generally enshrined in law, the areas mentioned above have specific legislation, which also needs to be considered in the context of ethical research. While university research may include the above areas, much of the research presented to university ethics committees can be considered under the relevant state or federal laws governing research. Epidemiological work , particularly that in public health, is not necessarily the type of research that raises concern within the scientific and lay community with regards to methodology and execution. However, questions and changes that result from ethics committee scrutiny may affect both the implementation and interpretation of the work, especially conclusions that may be reached and interventions that may be recommended. There is an imperative to obtain a balanced and unbiased sample so that the conclusions which are reached can be assumed to apply to the population as a whole.

At present in both Australia and the United Kingdom, the imperative to present research to an ethics committee is not legally binding from a governmental or statutory point of view [6-16]. In both of these countries, research ethics committees (REC) that are tasked with review and oversight of research do not in themselves have any legal standing. Within both the research community and within the general public they are perceived to have a regulatory and ethical standing. The United States of America has a more legalistic and law based

system, while still also having university and research based ethics committees which are mandated by statutes and regulations [17, 18].

Many bodies and organisations supply research funding with the caveat that the research is approved by an ethics committee (i.e. National Health and Medical Research Council (NHMRC), Australian Research Council (ARC), Medical Research Council (MRC), National Institute of Health (NIH)). There is no legal or statutory requirement for self-funded research to be presented and discussed. The United States of America has a more solid basis in law for the structure of its public health research as ethics committee are legislated and mandated for. This means that there is a legal requirement for research to be presented to an ethics committee before commencement. In Australia and the United Kingdom, ethics committees are an accepted, and in most cases an integral part of the academic research process, but there are no legal requirements for research to be presented to a committee for discussion.

Large scale background monitoring via reporting of incidents by practitioners, used successfully in some aspects of public health (such as communicable diseases and disease outbreaks), is not necessarily feasible or practical with monitoring for other areas such as nutrition or general health [19] . It also fails to consider that longitudinal perspective can help in seeing the effects of public health intervention. From a long-term public health perspective, and particularly an epidemiological view of public health, the present guidelines in both Australia and the United Kingdom, while adequate, could be improved to take into account current advances in both law and techniques. Surveys of health, while not always following the longitudinal cohort model, should be considered as an active process; methods should not vary but be repeatable over time to allow for comparative analysis to be undertaken.

Previous studies have highlighted that there can be a bias towards certain types of groups in large scale studies due to previously perceived discrimination by minority groups. This is especially obvious in the United States of America, where long-term studies from many years ago (i.e. the Tuskegee Syphilis Study) still impact the participation rates of African Americans in many studies [20-22]. A similar sentiment could potentially be portrayed within the Australian Aboriginal community with regards to participation [23].

Murphy [3] noted that the concept of ethical review and informed consent is one which may be at odds with the modern ethnographer. This is supported by Von den Hoonard [24] who noted that, in many inductive research projects (as well as some deductive ones), it is not

always possible to know the outcome of the research; despite this, having prior knowledge of a hypothesised outcome is seen as imperative to obtaining free and informed consent. Both of these concepts can be applied to epidemiological studies, as it is assumed that the outcome of the studies would be hypothesised before being presented to ethics committee for comment.

As is highlighted by Shuster [25], it is the combination of 3 different pieces of code which, when combined, gives us the dynamic ethical environment we are dealing with currently. These codes are the Nuremberg Code, the United Nations International Covenant on Civil and Political Rights and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. These three codes are the ones which ingrain informed consent into the basis of many laws related to research. Part of the purpose of this thesis is to explore how the interpretation of these three codes have affected the way in which epidemiological studies have been designed and carried out over time. Furthermore, this thesis will show how, in certain types of studies, changes in the ethical environment are reflected in methodologies and perspectives.

Specifically, Chapter Three provides a background to current ethical constructs by examining in brief various ethical influences throughout history and thus the development of a "line in the sand" with regards to ethical thinking and the new ethical research environment. This foundation is built upon in Chapter five, which examines the development of ethical codes and constructs from the ethical influences seen in Chapter three.

Chapter Four elaborates on the methodologies utilised to undertake these studies. Through a varying framework of literature searching and previous knowledge, data were obtained and analysed for the case studies.

Chapter Six provides a background to the ethical environments in which the case studies examined in Chapters six and seven have evolved. It assesses the historical and legislative context of ethics committees.

Chapters Seven and Eight examine in depth the case studies chosen for this thesis. They examine response rates, recruitment strategies and how they have changed over time.

Chapter Nine looks at these case studies in the context of the hypotheses generated in the preceding chapters, and determine if they have been proved or disproved. In particular, the concept of community is examined through the case studies, with final conclusions drawn.

Chapter Two - Statement of Research

Is there an association or causal link between changes in the constructs of ethical research at an international and national level since the 1940's? This question is examined in the context of long-term longitudinal studies with particular reference to the Tasmanian Iodine Surveys as compared with two international cohort studies.

The primary concern of this thesis is to explore how the ethics approval processes undertaken by Research Ethics Committees (REC's) affect long-term research. The other commonly encountered committee is the clinical ethics committee (CEC) which Leeber defines as a predominately ad-hoc committee that evaluates treatment regimes in a clinical setting [26]. Other authors define CEC's differently, depending on their area of origin. While Leeber presents a European view of the CEC, Slowther, Johnson et al [27] defines a CEC as the "*provision of support and advice to health professionals and patients on ethical issues arising from clinical practice or patient care*". McNeill found that in Australia CEC's had little influence in providing ethical advice to clinicians and primarily acted as a body for policy formation and to a lesser extent education [28]. In the United States of America the CEC is known as a Healthcare Ethics Committee (HEC). Its function is similar to both the United Kingdom and Australian equivalents with both policy making and ongoing clinical decision making being part of their remit [29].

Legally, both committees are perceived as having predominately advisory roles to either clinicians or researchers. The understanding of the historical context behind RECs is important to understand how the New Ethics Research Environment (NERE) has developed in all three of the countries in question. Researchers such as McNeill [2, 28, 30-33] have examined the influence of research ethics committees on research in Australia, and similar studies have been carried out in other countries by Ashcroft *et al* [34], Benster *et al* [35], Blunt *et al* [36], Beyveld *et al* [37], Neuberger [38], Dyer [39] and Hedgecoe *et al* [40].

While the influence of epidemiological codes and the need for such codes is explored by authors such as Fluss *et al* [41], Prineas *et al* [42], Weed [43-45], Weed and Coughlin [46], Weed and McKeown [47, 48], Beauchamp *et al* [49], Cook [50] and McKeown *et al* [51], no-one has looked at how changing ethical codes, and resultant changes in requirements of ethics committees, impacts on long –term studies.

Evolution of Research

The Tasmanian Iodine Surveys (comprising of three separate studies, including the Tasmanian Iodine Monitoring Programme) were chosen as the initial series of studies. The interest in these studies came about due to the personal involvement of the author in the most recent series of surveys. While working on the iodine studies, questions regarding potential influences that had changed the methodology were raised. This highlighted the impact which ethics was having on the ability to use different methods for recruitment. As this was a state-wide survey, with results used to determine the effectiveness of a voluntary measure of iodine nutrition, the effects of ethical constructs on the iodine program historically and currently became of interest. It was hypothesised that changing methodologies could potentially be ethically influenced with regards to implementation and recruitment.

In this context, the author has taken ethics to mean the consideration of what is legitimate and useful research in a greater scientific context.

This can be broken down into three smaller questions:

> How has ethics changed research since the 1940's?
> What impact have ethics committees had on research generally?
> Does ethical conduct of epidemiological research have a different set of considerations compared to areas such as clinical and biomedical research?

In this context, epidemiological research is considered to be both potentially qualitative and quantitative. While quantitative analysis is the primary indicator in the studies under question, qualitative analysis also has an important role in epidemiological research.

From these three statements, the following hypothesis/questions were generated.

> Have legal issues such as privacy impacted epidemiological research with regards to recruitment and follow up?
> Has research governance affected research ethics?
> Do changing ethical environments in longitudinal cohort studies have long-term ethical considerations with regard to various factors within the study?

The environment that developed from these hypotheses has been coined by the author as "the New Ethics Research Environment" (NERE). This concept will be introduced in the following chapters as a construct to allow for analysis of the case studies in question. The

evolution of this environment runs parallel with the evolution in ethical thinking and constructs. While it may be contested that the NERE is more an evolving regulatory environment based on underlying principles such as dignity and respect, it is the articulation of those principles, and how they are interpreted in the current context that defines the environment. The NERE can be considered to be a series of static moments, and the changes between those moments with their subsequent effect on research providing the basis for the development of the NERE environment.

This thesis will examine how changing ethics and the associated issues have affected longitudinal studies, using two well known long-term cohort studies from First World countries and a series of surveys undertaken over the same period from Tasmania.

Chapter Three - Historical Background pre 1940

The purpose of this chapter is to orientate the thesis to the historical background and development of ethical codes from several different perspectives. It intends to provide a brief overview of the development of ethical thinking and provide an introduction to the building blocks which will be utilised later on in this document. Central to these introductory chapters is a consideration of the movement from an individualist moral concept with regards to ethics to one that is legislated and corporative. The evolution of this movement is traced from differing perspectives with regards to religious and cultural views to the more legislated construct with which most researchers are today familiar. This chapter aims to show how ethics evolved up until the "line the sand" and how that "line in the sand" shaped the New Ethics Research Environment (NERE). While the "line in the sand" is a series of events that prompted outcry and reflection within the scientific community, the historical basis for those events could be seen to justify them. This paradigm shift is shown in the next chapter, with the advent of the NERE concept.

Introduction – the Tree Concept

To fully understand the current ethical environment with regards to research and public health, it is necessary to explore the history of ethics and philosophy as they relate to medicine and the patient. The philosophical basis of medical ethics can be approached in many different ways. For the purposes of this thesis the approach of Thomasma [52] has been used as the divisions he proposed interlink with the issues under consideration. This approach will be used within the analytical context of ethical constraints as undertaken by examination of the case studies.

Thomasma [52] proposes a tree like structure with the trunk being a base of philosophical theories such teleology, virtue and deontology which are being fed by the underlying ideas of philosophy, religion, science and culture. While some may contest that Public Policy Ethics and Clinical Ethics are applications of Applied Ethics, Thomasma takes the view that while these three types are interrelated, they each examine medical ethics on a different level and thus need to be considered separately [52]. He suggests that public policy medical ethics works at a macro level; applied medical ethics works at a meso level; and clinical ethics at a

micro level. Based on these assumptions and suggestions Thomasma's tree is presented in

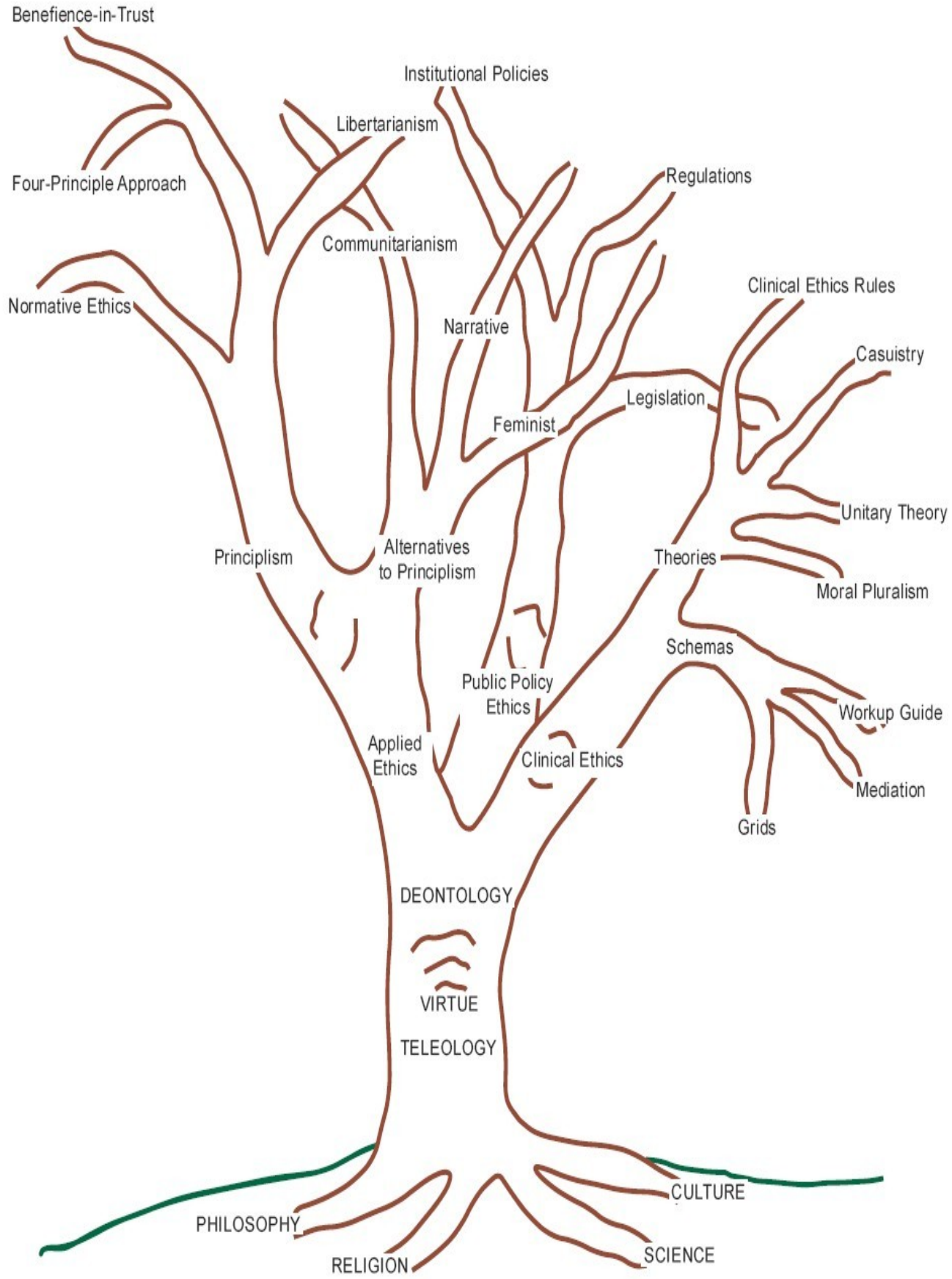
Figure **1**.

From a historical viewpoint, the philosopher Hippocrates provided what most people consider to be the original set of guidance for physicians with the Hippocratic Oath. However there is evidence of earlier moral codes for physicians. These codes, along with the Hippocratic Oath underpins what is considered to be best practise for physicians today [53-71]. While these codes are primarily pertinent to the physician or the medical historian, having knowledge of the concept of medical codes, their history and how they affect and potentially encompass research ethics will highlight how the Thomasma tree concept differentiates the different branches of ethics. Medicine as a treatment for disease and research into a disease were originally interchangeable, but over time they have developed independently into two very different concepts.

The tree concept also allows us to see how the practice of ethics through time has been affected by what has been defined as research. The movement and interpretation of ethics can be seen to evolve from a philosophical basis to one that is shaped and interpreted by the actions of those in government, and on the front line of implementation of ethical conduct. From this tree concept, a time line will be developed to allow ethical changes in research to be potentially linked to changes in methodologies.

Nicomachean ethics as articulated by Aristotle outline a virtue based theory. This theory has influenced the principles encountered in ethics of veracity, benefice, non- maleficence, justice and autonomy [72]. These principles can be seen to underlie many of the medical codes, which both preceded and followed the Hippocratic Oath. Veracity is considered to be the ability of the practitioner to tell the truth to the patient; benefice is the ability of the practitioner to provide benefit to the patient; non-maleficence is taken to be the assumption that the practitioner will not act with the desire to harm; justice is the ability to act in manner which treats patients with equality and without discrimination, and autonomy is the ability of the patient to make a choice.

Figure 1: Evolution of Ethical Thinking Using a Tree Analogy as Described by Thomasma [52].



Limitations of the Tree Model

As this model is a generalised model developed by one author for a specific purpose there are bound to be limits to what is presented. This model was specifically designed by Thomasma to complement an examination of the moral foundations of the patient/physician relationship [52]. Due to this narrow focus the tree is by no means a generalised account of the influences on medical ethics and their development. The tree is also limited by Thomasma's interpretation of what constitutes public policy, applied and clinical ethics. Particularly in the applied ethics branch the definition of applied ethics has been limited to the application of ethical principles to specific medical problems faced by practitioners [52]. Although a wider interpretation would be more advantageous, as the interpretations of both the public policy and clinical ethics branches are generalised enough to allow analysis without modification, the applied ethics definition will not be modified.

By its inherent nature, the model excludes other schools of philosophy and thought such as phenomenology, hermeneutics and the continental school. While these schools of thought are all valid and can potentially add to the understanding of medical ethics, this model was chosen due to its concentration on public policy, clinical and applied ethics which the author considered to be the three main areas of interest within the thesis. However a brief discussion of how these other school of thought could influence the assumptions of the thesis is undertaken to explore the potential limitations of the model used.

Continental School of Philosophy

The continental school of philosophy as it is known today developed during the late 19th and early 20th centuries, but has been around since the 17th Century [73]. It developed as an alternative to the analytical movement of the time. The continental school can be considered to contain such philosophical movements as existentialism, phenomenology, hermeneutics and French feminism [73]. Until the early 1970's, it appeared that Phenomenology and Continental School were used interchangeably in the academic world [74]. There is debate as to what the Continental School actually stands for, but it is generally accepted to be a non-analytical school of thought, supported by those philosophers who were not based in the United Kingdom [74]. As Critchley notes:

"*Continental philosophy is a highly eclectic and disparate series of intellectual currents that could hardly be said to amount to a unified tradition. As such, Continental philosophy is an invention, or, more accurately, a projection of the Anglo-American academy onto a*

Continental Europe that would not recognize the legitimacy of such an appellation -a little like asking for a Continental breakfast in Paris."[74]

This school of philosophy would not have added to the analysis of the case studies examined here due to it not having an analytical basis. The purpose of this thesis was to analyse the effect that changing ethical constructs have had on public health, and the continental school does not provide a solid basis for comparative studies. Two major areas of the continental school do, however, need to be considered separately.

Phenomenology

Phenomenology can be considered both a movement and a discipline within philosophy. It can broadly be defined as the study of structures of consciousness and generally approached from a subjective or first person point of view [75]. While this could potentially add a differing perspective to the analysis, it does not fit into the tree model, which takes an overview approach as opposed to a first person point of view. If time had allowed first person interviews both via telephone or email would have provided a first person point of view and thus allowed analysis using a phenomenological framework. This framework may have highlighted any unusual phenomena which may have influenced either the decision making process or the changing ethical constructs in the case studies.

Hermeneutics

This branch of philosophy evolved from a systematic, critical scientific method used specifically for the interpretation of theological and philosophical exegesis [76]. Currently it is taken to be the analysis of how humans understand experience [76]. While the study of human experience from a participant point of view would add value to the analysis of this thesis, the ability to obtain the remembrances of those experiences of participation would prove difficult. Thus, though an analysis of the behaviour of why people participate in surveys would be advantageous, it does not fit into the tree analogy/model neatly. It could be considered as part of the applied ethical branch in the tree model in the alternatives to Principlism.

The Roots

Pre-Greek Perspectives

The documentary evidence of moral codes for those that practice medicine extends back to the 3rd Dynasty in Egypt (approximately 2700 BCE) [58]. The Smith papyrus discusses cases based on body parts and follows the format of title, examination, diagnosis, treatment and glosses – which are a type of dictionary. However it is the format of both the diagnosis and treatment options, which show the major concepts that today would translate into Aristotle's concepts of veracity and beneficence. The diagnosis and treatment option section is written in the form of a series of caveats which the physician is told to add after the diagnosis depending on their assessment of the patient. These are:

"1. An ailment which I will treat, 2. An ailment with which I will contend, 3. An aliment not to be treated". These three concepts are limited by the physician giving a time period for treatment as either: *"1. Until he recovers, 2. Until the period of his injury passes by, 3. Until thou knowest that he has reached a decisive point*" [58].

The combination of these two sets of caveats suggests that the concept of veracity and benefice are being considered within the diagnostic concept. These two caveats are still very much evidenced in contemporary medical practice.

Prior to Hippocrates, one of the earliest ethicists/philosophers with regards to medicine was the Babylonian Hammurabi. They are responsible for authoring the "Code of Hammurabi" (1750 BCE) [53]. Within this code there are nine clauses that could be considered relevant to medical ethics. The most pertinent of these is an interpretation of the saying "*an eye for an eye*". The can be taken to mean that if the medical practitioner succeeds he gets paid, if he doesn't he loses his hands. The loss of hands and thus the practitioner's ability to practice would have negatively affected his livelihood. This highlighted the concepts of beneficence and justice as later articulated by Hippocrates. Beneficence is shown in that the practitioner is encouraged to provide the most beneficial treatment for fear of being punished. Justice is seen in seen in the ability to act in the right manner. Both of these actions would have been prompted to some extent by fear of losing their livelihood. Forbes [77] calls the Hammurabi code *"the oldest code of laws in the world"*. Forbes draws the distinction between the fact that Hammurabi is a code of laws, while the Hippocratic Oath is more a moral code that the

individual can follow [77]. This juxtaposition between a code of laws and a moral code is a theme that will be explored throughout this chapter.

Greek Philosophy

The Hippocratic Oath that medical students generally recite when being admitted to the fraternity of doctors is the form of medical ethics with which the general community is familiar. The Oath outlines what is perceived to be acceptable medical behaviour as a series of statements or codes [78].

The Hippocratic Oath is perceived and understood to be a set of moral codes, which guide the physician in how they act. This is essentially the first oath that is targeted at the physician and outlines both what a physician ought to treat and his attitude towards treatment of patients. It introduces the concept of confidentiality and of a moral code of behaviour towards patients as seen in "*Into whatever houses I enter, I will go into them for the benefit of the sick, and will abstain from every voluntary act of mischief and corruption*" [79]. Hippocrates was also the one credited with the saying "*First, Do no Harm*" in his treatise on epidemics [55].

As mentioned previously, this Greek perspective is a concept that is apparent in various religious and non religious perspectives through time as illustrated later on in this chapter. These alternative perspectives would appear to have developed independently from the Greeks, yet the concepts at a base level are very similar.

Religious/Cultural perspectives

The religious perspectives noted here are not definitive lists of the various religious values to which people subscribe. The following perspectives could be considered to be some of the major religious influences within a world-view. These influences are thus more likely to have an impact on the development of ethical codes, either consciously or unconsciously. Through most of them there is a concept of moral behaviour and perception as to what is right within a defined series of actions. The concept of moral behaviour has evolved through the lenses of a religious perspective. This in turn influences the non-religious base of the codes upon which researcher's today attempt to base their actions. While it is acknowledged that in some countries an intertwining of religion and culture can influence perspectives with regards to ethical codes and constructs, the consideration of the relationship between

religious and cultural ethical norms will not be considered in this thesis. Where this influence of religion on culture appears to occur, a combined religious/cultural summary is presented.

Indian Religious Perspectives

One of the largest influences of Hindu tradition, and one which carries through all medical ethics whether based in religion or not, is the extortion to "First, do no harm." In this instance, it is expressed as the concept as ahimsa – "*thou shall not do no harm to any living being*" [71, 80].

While Hinduism is the primary religion in India, the Ayurvedic code has taken its influence from both the Hindu and the Buddhist perspectives with regards to ethical conduct in medicine. The pervading sense of morals can be seen in the practice of Ayurvedic medicine. The concept of "moral behaviour" is seen in the Oath of Initiation (*Caraka Samhita*). This document is from first century CE. It instructs a physician to do all he can to save a life.

"*No benefactor, moral or material, compares to the physician who by severing the noose of death in the form of fierce disease, brings back to life those being ragged towards death's abode, because there is no other gift greater than the gift of life.*"[80]

This extract from a more extensive Ayurvedic code shows that religious influences have affected medicine in India [71]. This tradition outlines the expectations of both students and teachers, reminding them that their "*primary goal was not fortune for self and family but care of the sick".* The concept of confidentiality is also expressed in the two ideas of "*You should never give out to others the practices of the patient's home, and even if you be certain of it, you should not speak of the diminution of the period of the patients life when such speaking may shock the patient of anybody else"* [71, 80]. This is similar to the concept today of patient confidentiality. The *Caraka Samhita* also encourages discussion between colleagues – though it does not say if cases should either be discussed for insight, or if it is more of a discourse to exchange information on diseases.

Jewish Perspectives

Religious influences in medical codes are explicitly highlighted in the Hebrew tradition with the Jewish Daily Prayer of a Physician from Egypt in the 12th century CE. While the usage of this prayer is not known it highlights the concepts of beneficence, non-maleficence and veracity. It also urges the supplicant to be humble *"do not permit it to arrogate to itself the power to see what cannot be seen"*. There is also what appears to be an exhortation to

undertake continuous life-long learning in the statement: "*Never allow the thought to arise in me that I have attained to sufficient knowledge, but vouchsafe to me the strength, the leisure and the ambition ever to extend my knowledge*" [54]. While this is presented as a prayer, it could be supposed that this prayer is also an attestation of beliefs and morals, by which this person lived. These beliefs and morals influence their behaviour, and thus how they behave as a physician towards their patients. While this prayer has been attributed to Moses Maimonides, it is more likely to have been written by Marcus Herz in the late 1700's [81].

The Hebrew oath of Asaph (3rd century CE) may be seen as a statement that once again harks back to the moral concept of benefice and non-maleficence. It does this through the statement "*ye shall not harden your hearts against the poor and needy, but heal them*" [57]. This suggests that everyone is entitled to equality of care from the physician, regardless of standing in life.

Within the historical development of the Jewish perspective, the greatest influence has most probably been Moses Maimonides, a rabbi, physician and philosopher. Maimonides was responsible for the codification of Jewish law in the Mishmeh Torah [82]. He also applied Jewish rabbinical thinking to Aristotles concepts of nature [81]. Maimonides asserted that the development of medicine to heal was a matter of obligation and thus medical care could be pursued without violating ones religious obligations [81].

Islamic and Middle Eastern Perspectives

The Persian "Advice to a Physician" also espouses similar concepts as the Indian and Jewish perspectives. It is different in that it contains an exhortation for students to learn from their elders in *"...pay unremitting attention to the conditions and circumstance of their intimates, in company with the most astute professors of medicine"* [63]. This Persian physician (Halay Abbas) also recognizes the fact that medicine is an art in "*and of those things which were incumbent on the student of this art (medicine)...*" The evidence of hospitals and sick houses (i.e. buildings dedicated to the ill) is suggested in *"...he should constantly attend the hospitals and the sick houses; pay unremitting attention to the conditions and circumstances...*" These comments by Abbas, to medical students of the day, suggest that there was some kind of ethical conduct and belief within the Islamic system. This would have an influence on later European systems [63, 69].

The Hippocratic Oath has been inferred to have influenced the Middle Eastern perspectives on medical ethics [83]. Weisser [83] noted that it is the exhortations with regards to doctor patient interactions which have endured as opposed that of the teacher student relationship.

Weisser [83] also noted that ethical issues in early Islam are highly influenced by deontological thinking. That is, the issues are judged as by what is a moral action with regard to a situation. This thinking links forward to the branches of the tree concept which Thomasma has proposed [52].

Confucian/Buddhist Perspectives

These concepts of ethical conduct and moral influences are also seen in the Ming Dynasty (1368-1644) in China, where physicians were expected to keep to Confucian ideals of the highest standards [67]. A Chinese contemporary of Hippocrates, Bian Que, is considered to be the first to have formulated guidelines for medical practitioners in China – exhorting them to trust in medicine rather than witchcraft [84]. These standards are very similar to those espoused by Hippocrates in that they call for an appreciation of the value of life, to have sympathy with the patients, always strive to improve the skills and oppose others who work carelessly, equality of patients with regard to treatment, standing and ability as well as the reminder to *"respect other peoples' achievements and to abide by academic ethics.*"

Fan [67] noted that while Confucian philosophy and perspectives are still a part of everyday life for many in Asian countries, the concept of utilizing the physicians' virtues such as self cultivation, dedication and family care are not as prominent today. The trend towards a more business model highlighted the increase in patient autonomy and the decrease in the respect of the physician [67].

There are two prevailing schools of thought which comprise the Buddhist perspective [85]: the first is that ethics (rules and virtues) are instrumental, as the Buddha's teachings and path are provisional. This suggests that ethics cannot be an absolute or universal rule. The second school of thought suggests that ethics has a fundamental role in shaping thought. Neither perspective allows for ethics to be considered autonomously within the Buddhist construct, but can be interpreted as a virtue ethic, and thus be compared to the Nicomeadian tradition [85].

Christian Perspective

The Christian perspective has similarities to the Hebrew/Jewish perspectives in regards to the adoption of the concepts of Aristotle as a basis for ethical thinking. However, there are differences. Wear [86] noted that Christianity provides medicine with a differing set of ethical values. It is the first hint at doing something for the greater good as opposed to the individualistic care models, which were previously seen as the societal norm in the United Kingdom. As the care of the sick was one of the six works of charity of the early Christian church, the need to do right as a group as well as at an individual level was highlighted [86].

The Christian perspective can be divided into three similar, but distinct camps – the Orthodox, the Roman Catholic and the Protestant perspectives. While all three of these perspectives have their basis in early Christian values, the deviations from early values are seen as the different types of Christianity evolve.

The early Christian perspective with regards to medical ethics can be seen in the interpretation of the Golden rule: "*Do unto others as you would have them do to you*" (Luke 6:31). The concept of agape (the love of God or Christ for mankind) is the defining concept in early Christian medical ethics [64]. This concept is carried through later Christian perspectives but in slightly differing ways. The Orthodox Christians turn to a spiritual context in which all decisions are related back to the aim of trying to be closer to God [66]. The Roman Catholic perspective has two time period influences. From the early Middle Ages to the first Vatican Council in 1869, canon law and moral theology provided the basis for medical ethics [65]. This was due in part to the fact that the first systematic efforts to define the moral responsibilities of physicians came about in response to specific decrees of canon law [65]. Amundsen [65] also notes that early medieval canon law had a dominantly punitive character which has been a defining characteristic of Catholic medical ethics for much of its history. This was not much of a deviation from early Christian medical ethics. Little deviation in the concepts expressed by Aristotle in his Nicomachean ethics is seen. The concepts expressed up until the first Vatican council included:

"*Never administer medicines about whose effects they are in doubt of or test substances on a patient if they expose the patient to grave death or injury,*

Never seek to increase their "reasonable" fee by aggravating or prolonging illnesses,

Be honest with the patient and advise if a priest is necessary,

Refrain from advising sinful means of recovery of health."

From Vatican I (1868-1870) to Vatican II (1962-1965), the major changes were articulated by Pope Pius XII to the World Medical Association in 1954. Using the concept that the basic principles of medical ethics are part of the divine law and that medical ethics should have three fundamental principles, he proposed that:

"1. - *The medical morality should be based on the being and nature*

This is because it must respond to the essence of human nature and its laws and relations immanent. All moral rules, including those of medicine, necessarily arise from the corresponding ontological principles. Hence the maxim: "You will be what you are." That is why a purely medical moral positivist denies itself.

2. - The medical morality must be in accordance with reason, purpose, and guided by values

Medical morality does not live on things, but in men, in people, including physicians, in their view, their personality, their design and realization of values. The morale in the medical care is the issues of personal conscience: "What is their justification?" (I.e. what purpose do they propose to use?). "What value it expresses itself in their personal relationships in their social structure?" Put another way: "What is it?" "Why?" For what purpose? What is this worth? ". Moral men cannot be superficial, and if so, cannot remain such.

3. - The medical morality must be rooted in the transcendent

What ultimately, is established by a man, a man can ultimately, suppress and accordingly (if it is needed or so it place) can not comply. This contradicts the constancy of human nature, evidence of their destiny and purpose, and also

contradicts the absolute and inalienable character of their essential requirements." [87]

Walters [88] mentioned that Catholic medical ethics are not primarily a professional code but a more general ethical construct whose norms are relevant to the intentions and actions of both the physicians and patients. He also noted that most ethical philosophers in the 18th and 19th centuries were conditioned to think in terms of either Christian or Jewish ethics. Since then, there has been refinement and debate within the Catholic Church as to their standing on many issues on which medical science is today based. However, these debates have not changed the basis of the Catholic perspective on the biomedical ethical code, so thus will not be considered further.

The Protestant perspective on medical ethics does not come about until after Vatican I, which was convened to reflect on the Reformation. The Protestant influence had a large impact on scientific revolution within Europe and particularly within England. Within this context it was expected that the ideas of professionalism would be influenced by moral and religious values [68]. Ferngren [68] noted that as the medical profession became more secularized and less intertwined with religious constructs the influence of people such as ministers of religion – who previously would have also been doctors and healers – has diminished. This is due in part to the requirements of more rigorous qualification procedures but also to the separation of church and state, which took place around this time.

Pre -19th century Protestant literature does not contain any discussion on medical ethics [68]. No real attempt to deal systematically with medical ethics from the Protestant perspective is apparent until the late 1940's. At this time, Fletcher gave a series of lectures at Harvard based on the then radical concept that the patient had a right to choose what happened to them; this opposed the use of a distinct religious paradigm through which the physician could guide the thinking of the patient into choosing [68]. Unlike Catholicism, the varying interpretations of Protestantism mean that there are many different views on any given ethical dilemma. However, all Christian religions stress it is the right of the patient to make a choice. The Roman Catholic and Orthodox views suggest, however, that the patients' choice be guided by theological and moral constructs [68]. It could be assumed that as the influence of the Church on daily life decreased, the autonomy of the patient was not as influenced by religion.

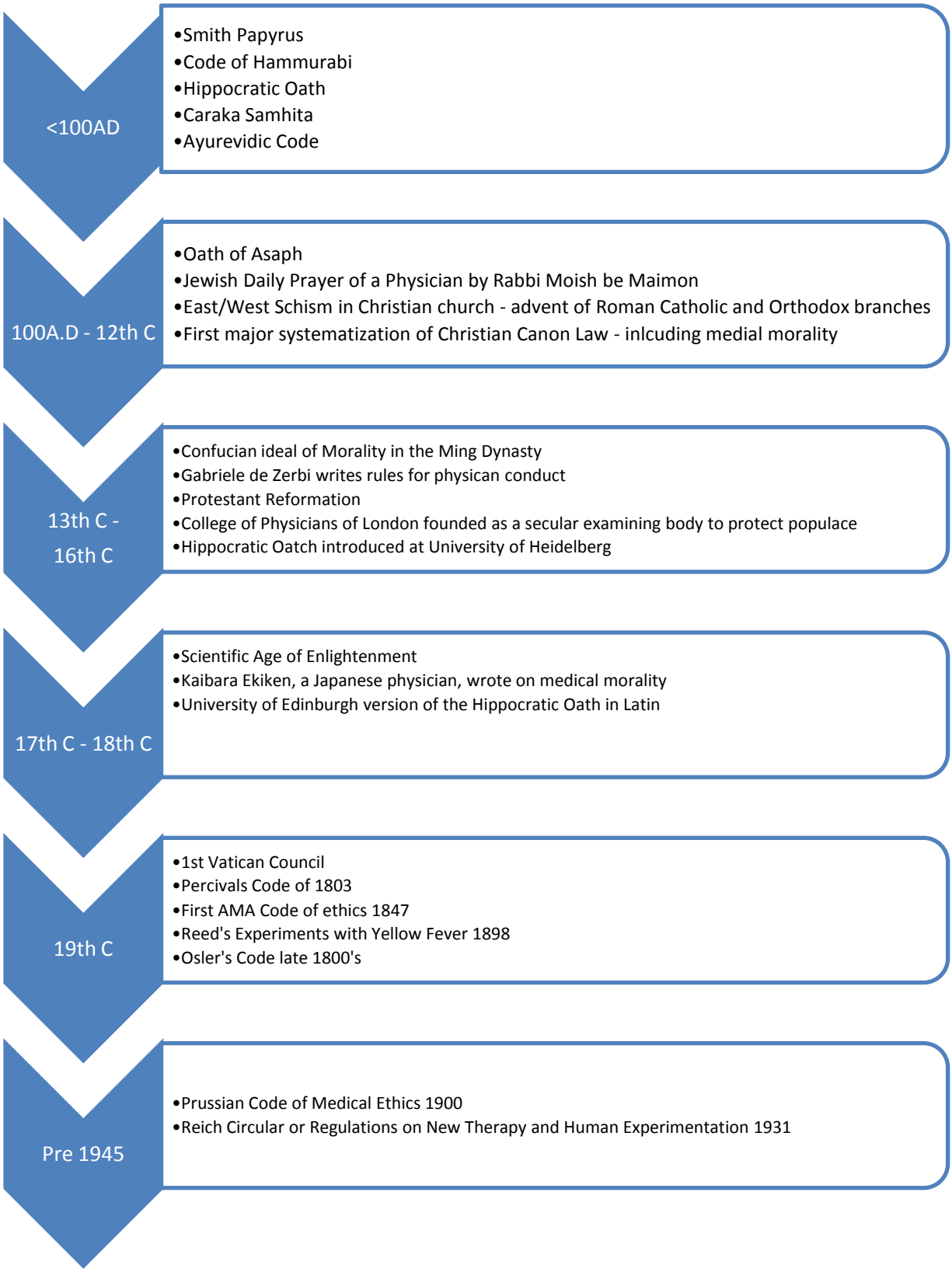
Scientific Perspectives

The evolution of scientific thinking, especially with regards to medical advances, has naturally influenced the way medical ethics is perceived. As science has advanced, the separation of scientific thinking from religious influence has allowed for the development of ethical codes without the influence of religion. In Christian civilisations, the church originally controlled much of the learning and dissemination of learning within a community. The Middle Ages were highly influenced by the church, but as the age of enlightenment developed (from the 1650's onwards) the scientific endeavours of medical research expanded from the universities and monasteries into a wider secular-based world. As the ability to learn evolved away from the church, it became more accessible to the higher classes. While many different influences were seen, breaking away from the Christian perspective and its restraints could be seen as one of the biggest single events in the development of contemporary ethics. This breaking away is reflected in the tree concept as the growth from the roots of to the trunk, which supports the varying ethical principles being discussed.

With the advent of a more secular influence to learning, and the accessibility of learning to a larger cohort, opinions with regards to what was and was not ethical became increasingly varied. These opinions helped form the trunk of the tree with regards to philosophical concepts, which, although expressed prior to the removal of the church's influence, became more pronounced as the medical field became increasingly secularised. The scientific perspective is still an evolving construct – as is seen later in this chapter, with discussion on early medical ethics codes.

Figure 2 shows a basic time line of ethics and the events that have shaped ethics to this point in time (prior to World War II). This time line also allows us to see the development of the trunk and branches of the ethical tree.

Figure 2: Time line of Ethical Thinking, Influence and Events Up Until World War II and the Advent of the New Ethics Research Environment. Based on Baker and McCullough [89].



The Trunk

The three philosophical concepts which Thomasma [52] proposes as the trunk of the ethical tree are all considered part of the Normative ethical construct. This construct highlights how actions can be integrated into a moral framework and how the standards of right and wrong applied to any given action. All three of these normative constructs have influenced in some way the development of the three main branches of ethics that are being considered in this thesis. While only one of these concepts encompasses the virtues as conceived by Aristotle, all three present differing constructs and frameworks from which the branches of the ethics tree grow.

Deontology

It has been said that much of the Judeo-Christian tradition is based on deontological principles [52]. Deontological ethics is a form of ethics which can be seen as duty based [90]. In its simplest form, this refers to the checking of an action again a set of pre-ordained obligations and duties to see if the action is right or wrong. From this definition, deontological ethics can be broken down into rights-based ethics, rules deontology and situation ethics [90]. While all of these ethical areas are valid, the way in which they are applied can influence the decision making process.

Rights-based ethics applies the principles of autonomy, beneficence, non-maleficence, justice and veracity to both the doctor and the patient. It is the doctors' obligation to adhere to these principles, while it is the patients right to expect and use them. Rule deontology is based on correct reasoning, not feelings, comparing a moral act to a set of rules or principles to determine if it is right or wrong as well as ethical or unethical. Situational ethics was coined by Fletcher in the 1960's, and suggests that while there are absolute moral laws, overall there is only love [90]. As can be seen from the discussion of the roots of the Thomasma concept, the concept of moral action is something that is found in many different religious perspectives. How that moral action is interpreted, however, is something which becomes a very personal choice, based on many different factors [52]. This type of ethics is considered to be one of the more common types of thinking when considering medical ethics [91].

Virtue ethics

Virtue ethics as a concept is probably best expressed by Aristotle in his work entitled "Nicomachean Ethics" [61, 72]. This work is the first which highlighted the concepts of veracity, benefice, non-maleficence, justice and autonomy [72]. Compared to deontological

ethics, the virtue ethics highlights and emphasizes the character of what is known as a moral agent, as opposed to the rules and consequences which other types of ethics are bound by. Johnson and Johnson [90] note that rather than making binding rules and duties, virtue ethicists suggest we should concentrate on changing peoples' attitudes and character which will then inspire them to do the right thing. Through its consideration as part of the normative grouping of philosophical constructs, virtue ethics places an emphasis on "being" rather than "doing". Virtue ethics still require a framework, and without that framework, virtue ethics, like other ethical principles becomes subjective [90].

Teleological ethics

Teleological ethics are also known as consequentialism. Consequentialists are known for rejecting the idea that universal moral laws can be distilled to a single decision [90]. They argue that the only way to discover if something is right or wrong is through examination of the consequences. However, the problem with this way of thinking is that it cannot anticipate long term results [90]. Within the school of consequentialism, the utilitarians show the purest form. They state that a moral act is one that allows the greatest balance of good over evil for the greatest number of people [90]. Teleological ethics differs from both virtue and deontological ethics in that it is based on potential consequences rather than the either the moral action of deontology or the moral agency of virtue ethics [50].

While all three of these constructs can be considered separately, it is the combination of moral action, moral agent and consideration of the consequences of the action by the agent that provides the basis for the trunk of the ethical tree.

The Branches

There are three branches of the tree concept which Thomasma [52] considers to be the main branches of medical ethics. All three of these branches take some of their basis from each of the normative constructs outlined above – however, these constructs only provide a basis for the thinking and development of the types of ethics being considered. Influence from outside sources such as advocacy groups, government, industry *etc*. also affect how the ethical constructs are presented and developed [92-94]. As tree branches grow and change, ethical constructs change with differing ideas evolving from the same basis.

Of these three branches, applied ethics and public policy ethics can be considered to be the major areas with which this thesis is concerned. However, clinical ethics can be considered if we assume that they involve discussion of the implication of an intervention.

Public Policy Ethics

This ethical concept in the tree analogy is the most generalized. It allows for addressing issues that can be considered to have broader society based impact as opposed to issues at an individual level [52]. Public policy ethics refers to the stream of ethics that those such as Chadwick and Snow were using unconsciously in their decisions about Poor houses and cholera respectively. Public policy ethics can also be perceived to be the ethics most likely to be utilised with regards to government policy.

Applied Ethics

Applied ethics in this context refers to the application of ethical principles to specific medical problems faced by practitioners [52]. Applied ethics is the action branch of the tree. It is this branch that allows a researcher/practitioner to exercise their own decisions and judgment based on information from the other two branches. The use of applied ethics is apparent in the development of many of the codes of practice, either personal or those which have developed through time; some of these codes have been championed by individuals, others by groups – and some even by countries.

Clinical Ethics

This genre of research concerns the focusing of the previous two branches into bedside care. While it is a branch of ethics of itself, clinical ethics also draws on the experiences of public policy and applied ethics in the decision making processes [52]. It is this branch of ethics which is most used in making decisions about the treatment of an individual as opposed to a larger group. Clinical ethics can be considered to be the closest to research ethics with regards to what is involved for the practitioner and the participant. While clinical ethics primarily examines the patient/practitioner relationship, in many cases the patient is analogous to the research participant, and the rights and feelings of the patient could also be applied to the research participant. Clinical ethics are more generally interpreted as ethics of treatment of an individual in a clinical setting, not of a research participant in a trial. Due to this distinction, clinical ethics will not always be considered in the analysis of the case studies.

Overlapping Branches

While the branches within the tree concept are presented as separate entities, like any living tree, they will overlap and support each other. The application of public policy and clinical ethics is an applied action, and thus can be influenced by applied ethics. The overlapping of these three branches is particularly evident when recruitment into studies is considered. Dependent on the study in question, you may be recruiting a patient to become a participant – in which case both clinical and applied ethical branches may be relevant. Recruitment for a study such as Framingham would include all three branches in their consideration of ethical practice.

It can be considered that a patient can be a participant, but a participant does not necessarily have to be a patient. This is particularly true in public health studies, such as the ones that will be investigated here; patients currently being treated or investigated for the disease in question were not recruited. The patient is a more vulnerable participant and, as Woodward [95] points out, the line between patient management and patient autonomy is becoming more blurred due to increasing influences on the patient-physician relationship. The development of these ethical branches and their potential influences on the patient as a participant can be reflected in the development of the ethical constructs of medicine over time.

Development of Ethical Codes in Medicine

Differing ethical constructs have developed over time in medical fields; while there may have been various influences on the development of these, as discussed above, certain private figures have had a substantial influence on the ethical development of codes.

For example, the first mainstream code of importance from an English-speaking nation was the Percival code of 1803. Percival was a doctor who first published a pamphlet on jurisprudence in 1794. Based on comments from colleagues, he expanded this pamphlet and changed its title to "medical ethics" [96], and the document subsequently provided the basis for the first American Medical Association code of ethics in 1847 [96]. This code was also the first that specifically mentioned experimentation in medicine in order to find better treatments. Percival also suggests that talking with a group of colleagues (an ad-hoc ethics committee if you will) before undertaking the experimental treatment is advisable; he is recorded as noting that:

"*New methods of chirurgical [sic] treatment should be devised but, in the accomplishment of the salutary purpose, the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy or well-authenticated facts. And no such trials should be instituted without a previous consultation of the physicians or surgeons according to the nature of the cause*." [97]

There is, however, no notion of asking the patient if they wanted the experimental treatment carried out on them, something that Beaumont highlights in the United States of America in 1833. William Beaumont was an army physician who carried out experiments over a number of years on Alexis St. Martin, who possessed a gastric fistula [98]. Roland Numbers [99] however propose that Beaumont's code of ethics misinterprets another researcher's hypothetical application of principles. He backs this assertion with reference to Beaumont's research notebooks and correspondence [99]. No other authors appear to share Numbers' reservations [99]. Even if Beaumont's code was not authored by him, the sentiments and interpretation are very similar to Percival. Beaumont acknowledged that experimental treatments are important for patients who are not responding to the conventional treatment. Beaumont justifies this in what is purported to be his code by:

"*Some experimental studies in man are justifiable when the information cannot otherwise be obtained...*

The investigator must be conscientious and responsible for a well considered, methodological approach is required so that as much information as possible will be obtained whenever a human subject is used. ***No random studies are to be made.***

The voluntary consent of the subject is necessary and the experiment is to be discontinued when it causes distress to the subject, or abandoned when the subject becomes dissatisfied."

(emphasis mine) [97]. The first sentence in this quote is comparative to sentiments expressed in Percival's code earlier.

It is suggested that Beaumont had said that *"No random studies are to be made."* This extract is the major point of difference between Beaumont and Percival, and showed an evolution in thinking. However, interpretations of this statement differ. It could be considered the exact opposite of that which generally happens today, with test participants randomly assigned to either the placebo or experimental treatment. It could also be interpreted as indicating that no studies should be made without a justifiable reason – something ethics committees today

monitor. Finally, it could suggest that the randomisation of someone into a study was not to be done, and that all participants should be carefully selected.

It was not until 1898 that there is documented evidence of informed consent. Informed consent is taken to be the obtaining of permission from experimental subjects before the study was carried out. This informed consent was taken by Dr. Walter Reed on his experiments with yellow fever transmission using US soldiers [100]. Each participant in the yellow fever trial signed a disclaimer acknowledging that they were aware of what they were participating in, and the risks associated with it. While prior to this participants would have generally had a choice as to if they participated or not, Reed, by obtaining written consent, documents the participants knowledge and willingness to participate in the research process. This act actively involves the participant in the research process and shows an evolution from just participating without acknowledging the risks that participation may entail, to informed participation.

The Prussian code itself was developed in response to the fact a Berlin based researcher named Albert Neiser had inoculated unknowing minors with syphilis serum to see what would happen. Grodin [97] hypothesised that this may actually be the first reported regulatory action relating specifically to the field of medical experimentation. The Prussian code could be considered to be the first instance of an action/reaction code - one that is put into place as a reaction to an event or action as opposed to a progressive code, and one that spurs change by what it stands for.

The British Canadian Sir William Osler is a potential link between Reeds' consent forms and the advent of the Prussian code of medical ethics. This latter code is the first time we see a recommendation for excluding certain parties such as minors and those deemed not competent, while arguing against medical intervention without clear consent given from properly supplied information [101]. Osler, while working with Reed in the United States Army, was also a member of the Berlin Institute. He was aware of the Neiser controversy and the reaction to it. Anderson [101] hypothesises that either Osler or his contemporary Welsch conveyed the fallout of the incident to Reed, which prompted his use of informed consent.

The final code that is considered in this chapter is from Germany – namely the Reich Circular or Regulations on New Therapy and Human Experimentation in 1931. This circular evolved from the earlier Prussian code. It was written by the Reich Health Council in an attempt to

regulate experimentation on humans [102]. The changes between this circular and the occurrences which prompted the Nuremburg code to be written are striking. The circular acknowledges the fact that there is a need for human subjects for medical experimentation, but it sets down quite strict conditions as to how this may be carried out, concentrating primarily on the need for consent and the overall well being of the test subject [97]. These guidelines were apparently in force until 1945, but the disjunction between what is written and what was actually carried out is a stark example of how guidelines may not necessarily be the way forward. For example, legally enforceable legislation is the only sure way of being able to prosecute those who do not follow the law. Many of the doctors within the German system joined the Third Reich with the belief that they would be contributing towards a better Germany by being part of the system. By becoming part of the system they tacitly agreed to follow the recommendations of the Reich system as opposed to judging for themselves what was best for the patient [103]. This failure to follow ethical principles in the most fundamental sense (i.e. a loss of the belief of the tenets of Nicomachean ethical principles) is one of the historical events – the "line in the sand" – that led to the development of international codes of conduct developed after the war.

There is debate in the literature as to the legal standing of this circular. The International Office of Public Hygiene does not cite the 1931 regulations as part of their ongoing monitoring of International and National Regulations on Health, nor is it mentioned in either the 1931 or 1932 bulletins from that office [102]. This would suggest that the greater scientific community regarded the circular as a set of guidelines that were desirable to follow as opposed to legally binding regulations. Sass [104] however suggests that the guidelines were legally binding up until 1945 and the fall of the Reich. Whether the circular was mis-interpreted or ignored to further scientific research is something that will never be fully clear. The experiments with which the public is generally familiar such as Mengle's twin studies are very much of the latter situation (that is, the circular was ignored to further scientific research).

The Circular, which was so misinterpreted or ignored, contained 14 points, of which points 5-7 could be considered the basis for most research ethical guidelines today. They state that:

"*5. Innovative therapy may be carried out only after the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information provided in advance. Where consent is refused, innovative therapy may be initiated only if it*

constitutes an urgent procedure to preserve life or prevent serious damage to health and prior consent could not be obtained under the circumstances.

6. The question of whether to use innovative therapy must be examined with particular care where the subject is a child or a person under 18 years of age.

7. Exploitation of social hardship in order to undertake innovative therapy is incompatible with the principles of medical ethics."

When we consider these points, along with the consideration that the Reichsgesundheitsrat (Reich Health Council) stated in the preamble to this circular that "*All physicians in open or closed health care institutions should sign a commitment to these guidelines when entering their employment."* The deviation from what could be considered to be an ethical and logical interpretation of the document is telling.

Even prior to Aristotle, the concepts of justice, beneficence, non-maleficence, veracity and confidentiality were considered by early medical practitioners. The continual referral to these principles through time, suggests that even today they would be within the considerations of an ethics committee when examining research. However, the first formal ethics committees were not necessarily constituted to uphold these virtues, but to act as guardians both of research and of those unable to guard themselves.

This chapter has highlighted that medical ethics throughout history has slowly evolved from a doctor-centred to a patient-centred approach. The rise of research ethics through the actions of key figures such as Reed and Osler reinforced a growing understanding that individuals potentially have a choice in participating in research studies. It is through choice that people take part in studies today, and the advent of choice can be seen to start with people such as Reed and Osler.

The nature of that choice to participate may be varied – it could stem from desperation due to illness, or from obligation. However, as long as the participant willingly enters into the project, they have made a conscious choice to participate. Sin [105] notes that there are many implications to participating in research, and it behoves the researcher to be aware of the possible effects they may have on both participant and study. The concept of informed consent, and the ability of a person to provide it is complicated by social constructions of 'normal', 'competent' and 'informed consent' [105]. They also highlight the fact that much

of the need for informed consent eventuates from the need to protect and safeguard the welfare of participants after the atrocities of World War II [105].

Lachman [106] notes that informed consent has to find the middle way between the hard line libertarians and the utilitarians. Libertarians would like us to believe that consent is not only necessary but also sufficient for almost all activities not actually forbidden by law. Utilitarians state that actions should be guided by whatever produces the greatest good for the greatest number. While neither of these ideas provides a complete answer, they all influence the choice that a person makes to participate in a research project.

It is when research starts to stray from these developed ideals that problems begin. This is seen starkly in the German and Japanese experiments in the Second World War. The world became aware quite quickly of German experimentation and the Japanese programs were just as horrific [107]. While those who oversaw the experimentation were tried at the Japanese War Crimes Trial, many of those persons directly involved were never brought to trial. There was no Japanese equivalent to the Nuremburg doctors' trial [107]. Both countries had legal processes, but the disjunction between what was ethically correct and what was undertaken was more apparent in the German cases, as the Reich Circular did advocate the right of the patients to choose to take part in studies. These events, which caused ethicists to draw a hypothetical line in the sand, started a cascade of both action/reaction codes and progressive codes.

Chapter Five expands on this concept of "the line in the sand", and looks at how codes have developed since then, with the evolution of the NERE based on the events outlined in this chapter. The next chapter, four, examines the methodology utilised to determine the case studies, as well as determining the literature.

Chapter Four - Methodology

Introduction

The methodology and justification have been developed using an iterative questioning process. An initial research statement was generated based on observed and experienced incidents with regards to ethics and longitudinal studies, which was subsequently refined during discussions with the authors' supervisors. A methodology for identifying relevant literature was developed, with an iterative process to update continually the literature search as needed.

Definitions

Due to differing interpretations of various terminologies within the literature, the definitions of various terms as they have been used for the purposes of this thesis are presented below:

Ethical Clearance

In the context of this thesis, an ethical clearance is the examination and discussion by a Human Research Ethics Committee (HREC) of a given research project and the subsequent signing off of the project in question with regards to its methodology and justification. Ethical and social norms at the time that the study was initially presented are taken into account for the initial ethical clearance. Also considered are any changes to the study that would require it to undergo ethics committee scrutiny after having initial permission to start.

Longitudinal Study

A longitudinal study as defined by Last [108] is seen as a specialised type of cohort study. A cohort study for the purposes of this thesis is a method of study where subsets of a defined population can be identified as being exposed to a factor which may or may not influence the outcome [108]. The main feature of these studies is observation of the factors under investigation over long periods of time – "longitudinal", therefore, defines the method of the cohort study.

Cohort

In epidemiology, a cohort is defined as a group who share a common experience or condition [108], whereas dictionaries tend to defines cohort more generally as group or company. For

this thesis, the definition of cohort will be taken to mean the epidemiological definition unless otherwise specified.

Ethical Issues

Ethical issues are defined as any incident or consideration that may impact on the ethical clearance of the study as required by HRECs to reach a decision regarding approval or ongoing approval processes.

Non Interventional Study

A non-interventional study for the purposes of this thesis is defined as a primarily observational methodology, with data collected through examination and non-invasive procedures. Here, the study can either be a single long-term study/survey conducted over a period of time, or a series of investigations looking at the same initial problem using similar methodologies and selection procedures.

Well Documented

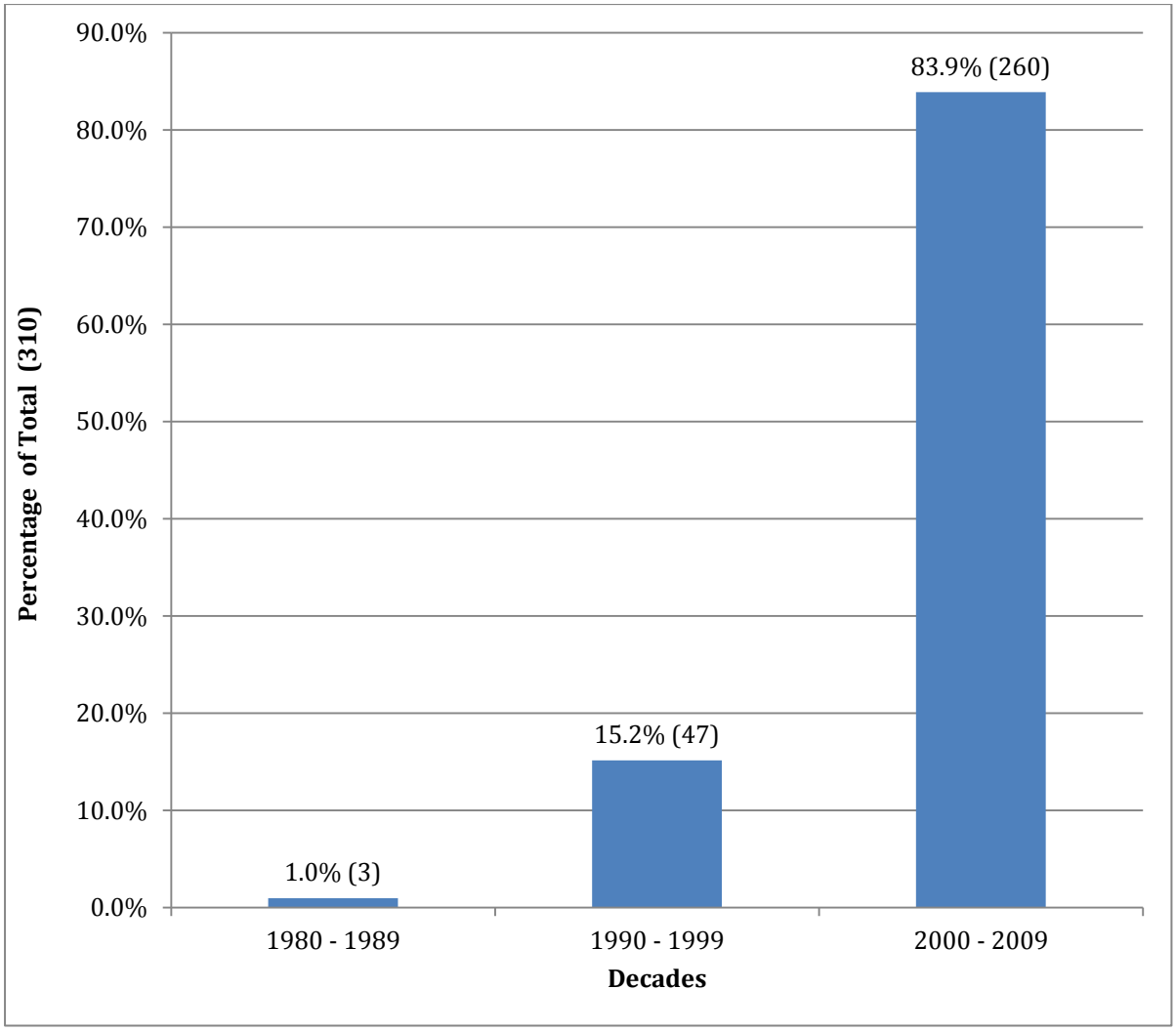
The term well–documented was used when data from a study under consideration was published in a peer-reviewed journal. Due to the extended time period that the case studies under consideration took place; ongoing publication was a selection criterion to enable comparisons of retention rates and other issues.

Defining the Scope of the Problem

Search strategy to Define Problem

A search of Scopus, Web of Knowledge and Pub Med was carried out using the primary key words of cohort, epidemiology, longitudinal and public health. The percentage of papers per decade from Web of Knowledge can be seen in Figure 3. This distribution is similar to Scopus and Pub Med as many papers were found on all three databases. The most cited and relevant authors from these results were extracted. The identified papers were read and then utilised to define the scope of the issues as defined in Chapter Two.

Figure 3: Percentage of Papers by Year Matching Search Criteria of cohort, epidemiology, longitudinal and public health in Web of Knowledge Database

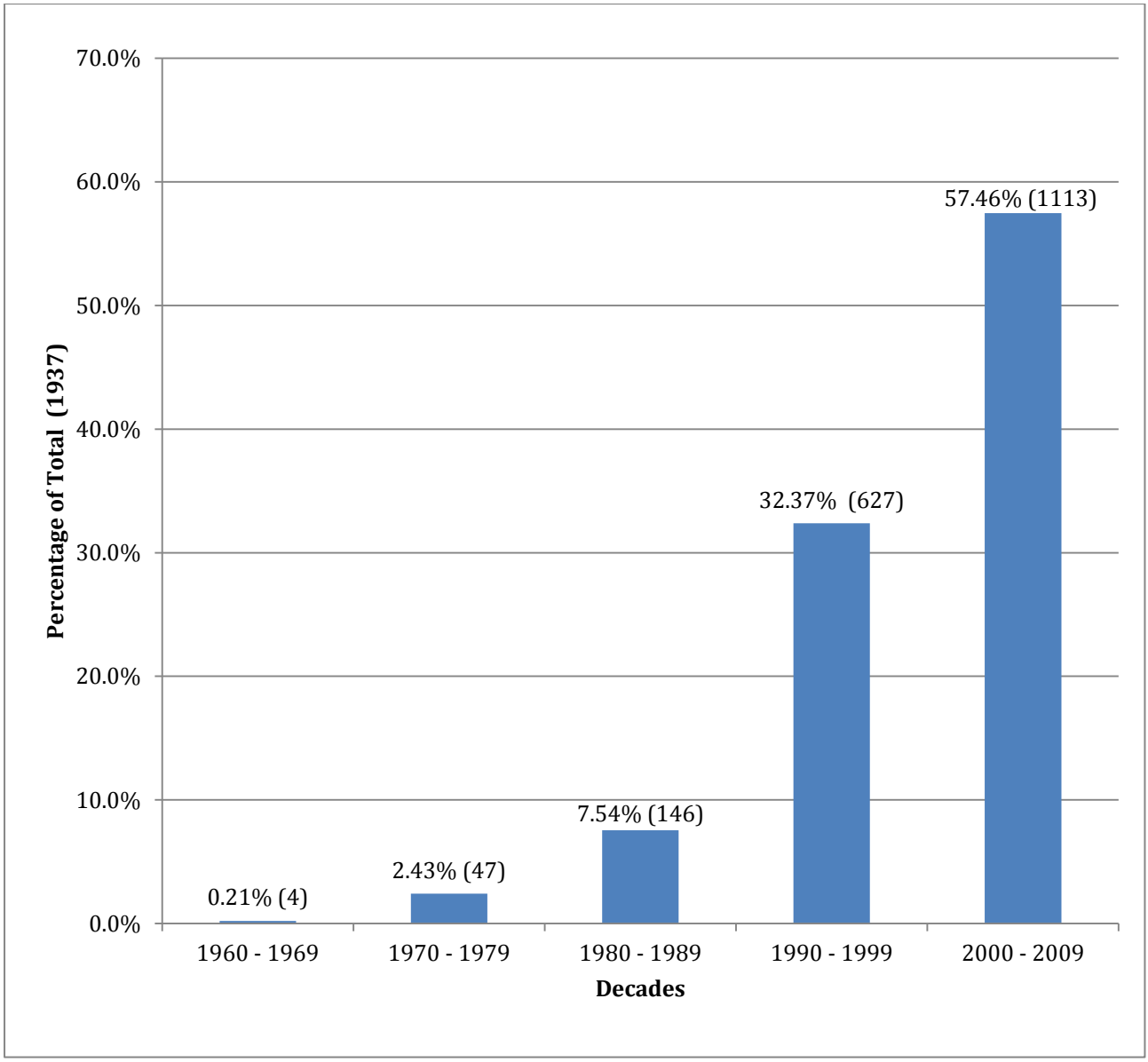


Search Strategies for Historical and Background Information in Ethics and Epidemiology

The search strategies outlined below allowed for the literature to inform the context of this thesis as well as to provide background information on ethical thought with regards to epidemiology and longitudinal studies in public health.

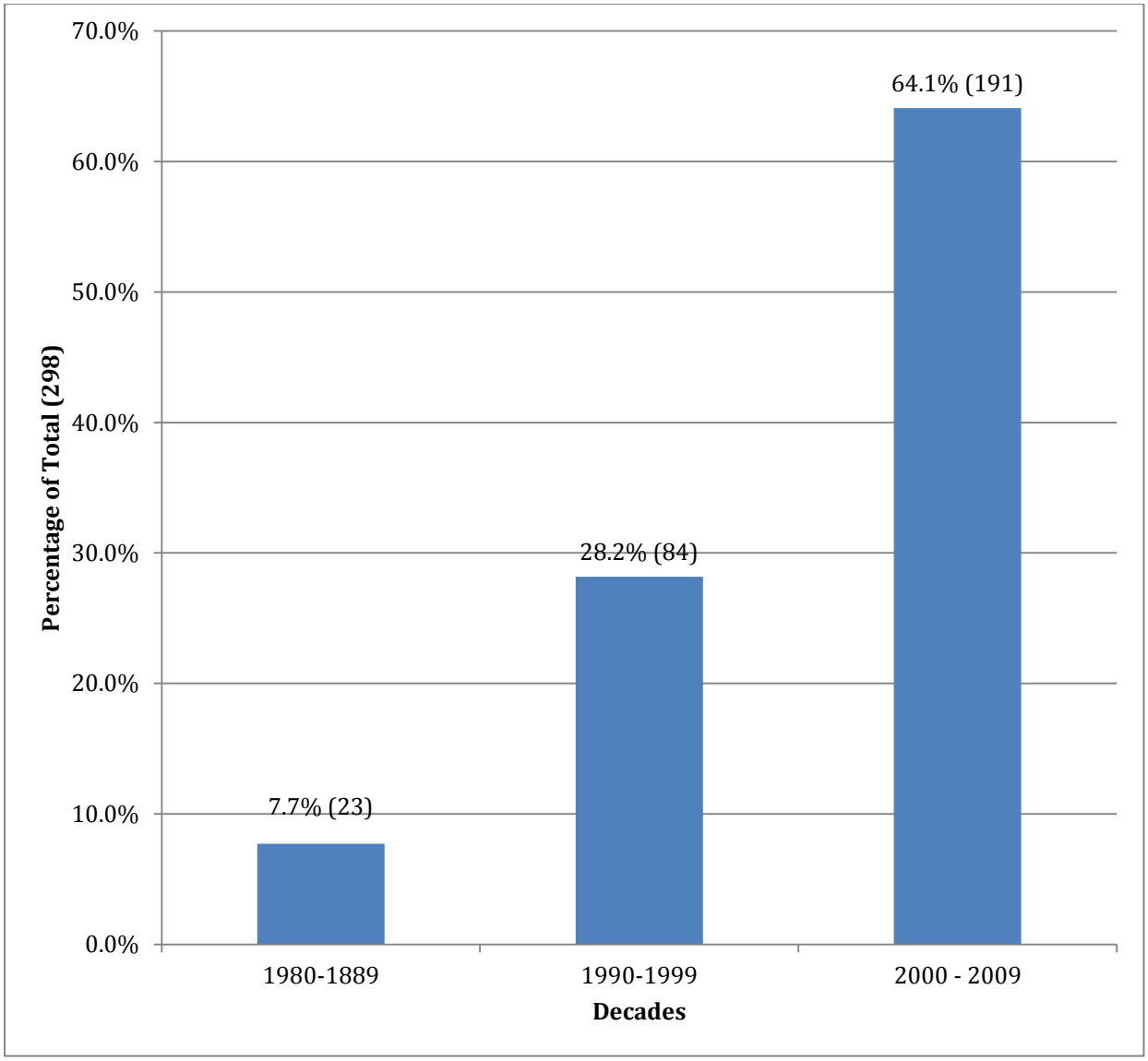
A systematic search of the literature was undertaken using Scopus, Web of Knowledge, Google Scholar, Pub Med and library databases. These searches were carried out using the key words *ethics* and *epidemiology* and limited to the subject area of medical ethics. Figure 4 shows the number of papers using these key words.

Figure 4: Graph of Citations Using ethics and epidemiology as Key Words from Web of Knowledge (1960-2009)



Another search using the words *committee* with wild card (*), *ethics* and *epidemiology* was also undertaken using the same limiters as the previous study (English language, limited to Medical ethics). The results for this search by year can be seen in Figure 5.

Figure 5: Graph of Citations Using ethics, epidemiology and committee* with * as a Wild Card as Key Words from Web of Knowledge (1960 – 2009)



From the results of these searches, abstracts were scanned and potentially relevant papers obtained. Once these were read and entered into an Endnote database, relevant abstracts from papers referred to in the first collection of collated references were obtained. If these appeared to be relevant, they were then obtained either electronically or through reference collections. Cross-referencing was also undertaken at this time. Where available, citation mapping software such as that supplied in Web of Knowledge and the British Medical Journal database was used on papers which met the criteria for inclusion. This mapping allowed for approximately a dozen relevant papers that may have otherwise been missed due to the keywords selected in the literature review.

A similar search was carried out on Google to identify websites with potentially relevant associations with codes of ethical conduct - for example, the American Epidemiological Association. This was done to ensure that both a legal and a non-legal perspective were obtained. Google was also used to identify websites of governmental departments and institutes, which may be have been involved in guiding how ethics committees are constituted and operated in the countries under consideration. This search was only carried out after the studies under consideration were determined.

In the case of the study based on General Practitioners smoking in the United Kingdom, a search of the British, Wellcome Trust, Kings, and London School of Hygiene and Tropical Medicine Library catalogues using search terms as used in the initial literature search (i.e. Ethics, Epidemiology, committees) was carried out. This allowed for many historical papers and books which would otherwise not have been considered to be added to the literature. It also allowed, in the case of the Kings and British Libraries, for grey literature – that is, pamphlets, circulars, information leaflets, training materials, web-based material and conferences abstracts – to be examined and integrated into context with the published literature and laws. These documents added to the understanding of the literature and ethical constructs within the context of the General Practitioners Smoking Study. The effect of the European Union (EU) directives was considered and a search on EU, ethics and health in the aforementioned databases (in addition to a search in the libraries mentioned above) allowed for relevant documentation and literature to be obtained and analysed.

Manual searching identified papers for grey literature, and, combined with suggestions from academics, this wider search enabled sources that may have otherwise been overlooked to be considered. For this thesis, grey literature was particularly important as it provided a non-academic alternative view to some of the problems which ethics may pose to both committees and researchers. It was also a source of guidance for researchers with regards to how various regulations etc should be interpreted. This is especially the case with regards to ethics committees in the United Kingdom for whom numerous training and informational material is available [26, 109-116].

Comparative Studies

Stage One

Comparative studies over similar time frames and underlying methodologies were utilised to investigate the proposed hypotheses. The Tasmanian Iodine Surveys were used to generate the initial comparative criteria due to the author's prior involvement in the surveys. The comparative studies were chosen for analogous use of descriptive methodological terms to the Tasmanian Iodine Surveys. I.e. they are longitudinal (which most long-term studies are), public health related studies that have a large well defined cohort. The Tasmanian Iodine Surveys, which were last undertaken in 2007, have similar descriptors and have been running almost continuously in various forms since 1949 [117-122]. Once the eligibility of the papers was determined they were examined critically to extract the necessary data to undertake the analysis.

There are slight differences in terminology used when referring to the Tasmanian case study as opposed to the potential case studies internationally. The reason for this is that, while the Tasmanian case study took place over the same time period, it was comprised of a series of surveys investigating a common goal with similar cohorts (as defined by the second definition) as opposed to a single study following a single cohort over time. This difference, while appearing significant, may actually allow us to see the catch up of ethics. This should allow us to see how methodology and selection processes changed to incorporate the New Ethics Research Environment (NERE).

Inclusion / Exclusion Criteria for comparative studies

To define the scope of the studies for analysis, a set of inclusion and exclusion criteria were developed based on the types of studies which were considered to be of interest for this thesis.

Many studies can be methodologically described as longitudinal cohort studies, looking at areas associated with public health. Numerous examples can be seen in the cohort profiles, which are a regular feature of the International Journal of Epidemiology. A classic example of these types of studies can be seen in the paper by Pearce *et al* (2009): here, the authors have published the cohort profile on the Newcastle thousand family 1947 birth cohort [123]. While superficially this cohort fitted many of the study criteria, for comparative purposes, it was not ideal due to having changing areas of study.

Studies of interest included the following criteria:

- Was a long running non-interventional study or series of surveys that started post 1939 but prior to 1955;
- The study/survey was still being undertaken in the early 2000's;
- Was well documented with regards to methodology and results;
- Had a public health basis;
- Had a large well defined study population;
- Comprised a large series (>10) of related peer reviewed English language papers.

In order for these studies to be compared on an equal footing, exclusion criteria were used to eliminate studies, which, although potentially fulfilling the criteria, did not fully match it.

- Studies/surveys that started prior to 1940 or after 1955;
- Studies/surveys without long term follow up of either methodologies or cohorts involved;
- Studies which were/are long-term pharmaceutical or drug trials.

Having a public health bias was a determining factor to allow for the exploration of recruitment methods in a community setting. Public health studies are generally an investigation into the causes of health/disease in a study population. Public health can also be taken as notifications of communicable disease, which enables epidemiologists to track the disease through a population. These findings, through disease tracking and other public health studies, can then applied to the population at large [124-127]. Changing ethics may have altered the processes by which long-term cohorts are tracked and followed up, and thus may influence the data available to researchers. Changing ethics and subsequent effects are aspects being examined in this thesis.

A large, well-defined study population was included as a criterion to examine the effect of recruitment methodologies within the public health context. The difference between countries in the requirements for gaining ethical clearances was a factor. Authors such as Hearnshaw [128] have highlighted the differences in requirements between countries: some countries require ethical approval for all studies involving human participants, while others, such as the Netherlands, have specific rules governing what must be presented to a committee. Hearnshaw also highlighted the fact that the United Kingdom has greater ethical

requirements then many other countries [128]. This factor was taken into account when examining the differences in the case studies using an ethical framework.

Studies that started prior to the 1940's or started after the mid 1950's were excluded to allow for long-term comparisons between the studies. Prior to the 1940's, real ethical implications of research were not articulated. Post World War II, the Nuremburg trials highlighted the beginning of ethical constructs within research. Post 1950's, studies were excluded for comparison as the original Tasmanian school iodine surveys started in the 1940's.

Long-term pharmaceutical and drug trials were excluded, as they did not generally have a public health basis. The usual design of a pharmaceutical or drug trial in being two armed also did not lend itself to the type of analysis being proposed. These types of studies are generally examined for response to treatments, while the types of studies/surveys of interest for this thesis predominately involve seeing how a population changed with regards to a known disease, tracking incidence rates and potential risk factors. While various aspects of the Tasmanian Iodine Study looked at how interventions were working in the community, it was not being compared with another type of fortification, and thus does not come under the banner of drug or pharmaceutical trials.

Studies which were considered, but discarded due to not fulfilling the criteria included:-

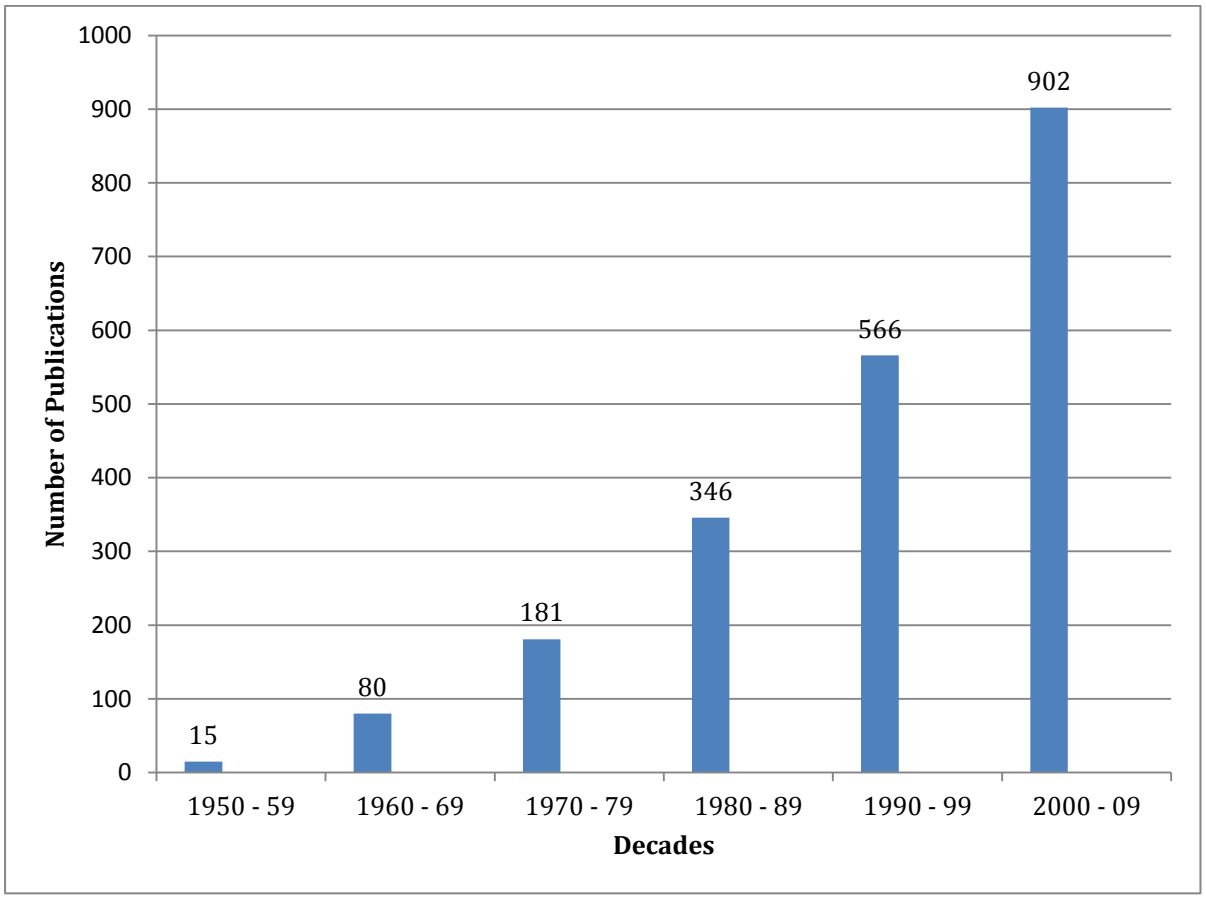
- The Busselton Health Study [129];
- The Whitehall Study I & II [130];
- The Nurses' Health Study [131].

The studies fitting this criteria and which can be related to the hypotheses are the Framingham Heart Study, which was started in 1948 and is currently ongoing [132-163], and the UK GP Smoking Study which started in 1951 and finished in 2001 [164-175]. Both of these studies are considered to be classic long-term epidemiological studies. They also encompass the changing ethical environment, which is of interest in this thesis. Both were started before formal ethical clearance was legally required for studies. In the case of Framingham, the changing demographics of the study group have required different groups to be recruited, thus the study had to undergo the ethical clearance process after the study started. This reiteration of the ethical clearance process allowed the author to investigate how various changing ethical environments have potentially affected the implementation and continuity of a study.

Stage Two

Once these studies were identified, a search using the databases mentioned previously was carried out, using key words such as Framingham, Doctors, Smoking, Heart and prominent authors' names to find relevant papers. A Google search highlighted a website [176] produced by the Framingham study, which had a comprehensive catalogue of the publications from inception to the present date which had eventuated from the study. Figure **6** shows the paper output from the Framingham study by decade. This catalogue was pursued with relevant abstracts/books/book sections being obtained and utilised in the data extract process.

Figure 6: Output of Papers Utilising Framingham Data by Decade - Modified from www.framinghamheartstudy.org [176]



Results

Using the search strategy outlined above, the GP Smoking Study revealed nine papers in which response rates could be linked to a distinct period and study group [165-167, 169, 171-175]. Using the above methods, the Framingham study produced 41 papers that were linked to a distinct period and study group [132-163, 176-181].

Iodine Surveys

The Iodine surveys were the catalyst that prompted the evolution of this thesis. Experiences of the author while working on the latest iteration of the surveys prompted thinking towards ethical constructs in research and the limitations they potentially highlighted in certain types of studies.

While other Australian based health studies such as the Busselton Health Study could be considered, the large consistent focused data which is available for the iodine surveys allows for considered comparison with other studies. Most of the data for these studies was obtained through either published articles identified through the previously mentioned search engines using Tasmania and Iodine as the key terms. Reports and raw data were obtained from a variety of sources including researchers involved in previous studies, the Department of Health and Human Services and State Archives. A search of the State Archives using Goitre as a search term yielded 27 possible results, of which one was immediately excluded due to referencing sheep goitre. A search using iodine gave eight results, none of which were relevant to the study of iodine in humans in Tasmania.

The archives were generally of the form of a box of records. They predominately related to goitre, and thus in the case of Tasmania, iodine. They were all read and relevant details recorded for historical purposes.

"*A History of Goitre in Tasmania*" was also utilised to supply methodological and historical data [120, 121, 182-185].

Data Extraction of Response Rates

The extraction of response rates allowed the author to compare studies over time and potentially see the influence of the NERE. The response rate extraction is detailed here and the results are shown in Chapters Seven and Eight.

Many journals now request that their authors use one of the many statements, which have been published by various working parties on which to base the writing of their papers. As this is essentially an observational epidemiological study, STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) [186] was used as a basis to develop an extraction document. STROBE was utilised as opposed to CONSORT (Consolidated Standards of Reporting Trials) [187], as STROBE is developed specifically for developing

and reporting observational epidemiological studies, while CONSORT was developed for reporting of randomised control trials [186-189]. Both are part of a wider initiative to strengthen the reporting of Health Studies through the Equator network. Other statements by this group include Standards for QUality Improvement Reporting Excellence (SQUIRE) [190], Standards for Reporting of Diagnostic Accuracy (STARD) [191] and Strengthening the reporting of genetic association studies (STREGA) [186-189, 191-194]. Each of these statements was considered as a possible basis for the extraction document that was developed; however, having its basis in Epidemiology, STROBE was deemed to be the most relevant.

The extraction document was developed by examining what was included in the STROBE checklist [186] and deciding based on the hypotheses outlined above which parts would be relevant. A copy of the extraction document can be seen in Appendix One.

Once this extraction document was developed, the previously selected papers were read and the relevant data extracted.

Combined Quantitative/Qualitative Analysis

To allow a time-series type analysis as proposed by Yin [195] to be undertaken, response rates were chosen as the event of choice. They were selected as they are they are commonly reported in the methodology section of a paper and can be compared within a study by use of percentages. Response rates are a data point, which if not reported, can generally be derived from data presented within a published paper. For the recently completed iodine surveys, the response rate can be obtained at both a school and class level. Most of the response rates have been previously published; however, some unpublished data have been obtained and used with permission of the Tasmanian Department of Health and Human Services. Data from earlier surveys were extracted from Tasmanian Archives as well as earlier published papers by Gibson and others [117-121, 196-203]. For the Doll and Hill studies, as well as the Framingham studies, response rates were obtained through use of the literature and personal correspondence.

The types of analysis undertaken should show that there is some cause/effect with regards to ethics and the changes within the methodological framework.

Qualitative Analysis

Although case studies are generally considered to focus on a single entity (be it an individual, group or event) they can be used comparatively when you wish to examine the likenesses and differences between two entities [204]. In this case the entities under examination were the studies extracted using the inclusion and exclusion criteria. While the Tasmanian Iodine case study is a series of surveys, it can still be considered a case study.

To be able to relate the changes in methodology to changes in ethical constructs/legislation, there needed to be a framework for comparison. A time/event analysis was considered, but discarded due to the fact that the time gap from a change in ethical legislation to an event potentially affected by it (in this case, a change in methodology/response rate) would be based more on when the methodology/response rates were published in the literature, and not when they were implemented. While implementation could be estimated from the papers, accurate dates would not always be available. This problem would also rule out other time based analysis strategies such as modified survival analysis or linear time progression.

The case studies under consideration were considered as straight chronologies, in that events happen over a specified time frame. An event can be considered a methodological change or an unexplained change in response rates. The cause of such an event comprises part of the investigations of this thesis. Yin [195] suggested that straight chronologies can be considered a special form of time-series analysis; the analytic goal of that time-series analysis is to compare the chronology with that which is predicated by an explanatory theory (in this case a change in ethical thinking). This theory has specific conditions of which at least one must be fulfilled. These conditions are:-

- Some events must always occur before other events with the reverse sequence being impossible;
- Some events must always be followed by other events on a contingency basis;
- Some events can only follow other events after a pre specified interval of time;
- Certain time periods in a case study may be marked by classes of events that differ substantially from those of other time periods [195].

Of these conditions in this context, the second and fourth were considered valid. Condition two is valid based on the assumption that ethics changes at a national/international level should be followed by some sort of response rate change as methodology and recruitment

strategies were adapted and changed to comply with the new ethical norm. Condition four is valid by the fact that the changing of ethical research legislation is not a constant process. Thus time periods and iterations of a study are not necessarily going to be identical in the way they are carried out or formed. Due to the fulfilment of two of the four criteria mentioned above, time-series analysis as suggested by Yin [195] could be carried out.

To support these hypotheses in the context of these case studies, major events in the ethical framework were identified, and their potential effect on the studies under investigation examined. Point two in the above list was examined through identification of process changes in the studies and an examination of if there was a preceding ethical event that may have affected those processes. Point four was investigated using similar methodology to point two.

Yin [195] noted in his summary of conditions for time-series analysis that the important case study objective is to examine some relevant "how and why" questions about the relationship of events over time, not merely to observe the time trends alone. An interruption in a time-series would be the occasion for postulating potential causal relationships. Later chapters examine the relationship of an event (methodological change) to the "how and why" to explore whether it was an ethical change which precipitated the methodological change and whether it affected the response rate.

Yin [195] also noted that the if the events of a case study have followed a predicted sequence of events and not those of a equally valid alternative sequence the single-case study can again be the initial basis for causal inference.

Limitations

As this thesis is based on comparative studies, many of the limitations were technology based. Electronic databases are not the most comprehensive data sets available. They are limited by what has been uploaded, and by the search terminology used. If time were not an object, comprehensive manual searching of earlier papers to ensure a more complete coverage would have been undertaken.

Funding prevented interviews with various researchers involved on the projects to elucidate personal experiences with regards to ethical constructs, and the thinking behind some of the research decisions made. Personal opinions with regards to experiences and how researchers

perceive the research is a concept within the research construct which needs to be explored further. While McNeill [8, 28, 32, 33] has undertaken some of this research in Australia, he has limited his research to committees and perceptions within and of them. A more integrated comprehensive view would have been obtained through targeted interviews. However time constraints prevented this from being undertaken.

The data obtained is limited by what is published in the literature. Particularly with the Framingham study, exact reporting of response rates decreased over time as more interesting questions were examined. The early response rates with the iodine data have been simplified based on assumptions generated from the literature. These assumptions are outlined in the results, but could potentially affect any conclusions made with regards to the NERE.

Interviewing of the researchers involved in the studies would have been advantageous and potentially allowed for more detailed analysis and understanding of how studies had changed over time. However, due to time, the only interviews that could have been undertaken would have been with the Tasmanian Iodine Researchers, which would have not allowed for comparative interview data to be generated.

The methodology could, potentially, have involved a discourse analysis, but this was discounted due to the need to examine in more depth the methods behind the response rates as opposed to the way those rates were presented and obtained. Given more time, an analysis of the length of time between obtaining results and publication would have been interesting to determine the lag time between any changes in methodology been undertaken, and then being published in the literature.

Chapter Five - International Ethical Code Development

The Line in the Sand

Prior to World War II, countries tended to make and keep their own laws and codes; as such, there were no overall guiding principles at a global level that gave worldwide accountability. Many of the codes were ones that an individual person had to make a conscious decision to abide by. This self-regulation, and its' failure during World War II and beyond, has lead to the development of codes which have accountability at a state or national level. The development of these codes shows how they have endeavoured to maintain an equal power differential between the researcher who is looking for scientific value, and the participant who is contributing to the greater good. Particularly in interventional studies, this regulation was needed. While it is important to explore the duty of care a researcher has to a research participant, these constructs are much more evident in clinical trial practice and the medicinal context. These constructs provide the basis for the movement from an individualistic moral position to a more legalistic tradition. This thesis aims to show why these constructs, while valid, may not always be appropriate for monitoring type studies. The purpose of the next section is to trace the development of codes from an individualistic moral position (as seen previously) to a more legalistic position, and to highlight the bias towards trial and clinical medicine.

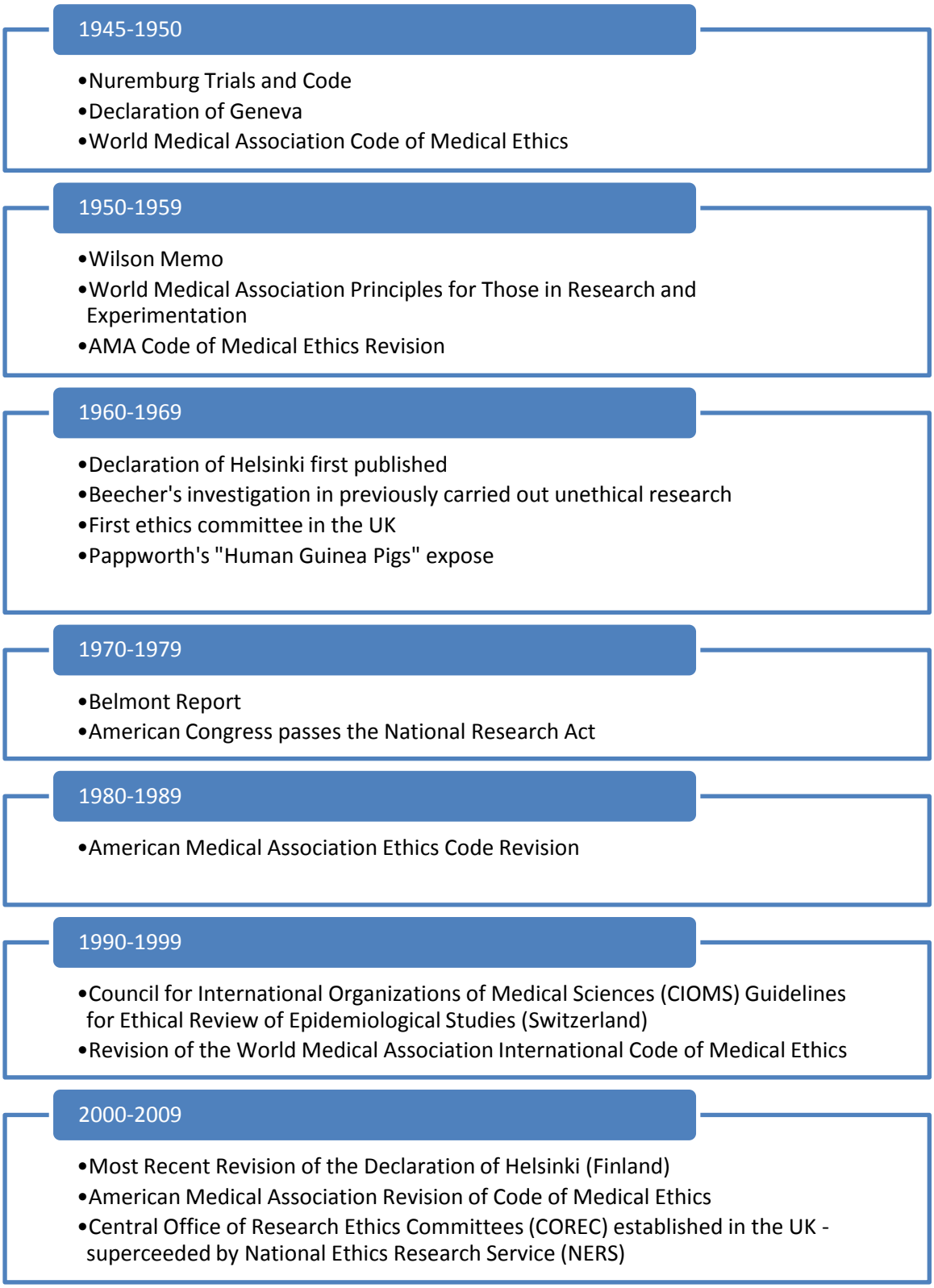
Post-Nuremburg, there are subtle but obvious changes over time with regards to how research is perceived and investigated. Susser [205] looked at how Epidemiology as a research construct has changed since the Second World War, with the advent of professional committees and codes of practice. This is seen in other types of research with voluntary codes of practice. However, the change from self-regulation to regulation by committee was inevitable after the Nuremburg trials. This can be traced through various events in the legislation, and to where the patient now has ultimate control over their participation in a research situation. While the participant may be acting autonomously by their participation in a research project, prior to their participation, the design and implementation of the study has been carried out by researchers to obtain the best possible results from their participation. Willams et al [206] notes that the potential for biased results is increasing as participation rates decrease. They propose utilising various persuasive communications to increase what

they term altruistic behaviours to increase participation rates [206]. While this may enable researchers to gain some control with regards to reducing bias and potential confounders in a study, Fry [207] notes that benevolent intentions may not always have positive outcomes. It is the potential for non-positive outcomes that has made potential participants a part of the planning process.

This control by the participant in regards to their participation can be seen in the changes in studies from Tuskegee through the Belmont report (which was the start of corporatization of the research experience) through to activism in areas such as HIV and breast cancer. This activism takes the form of advocating for the rights of the group to be considered when designing studies which aim to benefit them [208, 209].

The Nuremburg trials have been taken to be a metaphorical line in the sand with respect to the development of overall principles to guide the researcher. Prior to this, self-regulation of doctors and researchers was an accepted part of the research process. While the Nuremburg judges recognized the importance of the underlying Hippocratic Oath and the maxim of "First do no Harm", they also recognized that greater protection of human subjects was necessary [25]. While the Nuremburg code has not been adopted as is by any country or as a statement of ethics by any major medical association, its influence is seen in the development of codes by bodies such as the World Medical Association [25, 210]. Figure 7 shows the evolution of national and international statements in ethical thinking post World War II.

Figure 7: The Development of Ethical Codes Relevant to Medical Practice and Related Health/Medical Experimentation Post World War II



Post World War II

Post World War II saw the beginning of the development of generalised ethical code. These codes, while not event specific, are all in some way a reaction to the events discussed earlier.

Nuremburg

The first international statement on medical or research ethics is drawn from the Nuremburg code. This code originated from the trials held for 32 Nazi Doctors at Nuremberg after World War II. The trial was precipitated by the human experimentation that these doctors carried out during World War II [97]. It is not the first code of medical ethics to stand alone offering guidance, but it was first international code or guideline related to research concerning humans. The code itself comprised ten principles, which were contained in the final judgment of the court in Nuremberg in 1947. The ten principles expressed the acceptable limits with regards to human medical experimentation [97].

These principles can be summarized up as follows:-

1. The voluntary consent of the human subject is absolutely essential.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject [25].

These principles were developed in the context of the trial of the Nazi doctors. They are not a mandated set of principles for research and experimentation upon humans but are part of the judgements in the Nazi Doctors Trial [97]. Annas *et al* [102] expressed the opinion that the Nuremberg code embodies in many ways, all previous ethical codes governing biomedical research. It highlighted the principles of justice, beneficence, non-maleficence, veracity and confidentiality. It is, however, still only one document, even though its influence on biomedical research is obvious by its use as the basis for many research codes. Within the concept of the Thomasma ethical tree, these principles relate to both applied and clinical ethics.

Post Nuremburg

There is evidence that around the time of the Nuremburg trials, both the United Kingdom and France made submissions to the Drafting Commission for International Human Rights. Both of these submissions suggested that it should be unlawful to subject any person to medical or scientific experimentation against their will [102]. These submissions became incorporated into Article V on the International Convention of Humans, the first international document derived from the Nuremburg code [102]. Article V was specifically included to dissuade any return of the abuse and atrocities committed in Germany during the war [102]. It stated that: "*No one shall be subjects to torture or to cruel, inhuman or degrading treatment or punishment.*" While Article V does not specifically mention medical or research ethics, it provides a basis for development of more specialised statements. It is, however, not necessarily the first published international document which refers to medical ethics [211].

World Medical Association (WMA)

The WMA was established in 1947 by a group of physicians as a response to the events in World War II [212]. The first document the WMA published, and one of the first documents specifically dealing with medical ethics, was the Declaration of Geneva in 1949. This modern take on the Hippocratic Oath was originally encompassed in an article entitled "War Crimes and Medicine: The German betrayal and a restatement of the ethics of medicine" in the World Medical Association Bulletin [213]. A year after this, the WMA published their own "international code of ethics" – primarily focused on the duty of the doctor but once again drawing inspiration from the Nuremburg code in its assertions that "*a physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient*." [214]

Both the Declaration of Geneva and the International Code of Medical Ethics have been revised since their first appearance. The intent behind them both remains the same. While not explicitly mentioning research carried out on humans, the implication is one of "First, Do No Harm". It was not until 1954, however, that the WMA published their "Principles for Those in Research and Experimentation" – the first explicit mention of doing no harm from a body with worldwide membership. It was written to help researchers clarify their moral obligations in relation to research, and was a document written by doctors for doctors – unlike the Nuremburg Code which was written by jurist in a trial judgement [102]. These principles also helped separate out the different types of research: Research that was in new diagnostic and/or therapeutic methods and research which was undertaken to serve a different purpose than to simply cure an individual. It is this second type of research that is the focus of this thesis.

The last code that the WMA drafted was the Declaration of Helsinki in 1964 [114, 215, 216]. It augments the Declaration of Geneva and the International Code of Medical Ethics by explicitly stating the principles involved in undertaking research on human subjects. Signatories to the original code include the major medical associations of Australia, the United States of America, and the United Kingdom, as well as most of Europe. It also extended the scope of the codes to include biomedical research, something neither of the previous codes did. Although it has been revised or clarified eight times since 1964 (the latest being in 2008), it still does not have the legal standing that one may desire from a document that purports to have international significance: it is non-binding and intended only

as guidance. The WMA has also published a medical ethics manual which articulates the principles of ethical medical practice and how physicians should interact with the patients, their colleagues and society. It also briefly touches on medical ethics in research, and the function and roles of ethics committees. This document is intended as a training document for new physicians, and for those who wish to extend their understanding of ethics [217]. Both the Declaration of Geneva and the International Code of Medical Ethics have been revised since their first appearance, but the intent behind them remains the same.

World Health Organisation (WHO) and Council for International Organisations of Medical Sciences (CIOMS)

A document which does articulate clearly the needs for ethics in research, although now not as specific as it originally was with regards to large scale studies, is the World Health Organisation (WHO)/ Council for International Organisations of Medical Sciences (CIOMS) guidelines. These guidelines were originally published in 1991 and were the first international guidelines specifically aimed at epidemiologists and the types of studies they were likely to carry out. These are still the only international guideline directly targeted at epidemiologists. CIOMS has also published the International Ethical Guidelines for Biomedical Research Involving Human Subjects in 1993.

The WHO/CIOMS guidelines for epidemiologists were first put up for review in 2003, and it was initially thought that the 1991 document could be revised. However, it was found through responses to surveys that many researchers found it difficult to reconcile the 1991 document with the 2002 International Ethical Guidelines for Biomedical research from CIOMS. It was decided that a supplement to the 2002 guidelines concentrating on Epidemiological studies would be written, as opposed to the 1991 guidelines being revised [218].

When the draft proposal for the revised guidelines was published in 2006, it was well-received by the larger scientific community, but epidemiologists were not supportive. It was suggested that the draft guidelines did not fully take into account the fact that "*the supplement would not provoke ethics review committees that principally review biomedical research to sufficiently adjust their expectations –and also their membership –* ***to take account of important differences raised by epidemiological studies***" (emphasis mine). These differences will be seen during the investigation of the case studies, which will be presented later. This thesis attempts to propose a solution to this problem which is certain to

become even more common as public health studies in Australia and beyond become more prevalent [219, 220].

New Ethics Research Environment

The New Ethics Research Environment (NERE) as coined by the author is one that has developed in the last 40 or so years in response to the changing ethical constructs surrounding research regarding humans. While much of the NERE is influenced primarily by changing legislation, parts of the new environment have come about by the changing perceptions of how ethics should be practiced and recorded [221]. The new environment has also being influenced by perceptions of good research as well as the perceptions of ethics committees and their roles per se [8, 28, 32]. This environment and its history show how the changing perceptions of ethics have influenced the way that researchers approach the ethical constructs of research.

This NERE provides a context in which the following case studies will be considered. The development of the environment can be traced through the development of studies such as the ones under consideration here. As the ethical research environment evolves, a corresponding evolution of ethics within research studies should be observed.

Susser *et al* [19] sums the "line in the sand" concept up in epidemiology and thus the evolution of the NERE when he noted that:

> "*An examination of ethics in epidemiology is thus an examination of the way in which the vales of science and its potential benefits to public health are balanced against the values of individuals and communities*."

He also noted that the choice of research questions, study design and participation all influence the success or failure of a study and the scientific rigor to which it, and the research process which formed it can be subjected [19]. Using the example of Goldberger's Pellagra studies in the early part of the 20th century, Susser highlighted how the concepts of voluntary and involuntary participation have changed even in this short amount of time [19].

While Susser *et al* highlights the fact that there is a potential tipping point between benefits and the value of research to individuals and communities, he also looks at how epidemiology as a research construct has changed since World War II, with the advent of professional

committees and codes of practice [205]. However, he does not consider the researchers and the influence they may have on the ethical constructs of a study.

The researcher is not a neutral bystander in these constructs. It is the researcher who drives a study forward through their active participation in the design, recruitment and analysis of a study. Any study will be shaped in some way by the ethical beliefs of the researcher designing it, even while it conforms to the constructs of a study that will pass an ethics committee [222]. Foster also notes that research can potentially follow a three pronged approach to ethical decision making [222]. This three pronged approach is analogous to using the trunk of Thomasma's [52] tree to guide the decision making process.

The case studies presented in the following chapters' show how the lens of the NERE may influence how the case studies methodologies and response rates changed and evolved over time. However, before the case studies can be explored, an understanding of the evolution of ethics committees in the context of research in different countries is required to allow comparative studies to be undertaken during the case examinations.

Chapter Six - Comparative Research Ethics of Countries from the Case Studies

Introduction

This chapter aims to explore the differences in approaches used by research ethics committees in the United Kingdom, United States of America and Australia. Utilising the legislation available to them and the current interpretations of that relevant legislation, the following chapters use a frame-work for the analysis of the case studies. The following research question will be examined in this chapter:

> Has research governance affected research ethics?

With multi-national collaborations becoming more common, the question of how best to manage differing ethics requirements is a pertinent one. While this thesis does not examine the ethics of multi-national studies, the ability to compare studies from different jurisdictions is explored. This chapter will examine briefly the basis of the ethics requirements in three English-speaking countries – the United Kingdom, Australia and the United States of America. The differences in their ethical requirements are examined from a historical perspective to one of current day expectations and requirements.

Australia and the United Kingdom both have advisory approaches to ethics committees, in that; although there are statutory regulations with regard to how research can be carried out to receive funding, private research is not necessarily regulated. The United States of America has a more legislative and regulatory approach with the need for ethical review for all research which is mandated by federal legislation [17].

This chapter will consider research ethics committees and not clinical ethics committees. Research ethics committees (RECs) are more likely to be the committees that approve large scale public health studies, while clinical ethics committees are more concerned with ethical issues arising in clinical medicine [28]. For the purposes of the thesis, RECs will be taken as committees that are formed to evaluate the ethical and legal legitimacy of research undertaken at a tertiary study institution (e.g. a University or teaching hospital). Clinical ethics committees (CECs) can be defined as predominately ad-hoc committees which

evaluate treatment regimes in a clinical setting [26, 28]. Legally, both committees are perceived as having predominately advisory roles to researchers, clinicians or the organisations they are employed by. It is the context and structure of these research committees, as well as the legitimacy of their standing with regards to advising on research that will be investigated in this chapter. The scope of RECs in this context is that of a regulator/gatekeeper to research, not as an advisory body on clinical outcomes and treatments [223].

Certain aspects of the study of bioethics have a basis in regulatory law and literature. These areas, especially in genetics, end of life and reproductive technologies, have been legislated for and discussed due to the fact that they are areas for which the general public has a perception that regulation and risk management are necessary [224]. This is primarily due to the debate that these topics generate through news reports and other media. While the public may be aware of these areas, the ethical debate about them is also shaped by the researchers and the investigations that they carry out.

Other areas that may have bioethical concern, such as university research, tend towards a more flexible interpretation with regards to legal liability and risk management. In both Australia and the United Kingdom, the imperative to present research for review by an ethics committee is not legally binding from a governmental or statutory point of view [225, 226]. In both of these countries, RECs have the job of review and oversight of research but do not in themselves have any legal standing. They do have a regulatory standing and provide ethical oversight within both the research and public communities [28, 32, 37]. The United States of America has a more legalistic, law-based system while still also having university- and research-based Ethics committees [17, 227].

Large-scale background monitoring via reporting of incidents by practitioners, which is used successfully in some aspects of public health (such as communicable diseases and disease outbreaks) is not necessarily feasible or practical with monitoring for areas such as nutrition or general health as noted by Susser [19]. From a public health perspective, and particularly from an epidemiological point of view, the current guidelines in both Australia and the United Kingdom, while adequate, can still be improved to take into account current advances in both techniques and law. These advances have included databanks, centralised reporting as well as utilisation of freely available information. As mentioned in Chapter one, many bodies and organisations supply funding with the caveat that an ethics committee approve the

research. However, there is no requirement for self-funded research to be presented and discussed [8]. The United States, while operating under a different basis for its rules, has a more robust legal basis for the structure of its public health research [228]. While ethics committees are an accepted, and, in most cases, an integral part of the academic research process, there is no legal requirement for all research to be presented to a REC for discussion.

While epidemiological work, especially in public health, may be presented to a committee for comment, it is not necessarily the type of research that raises red flags due to the fact this type of research generally uses databases and reported incidents, with the emphasis on non-invasive medical procedures. However, it is the results of those non-invasive medical procedures, and their potential to modify future research, which may generate concern in an ethics committee. It is this questioning of the outcomes and potential changes to methodology that may result from the REC, which may affect both the implementation and interpretation of the work. This is particularly relevant where conclusions that may be reached by the REC prompt interventions that may be recommended. Changing implementation and interpretation at the behest of RECs may change the ability to answer the questions asked.

Duty of Care

The duty of care of a researcher to a participant, whether in a clinical trial or a research study is the same. However, within a clinical trial the imperative of the researcher differs slightly. Various codes of conduct such as the EU Directive [229], or accepted best practice [230] are followed by clinicians during clinical trials. The National Cancer Institute [230] outlines very clearly when a trial should be stopped early. These instances include "*Significant and clear advantage of the tested treatment or clear evidence of no additional benefit to tested treatment.*" While this is the case with clinical trials carried out in hospitals, participation by doctors in clinical trials of pharmaceuticals can change and influence prescribing patterns [231]. Sleight [232] notes that clinical trials have changed in both their scope and the attitude of researchers. He notes they have moved from very small sanctioned trials to large randomised placebo control trials that may be multi-national in scope. While each country may have different requirements for a study to be undertaken, the imperative is always with the researcher to ensure the safety of the data or participants. Claudot notes that even if a study methodology is accepted in one country, it does not mean that it will be allowed in

another due to differing expectations of research [233]. It is partially these differing expectations that will be explored in this thesis.

Australia

In Australia, having a REC comment on research is not a legal requirement, but one of good practice in which researchers participate. While much of the New Ethics Research Environment (NERE) is influenced primarily by changing legislation, parts of the new environment have come about by the changing perceptions of how ethical research should be carried out [221]. The new environment has also being influenced by perceptions of good research as well as the perceptions of RECs and their roles [8, 28, 32]. This environment and its history show how the changing perceptions of ethics can influence the way that researchers approach the ethical constructs of research. While this statement may appear to answer the primary question of this thesis, the author wishes to explore what precipitated the change and if that change has made designing and carrying out ethical research easier under the current constructs.

Research involving humans has a regulatory overview by the National Health and Medical Research Council (NHMRC) Statement on Human Experimentation in Research as well as the Australian code for the Responsible Conduct of Research [6, 7, 226, 234, 235]. Both the statement and code provide guidance for researchers in the form of a series of actions as to what is considered ethical research practice. This quasi-regulatory statement is intended to influence both the researcher and the institution housing the researcher to act in a particular way, whereby they identify ethics as a significant over-arching aspect of any research which they may undertake [236]. In addition, the interpretation within such statements suggests that ethics as a concept and practice should be shaped discursively, that is, that the act of ethical thinking is generally formed through a discourse between the researcher and the research.

As part of this discourse researchers should consider the participant who will be part of the research, and ensure that they have an active voice in the research process. This active voice of the participant is something that has not always been considered in designing research. While Cave and Holmes [237] note that the European Trials Directive appears to favour facilitation of research over the protection of the dignity and welfare of research participants, there does not appear to be an equivalent approach in Australia. The incorporation of the voice of the participant can be done through use of stakeholder groups as well as small trials

of studies to test useability and other methodologies. Neither of these methods is mandated, but would help to develop participant good will and understanding.

However, the clinical research origins of the statement are evident from its focus on the issues prevalent to clinical research, and the minimal consideration of the ethical issues inherent in public health research. Within the Thomasma model, this type of consideration would involve a combination of all three ethical branches. Applied ethics can be considered as the actual interaction of ethical thinking with the development of study design. Public policy ethics can be considered to be the ethics of the study as viewed through the requirement of the NHMRC and clinical ethics can be considered as the logistics of undertaking studies with may require use of clinical skills.

The role of the NHMRC is to:

- raise the standard of individual and public health throughout Australia;
- foster the development of consistent health standards between the various States and Territories;
- foster medical research and training and public health research and training throughout Australia; and
- *foster consideration of ethical issues relating to health* [9].

The NHMRC mandate does not cover research that is not funded by a government body. There is no requirement on researchers who are funded by industry, or conducting research in a commercial situation to submit their work for scrutiny by an REC before it is undertaken. Research that is funded from the corporate sector may require ethical clearance before it is undertaken, but to there is no legally binding requirement for research to be presented to an REC or any other regulatory oversight. The only onus on privately funded researchers to present to an ethics committee is that journals now require evidence of ethical approval before they will consider publication of papers resulting from the study [238].

Research in universities does require ethical approval – regardless of the source of funding - for the project. In contrast, research that is not carried out within an institutional setting has no requirement for ethical approval. This situation carries the risk that some investigations, while potentially adding to the body of knowledge, may not be carried out in an ethical

manner. In this scenario, any potential research participants in that study would have no recourse for complaint, nor would they necessarily be able access the results of the study.

Background to the Development of Ethics Committees

The NHMRC has recently reviewed the *National Statement on Ethical Conduct in Human Research*, and an appreciation of the history of this body is important in understanding the Statement's past, and future evolution. The evolution of the National Statement is implicitly tied into the formation and evolution of the NHMRC.

The NHMRC was formed in 1936, a year before the Medical Endowments Fund (1937) was legislated [7, 239]. It followed on from the Federal Health Council, a group comprising of the Commonwealth Director General of Health and the Sate Chief Health Officers. This council was established in 1926 following a Royal Commissions Recommendations [240]. The fund was nominally administered by the Federal Minister for Health with advice from the fledgling NHMRC, and was the pre-cursor to the NHMRC that exists today.

Twenty-eight years later, in 1964, Australia ratified the World Medical Association's *Declaration of Helsinki*. As mentioned previously, the Helsinki Declaration is a fundamental statement of ethical principles. It provides guidance to both researchers and research participants who are undertaking and partaking in medical research involving human subjects or identifiable human material or data [216]. By ratifying the Helsinki Declaration, Australia committed itself to upholding the principles that Helsinki represented.

In 1966 the NHMRC produced its first *National Statement on Human Experimentation,* which drew expressly on the original Helsinki declaration [6, 9]. This document was not legally binding, and aimed to provide guidance and advice to researchers whose work impacted on its human participants.

In Australia, the early 1970's saw the formation of a clinical ethics research subcommittee as part of the Medical Research Council (MRC). Its stated purpose was the revision of the 1966 statement on human experimentation. Four years later, in 1976, Supplementary Note No 1 was added to the national statement [6]. This note required a review by Institutional Ethics Committees (IEC) for every research proposal or protocol that involved human subjects. It is here that IEC became a government-mandated requirement for research, by virtue of this Supplementary Note, as opposed to a voluntary ad-hoc committee within an institution. The revised statement also reworded the opening paragraphs to become more encompassing and

to take into account social and behavioural research on humans as well as the medical research that was mandated previously. The supplementary note does not give any legal standing to the IEC except as a regulatory body for approving research [6].

Ironically, the NHMRC at this time was essentially an advisory body with no legal standing, despite its establishment under an act of federal parliament. The early 1980's saw the Medical Research Ethics Committee (MREC) established as a subcommittee to the NHMRC to assist with the review and recommendation on ethical principles in research. The MREC was also charged with facilitating the review and reporting of IEC to the NHMRC [6].

In 1985, a recommendation was adopted that required compliance with Supplementary Note No. 1 in order to receive funding from the NHMRC. This recommendation proved to be an effective basis for institutions to establish ethics committees. By 1990, it was estimated that there were over 100 IECs in Australia, increasing to over 220 by 2005. During this time the nomenclature of the committees changed from IEC to Human Research Ethics Committees (HREC), by which they are commonly known today.

Establishment of the NHMRC as a statutory corporation took place in 1992 with the enactment of the National Health and Medical Research Council Act 1992 [241]. This act also established the Australian Health Ethics Committee (AHEC) as the principal committee of the NHMRC, as opposed to the various permutations of the MREC that had existed previously. This committee is still technically only an advisory body with no legal standing [7].

In Australia, the requirement of a research ethics committee to comment on research is not a legal one, but a case of good practice in which researchers participate. The launch of the National Ethics Application Form (NEAF) in 2006 by the NHMRC intended to make the process of applying for approval much more transparent, as well as introducing a certain amount of ease to the application process [242]. This process has the support of the Australian Vice Chancellors Committee (AVCC) and the Australian Research Council (ARC). The advent of a nationally consistent form has the potential to allow researchers to apply at multiple centres using the same form – thus hopefully eradicating a degree of paperwork [242]. This process has been supported by the Harmonisation of Multi-Centre Ethical Review (HoMER) initiative. It is in the process of being implemented and rolled out with final development and release of certification scheme to be operational in 2010 [243]. This scheme is similar in its premise to the former Central Office Research Ethics

Committees Scheme (COREC) in the United Kingdom, which is now known as the National Research Ethics Service (NRES).

Multi-centre trials have always been problematic with regards to gaining ethical clearance. Early trials would require clearance from the ethics committee of every site involved, which could cause problems when different committees had differing interpretations on what was considered ethical. If enough committees asked for changes, the comparability between sites could potentially be compromised. HoMER endeavours to remove this possibility by providing a "clearing-house" concept to ethical review [243]. Certification of larger ethical review centres will enable multi-centre research to be cleared through one of these committees, with the other committees highlighting specific logistical problems only within their study site. Ultimately, this will allow the recognition by *all* jurisdictions of a review by *any* HREC in any jurisdiction [244].

Processes in Australia

Appling for ethical approval has changed very little since the requirement for presentation to ethics committees became common-place. Prior to the advent of NEAF, every committee had their own forms, which a research team was required to fill and submit with the relevant paper-work. For multi-centre studies, this could involve upwards of 10 or so slightly different forms for each of the separate committees. Each committee's concerns had to be considered, and if necessary, the protocols adjusted to address the specific issues raised.

Current Procedures

In Australia, the procedure for a single-centre study is currently quite simple. Standardised forms are filled out and presented to the local HREC who then debate the merits of the research and any potential problems there may be with recruitment, execution, and/or logistics. It is assumed that if one committee gives approval, there will be approval from the other approached committees. There is a move towards having designated oversight committees and local committees only commenting on potential methodological problems at their site through the HoMER initiative [243-245]. The current and proposed methodologies can be seen in Figure 8 and Figure 9 below.

Figure 8: Pre 2010 Process for Multi-Centre Review of Human Research Ethics Applications in Australia [246]

Coordinating Investigator (CI) and/or the Principal Investigator (PI) at each participating institution submits an ethics application to multiple HRECs.
Each institutional HREC conducts its own ethical review of the research proposal (i.e. multiple ethical review occurring for one research proposal).
Coordinating Investigator has to handle requests from multiple HRECs.
The CI receives the outcome of multiple ethical reviews and may be required to enter into dialogue with all HRECs to achieve a consensus position

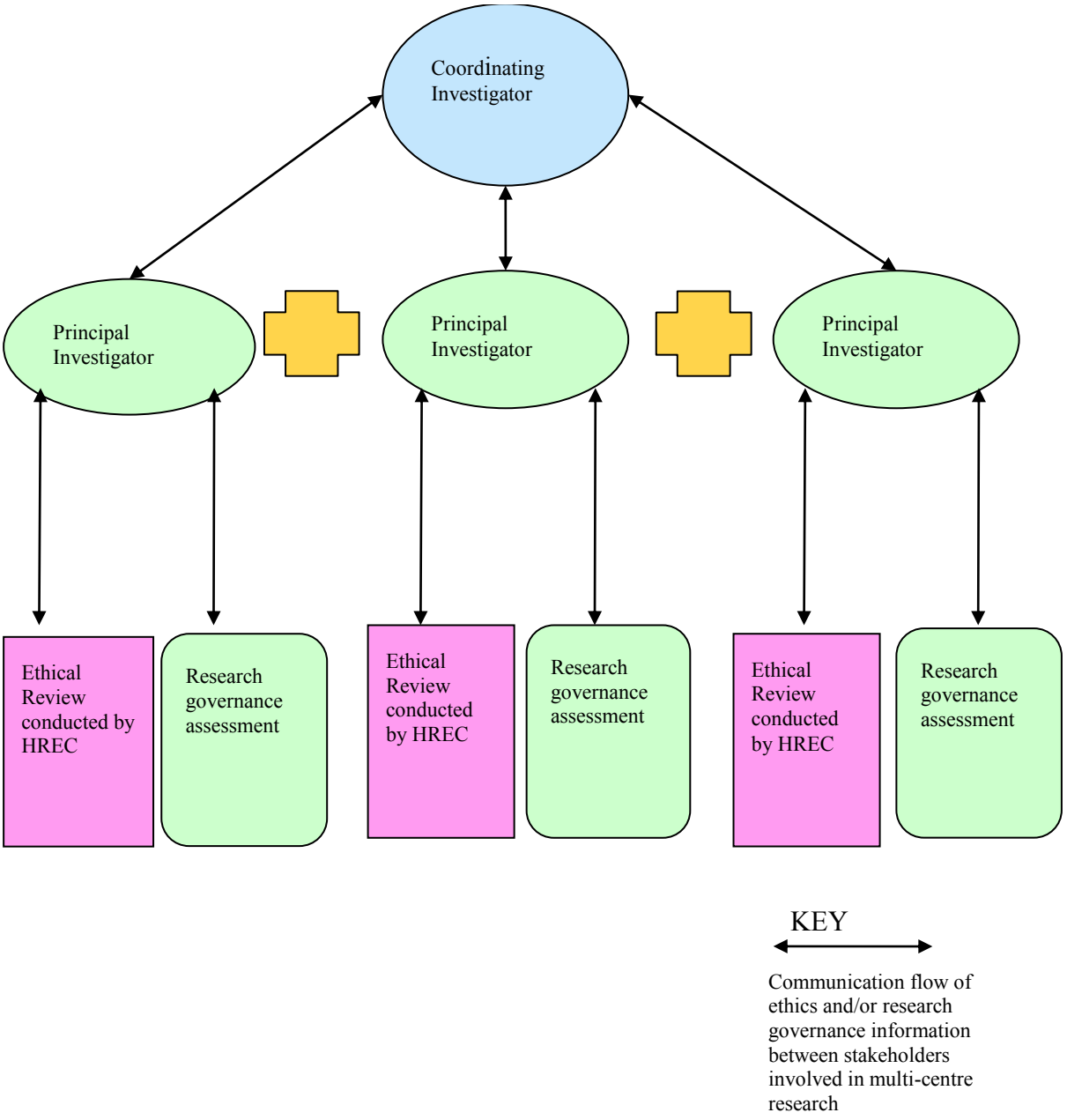


Figure 9: Post 2010 Process for Multi-Centre Review of Human Research Ethics Applications in Australia [225]

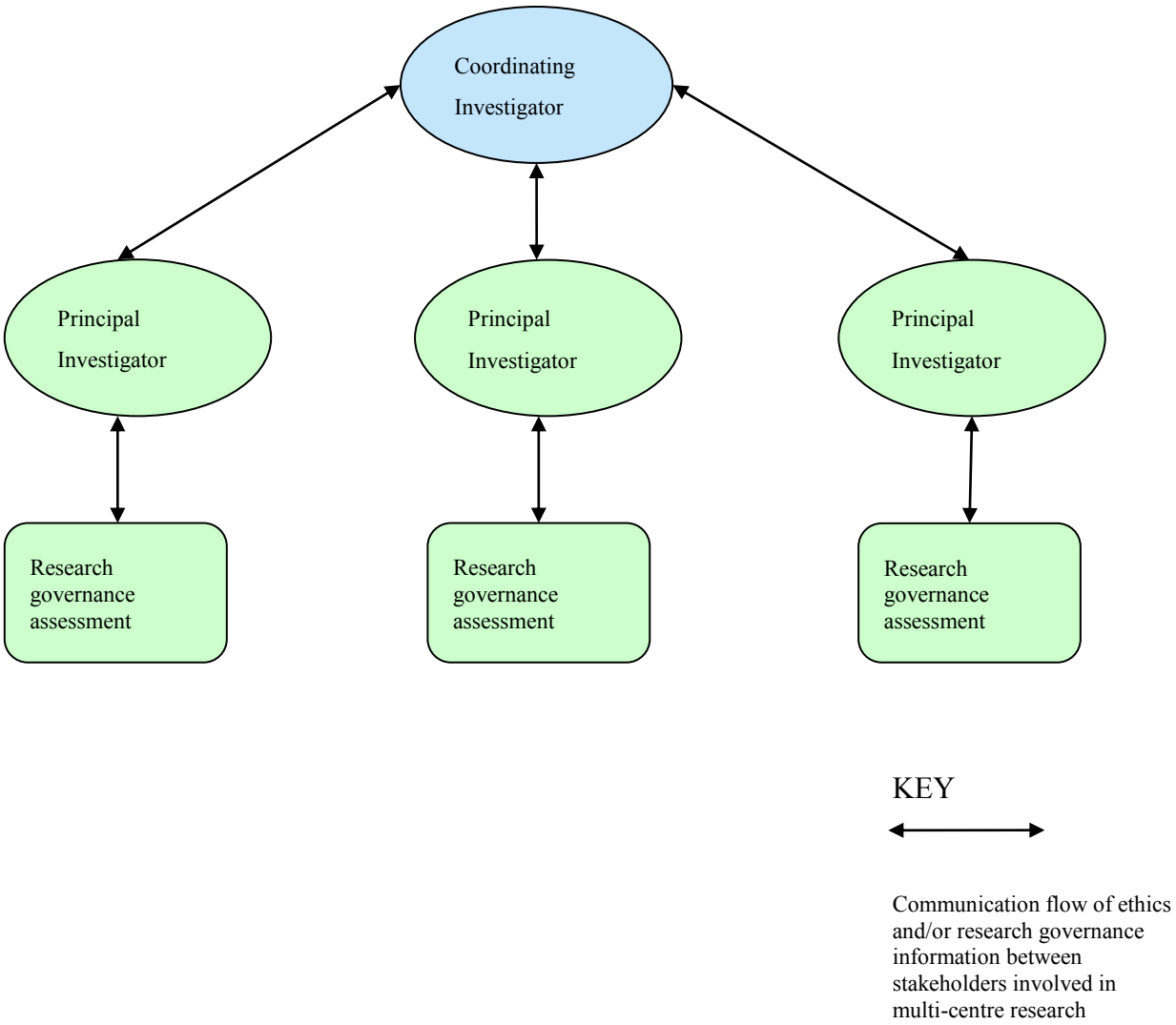
Coordinating Investigator (CI) submits an ethics application to one HREC that is using certified ethical review processes.

One HREC conducts an ethical review of the research proposal (i.e. single ethical review occurring for one research proposal).

CI receives the response of one HREC.

Principal Investigators at each participating institution provide the outcome of the single ethical review to their respective institution.

Each participating institution uses the outcome of the single ethical review and their site-specific research governance information to determine whether or not research will commence at their institution.



The HoMER initiative aims to

- Reduce timelines for ethical and scientific review of human research;
- Reduce duplication of ethical and scientific review of multi-centre health and medical research;
- Coordinate approval of multi centre studies;
- Standardise procedures and processes;
- Improve the efficiency of resource use.

If these standards are met, many of the problems that can potentially derail long-term longitudinal cohort studies may be avoided. However, the lack of a centralised office (as seen in the United Kingdom model) may, in the long run, prove detrimental. It leaves the onus on the researchers to ensure the correct procedures are followed, which in turn depend on which jurisdiction will have primary responsibility and thus give overall ethical approval. Currently, all states are at different stages of implementation. Queensland Health appears to have taken into account the need to have a centralised office to enable co-ordination on intra- and inter-state studies ethical clearances [247]. This also appears to be the case in Victoria with a Consultative Council for Human Research Ethics [248] and Tasmania has also moved to a state based system [249]. However, state based offices will still only be able to monitor the research which has a primary ethical approval in that state, unlike the British model outlined below which has a national centralised office.

HoMER aims to help eliminate the outcomes of studies such as Sarson-Lawrence et al [250] who found that the average median time to gain approval at multiple hospital HRECs for a cancer trial was 111 days. They found that there was the majority of the comments or clarifications made had no scientific or ethical bearing on the study [250]. From this they developed the mutual acceptance model, which mirrors in some ways the HoMER and NEAF systems. This model showed an improvement of twenty-seven percent in approval times [251]. This gain equates to a drop of twenty-nine days in the time taken for approval.

As these systems are still quite new (general roll out was early 2010), there is nothing in the wider literature yet to suggest how successful the change has been. At a national level, HoMER aims to streamline ethical approvals for multi centre trials. At an individual level, however, the researcher would still have to deal problems such as site specific concerns which could impact the study and inconsistently applied usage of the HoMER process. As

mentioned previously, the lack of a centralised office is most probably to HoMER's detriment due to the state based nature of ethics committees.

The Need for a National Ethics Application Form

Prior to the implementation of NEAF there were many calls for national ethics committees and systems in the both the letter pages of the Medical Journal of Australia and in articles for discussion. The discussions prior to the implementation of NEAF explore the need for a national committee as well as the logistics of such an implementation [10, 245, 252-256].

Some of these discussions, for example, those proposed by Walsh *et al* [10], examined how ethics committees and research governance can work together. They paid particular reference to the research governance behind the ethics committee (that is *the framework through which institutions are ultimately accountable for the scientific quality, ethical acceptability and safety of research conducted in the institutions [10]).* They found that a greater emphasis on the governance of research (i.e. the support and logistics behind the human research ethics committee) can help with the role of the REC. Walsh *et al* [10] also highlighted that a centralised ethical review of multi centre research, combined with greater use of expedited review of minimum risk research, would be useful as way of saving resources. While Walsh *et al's* [10] paper is not taken from a researcher's point of view; it offers support for the concept of centralised multi-centre research in the context of improved research governance at a local ethics committee level.

Other authors were part of a discussion in the Medical Journal of Australia letters section which was prompted initially by a letter outlining the problems that researchers on a multi centre study were having with the interpretation of the of the Victorian Health Records Act, and its effect on privacy of individuals [257]. Breen and Hacker [258] noted that the concerns raised by Carapetis *et al.* [257] were issues which the Australian Health Ethics Committee was at that moment grappling with in the context of the 1999 National Statement. They acknowledge that new state and federal privacy legislation may have initially caused more problems, but were confident that a review after two years would help to fix any large-scale problems that may be encountered at a federal privacy level. They also note that the (at that time current) National Statement encourages ethics committees to reduce and minimise unnecessary duplication. Whiteman *et al* [256] highlighted similar problems to Carapetis *et al.* [257] with regard to the energy/time and money expended on multiple ethics approvals to multiple committees for research.

Dickson *et al* [253] indicated that although Roberts *et al* [245] has gained approval from the ethics committees, he had failed to take into account the resources which may be required. This leads them to conclude that although the centralised ethics committee is a good idea, each individual committee must be able to decide for themselves if they have the resources available to undertake the proposed study. Breen [252] in response noted that many see the "gatekeeper of resources" role as not being appropriate to ethics committees. They also note that the national statement permits and encourages the acceptance of another ethics committee's decision for a multi centre trial, it does not enforce it, and thus ethics committees are free to make their own decisions of suitability.

Maxwell and Kaye [259] note that under the guidelines current at that time any Quality Assurance activity in which there is "*consistency with National Privacy Principle 2.1(a); and all people involved in the activity are unlikely to suffer burden or harm"* could proceed without HREC approval. However, fifty percent of the hospitals they approached to participate in the NSW arm of the CAPTION project (Community-Acquired Pneumonia: Towards Improving Outcomes Nationally) asked for a HREC to be completed, despite the project using retrospective medical records to obtain its data. To prevent HREC requests extensive literature and tools outlining the nature of the project and how the audit worked were presented to the hospitals. The researchers did, however, ask for the support of various bodies within the hospital, which may have been what triggered the HREC review [259].

Van der Wyden [254] weighed in to the discussion with the comment that while the national statement does in fact cover some of the points raised by the authors, it is up to the ethics committees themselves how they interpret that statement and act on it. He made the point in closing that clinical research and quality assurance should not be at the mercy of inefficient HREC's.

While a national form may help alleviate some of the problems these authors have highlighted, unless there is consistency within the committees, or one committee willing to take oversight in multi-centre proposals, the potential for discrepancies remains.

Discrepancies in this context are taken to mean differing interpretation of a study by different committees. When receiving comments from multiple committees on a proposal, the researcher is forced to prioritise which comments will actually enhance and strengthen the proposal. A single head committee model, such as has been implemented in NSW, should enable the researcher to take into account varying opinions while only dealing with one

committee [260]. Site specific assessments, as proposed by Fraser et al [260], are something which the United Kingdom has utilised successfully for a number of years. While the methodology and implementation are only assessed once, the ability of a particular site to carry out the study is assessed individually. Discrepancies between sites can then be accounted for in implementation and analysis as opposed to changing methodologies to suit the lowest common denominator.

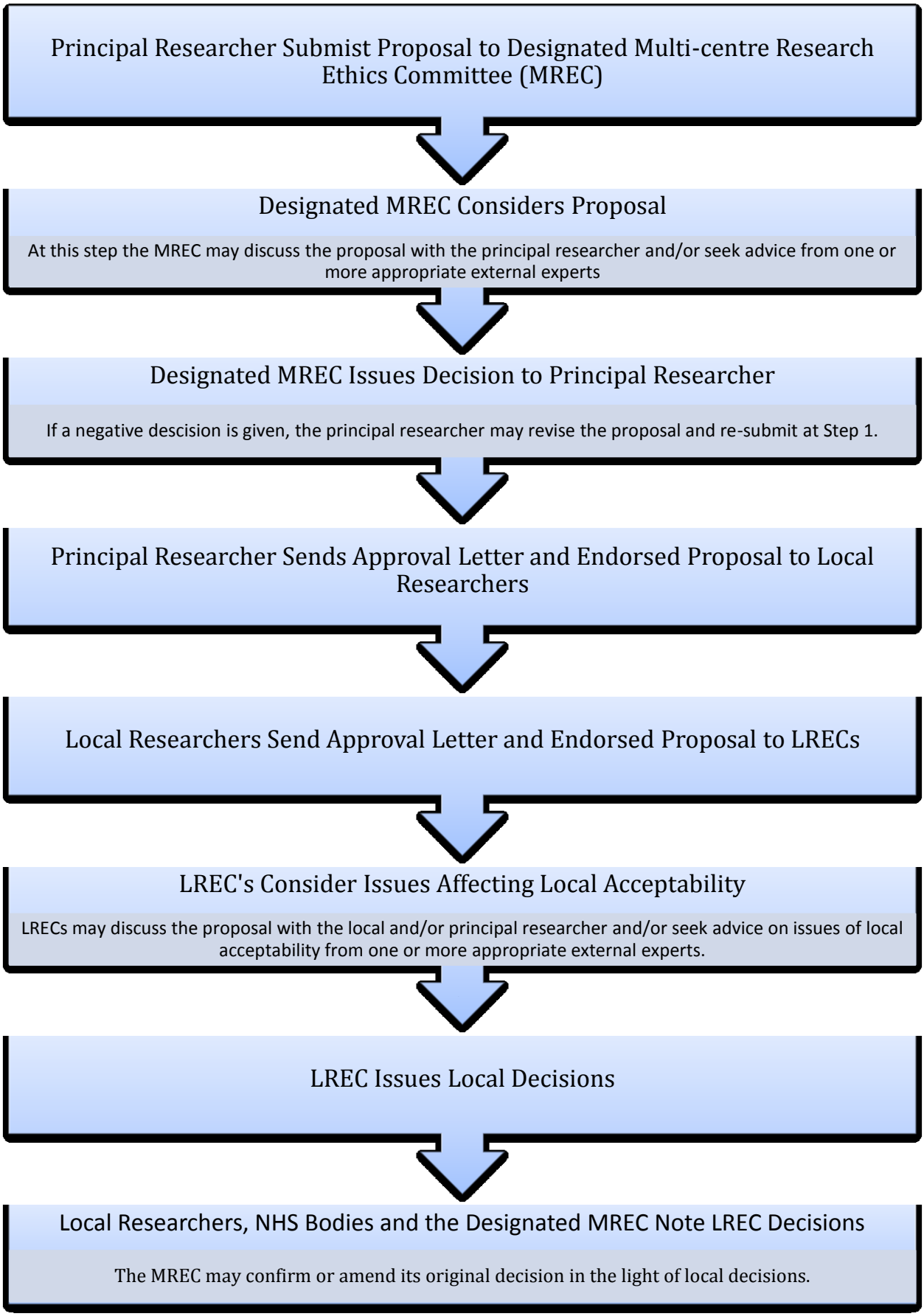
United Kingdom

Ethics committees in the United Kingdom are constituted and mandated differently to those in Australian and the United States of America. Although the UK has both REC's and CEC's, whose general remit is similar to their Australian counterparts, the process of governance and funding is quite different. The UK, while bound by its own laws, is also answerable to the European Union (EU), whose directives have precedence over member state laws. In most cases, however, the member state laws are worded so that they are comparable to the EU directives [229].

The history of RECs in the UK can be traced back to the 1950's and 1960's when the REC developed in response to whistle blowing by various researchers [261]. At this stage the RECs were local and independent, being generally attached to a National Health Service (NHS) trust or university, and only reviewed research being carried out in the region of the committee. Self-regulation was the norm within the committees, but this ended with the implementation of EU directives in 2004 [262]. The committees had no formal standing until 1991 when Department of Health guidelines incorporated them as part of the Citizens' Charter. One of the stated aims of this charter is improving accountability and transparency within the public service, including research [225]. The rise of multi-centre research in the late 1990's saw a massive increase in paper work for researchers who wished to carry out studies in more than one locale. This resulted in the Department of Health in 1997 seeking to introduce a degree of centralisation of the REC [109, 110, 225, 263]. This process is ongoing, and is continually being refined. The latest initiative, which was implemented in September 2006, was a screening function at the Central Office of Research Ethics Committees (COREC). The purpose of this was to *"identify at an early stage applications which fall outside the remit of NHS Research Ethics committees, are patently poor scientific quality or are poorly presented, apparently present no material ethical issues or are studies that are complex or involve potentially unfamiliar research methods."* [264] While COREC no longer

exists (having been superseded by the National Ethics Research Service (NERS)); the sentiment expressed is still valid within the new body. The process of centralisation allows studies to either be considered by a small sub-group or the whole ethics committee – dependent on the type of research being carried out [264]. A typical flow of ethical approval can be seen in Figure 10 below. Contrasted with the Australian processes outlined above, the differences are subtle: local research committees still exist and can influence the research, but not to the extent the pre-2010 model in Australia could.

Figure 10: Multi-Centre Research Ethics System Flowchart as Utilized Prior to NRES in the United Kingdom



The United Kingdom publishes a Manual for Research Ethics Committees (currently in its 6th edition), which provides guidance to research committees in areas such as how research should be carried out and the legal obligations of ethical research [265].

In the fifth edition of this manual, Ian Kennedy stated that:

> "*It should be noted at the outset that in law there is no obligation on a Health Authority, a Hospital a Pharmaceutical Company or other such body to set up a Research Ethics committee when involved in research on patients or healthy volunteers*."

He also noted that:

> "*There is no obligation in law on a potential researcher to submit a protocol to an ethics committee for approval. Thus, any authority which an ethics committee wields is informal and extra-legal*." [266].

The sixth edition of this document has a similar sentiment expressed by the same author [267]. These statements are based on the Department of Health's Circular HSG (91)5 which requires District Health Authorities to set up Research Ethics Committees. By virtue of the fact that HSG (91)5 is a circular rather than legislation, it is not legally required to be acted upon [266].

In her report on Ethics and Health care and the role of research ethics committees in the United Kingdom, Neuberger noted that:

> "*The role of RECs is essentially that of a public watchdog; to try to protect subjects from harm, to ensure that they are adequately informed, to see that valid consent is given and that no undue pressure to participate is exerted upon subjects, and to reassure the public that this is so*." [38].

Although being perceived as a public watch dog, the REC actually have no legal means to prevent unethical research of which they may be aware from being carried out, if it has not formally being presented to them.

For example, Beyleveld *et al* [37] note that some drug companies have set up an REC for Phase I drug trials. These however have no formal standing within the UK research community and cannot really be considered independent of the research process, as they are

formed and funded by the same body sponsoring the research. This potentially initiates a conflict of interest. Beyleveld *et al* [37] also noted that RECs operates in a regulatory context that includes other committees and bodies which may also have their own ethics committees and guidelines. The background context, which they offered in their paper, shows a cornucopia of various committees and bodies all working in a regulatory context, but not necessarily complementing or supporting each other. They identify five major forces of possible relevance to IEC operations in the United Kingdom. A listing of some of the bodies, committees, statues and guidelines that are of particular relevance to the operation of what they signify as IECs is intended to support the identification of the five major forces [37].

The first of these forces is the relevant international law and guidelines. These include the EU Directives, United Nations International Covenants on Civil and Political Rights and Economic, Social and Cultural Rights as well as the European Social Charter. The EU Directives are examined in further depth at a later stage in this chapter. However, the relevant directives to ethics in research are encompassed in Good Clinical Practice, as well as the directives on Medicines, Medical Devices and Legal Protection of Biotechnological Inventions. The British Department of Health also has within its requirements for ethics committees the recommendation that committees follow the International Committee of Harmonisation Tripartite Guidelines of Good Clinical Practice (ICHT-GCP) which the department noted is essentially the EU Directive on Good Clinical Practice [225]. These are in addition to the guidelines, which are published by the British Department of Health and which detail procedures for researchers and general framework for research governance [112, 113, 268-272].

Further to both international and European laws are the governing bodies that are constituted under various acts of parliament. The ones which Beyveld mentioned as potentially being relevant include the Medicines Control Agency, Medical Devices Agency, Human Fertilization and Embryology Authority and the animal Scientific Procedures Act [37]. Along with these regulatory bodies constituted by law are the various medical regulatory bodies such as the General Medical Council and other bodies that are regulated by non-statutory committees. The various medical specialities and their resultant royal colleges and societies also have their own guidelines which they expect practitioners to follow [273]. All of these differing influences affect how studies presented to RECs can be interpreted. They also provide a similar legislative basis for intra European studies. In the Thomasma ethical

tree, these influences can be applied at a branch level, and influence particularly the clinical and public policy branches.

In addition, there are charities and research councils who are the major funders of research within the United Kingdom. The two major independent bodies who guide ethical research are the Nuffield Council on Bioethics and the Kings Fund - neither of which have any legal standing – yet they are both appear to be influential in the formation of ethical guidelines. The final force of influence on IEC is industry. Certain areas of industry, especially the pharmaceutical area, issue their own guidelines for research. How much impact these industrial guidelines have with regards to research is unknown.

It is within this framework that IEC are expected to review and comment on research which is being carried out.

European Union Directives

While the British system appears to be complicated by the necessity to comply with EU directives, the overall effect of the directives is minimal except where research into therapeutic drugs is carried out. The Privacy in Research Ethics and Law (PRIVIREAL) project actually mentioned that the UK has one of the broader takes on the Data Privacy Directive. It stated in the notes accompanying their final report that:

> *"…the UK, in passing a statutory instrument to legitimate research in the substantial public interest has implicitly recognised that not all research is in the substantial public interest, but leaves open the question as to whether all medical research might be held to be in the substantial public interest*"[274].

This interpretation of the complexity of the statutory nature of the UK laws, suggests that the potential for "grey area" research is quite high, and may not be covered by the laws and statutes as written.

The PRIVIREAL group was conceived as part of the European Commission Framework 5 to examine the implementation and effect of the European Directive 95/46/EC in relation to medical research and the role of ethics committees. European Directive 95/46/EC relates to data privacy and the ability of member states to use that data. PRIVIREAL found that although the overall aim of many of the EU directives (and in particular, 95/46/EC) was to enable research to be carried out seamlessly between member countries this is not necessarily the case. It was seen that many member states interpretation of the directives into common

law differed enough to change the interpretation of the directives [274]. The recommendations by this body highlighted the confusion as to how medical research is defined as in the context of data privacy [274]. Townend [275] noted that even though the EU directive was aimed at introducing a modicum of homogeneity to member states, with regards to the laws surrounding data privacy, the exceptions to the law sometimes appear greater than the law itself.

As the United Kingdom is a signatory to the European Union, EU laws and directives take precedence over local laws [276]. Most EU directives are issued with a period for them to be integrated into a signatory countries law. In this case EU Directive 91/507/EEC which regulates Applications for Grant of Product Licences—Products for Human Use, requires that Research Ethics Committees ensure that the Good Clinical Practice Guidelines are met while research on drugs intended for human use is carried out. The UK is also beholden to EU directive EU 2001/20/EC, which is a directive on good clinical practice. This directive however is only for the

"conduct of clinical trials of medicinal products for human use" [277].

The six directives with relation to pharmaceuticals span from when the European Union was still the European Economic Community (EEC) (1965) to the present day. In order of implementation they are, Directive 65/65/EEC1; Directive 75/318/EEC; Directive 75/319/EEC; Directive 93/41/EEC; Directive 2001/20/EC and Directive 2001/83/EC.

However, it should be noted that these directives from the EU and the laws that they cause to be mandated, do not cover research that does not have a therapeutic drug outcome. EU directive 2001/20/EC specifically states that it is

> "*…on the approximation of the laws, regulations and administrative provisions of the Member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*" [229].

It is not obvious if there is an EU directive for trials not involving potential therapeutic drug use as the directive for good clinical practice has a drug bias. The closest any other directive comes to encompassing the ethics of research is Directive 95/46/EC, which covers the protection of individuals with regard to the processing of personal data and on the free movement of such data. This directive (according to European Public Health Alliance) has

been implemented slightly differently in member countries, thus making the effect with regards to medical research, privacy and the law and ethics committees unclear [278].

Other Bodies in the United Kingdom

As well as the EU, the United Kingdom also takes into account in its laws the World Medical Associations Declaration of Helsinki. This declaration is taken to be one of the most important sources of ethical principle outside of the law. Any research which does not fall under the EU directive appears to be covered by the Department of Health guidelines which detail procedures for researchers and general framework for research governance. The framework sets out rules for research which is done under the responsibility of the Department of Health, and incorporates both some of ICHT-GGCP and also of the EC Directive on good clinical practice mentioned earlier [26].

The ICHT-GGCP was implemented to institute a set of minimum standards for development and registration of investigational products across the European Union, Japan and the United States of America [279].

It is interesting to note that, with regard to the ICHT-GGCP, there are 13 principles to which it subscribes. Of these principles the second and sixth are of interest from an ethical standpoint as they highlighted the concepts of beneficence and non-maleficence in a contemporary way.

The second principle stated:

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

While the sixth principle stated:

> "*A trial should be conducted in compliance with the protocol that has received prior institutional Review Board, Independent Ethics Committee approval or favourable opinion. This means that a clinical trial should not be initiated unless prior Institutional Review Board or Independent Ethics Committee approval is obtained*."

The second principle appears to have as its basis modern virtue ethics. This contemporary approach tends towards the value and meaning of life [280]. This finding of the value and meaning of life could be considered analogous to the concept of finding of the balance point

between researchers and participants. The discourse between researchers and those that participate in the research study, as well as that between ethics committees and their researcher can influence the effect that the second principle may have on the shaping of research, and especially clinical trials.

The sixth principle has the potential to contradict the rest of the ICHT-GGCP as it is used as a guideline for ethics committees evaluating research, thus causing a circular argument [281].

The basis for research ethics committees in both and Australia and the UK is one of encouraging good practice and good quality research. In both countries there is no legal requirement for research to be presented to an ethics committee – although most funding bodies do require some type of ethical clearance before releasing the funding. As mentioned previously, while the imperative is not necessarily there for privately funded research to be presented, most journals will require some evidence of ethical presentation and/or clearance for a publication to be considered [238].

United States of America

In the United States of America, the role of ethics committees is seen as a more statutory and legalistic construct compared to the directive and statement based committees of the United Kingdom and Australia. This is primarily due to the fact that much of the ethics legislation in the United States has its basis of requirement in statutory law, as opposed to the suggestions and recommendations of both United Kingdom and Australian law.

While there are examples in the United States of informed consent and ethical discussions on research prior to the Belmont report, it is this report that is seen as the stepping stone to regulations [227, 282].

The basis from which the ethical regulations in the United States are derived is the Belmont Report. This report – published in 1979, and prompted by the Tuskegee Syphilis Study as well as others, was the fulfilment of the second mandate of the 1974 Public Law 93-348, which established a National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research [227]. This mandate asked the Commission to distinguish between medical research and practice and to develop the basic ethical principles to govern research with human subjects. The Belmont Report distinguishes between three basic ethical principles – Respect for Persons, Beneficence and Justice. These three

principles are the basis on which most American research ethics is based. The Belmont Report also looked at how these principles could be applied to general research and what sort of consideration should be given to items such as informed consent, risk/benefit assessment and the selection of subjects for research.

The Belmont Report led to federal regulations regarding the Protection of Human Subjects of Research, which is formally known as "*Title 45 of the Code of Federal Regulations, Part 46 (45 CFR 46)*."[228].

These regulations were published in the Federal Register in 1991 and are the official policies concerning research on humans in the United States [283].The US Federal regulations are divided in parts. Sub-part A is the basic Human Health Services (HHS) policy for protection of human research subjects. This is the area which outlines to whom the regulations apply, what they apply to and how they need to be applied [283].

The regulations can be perceived to apply to all research that is funded wholly or in part by the Department of Health and Human Services (DHHS), and anything the DHHS itself may undertake in the research arena at a Federal level. It encompasses all research, which involves human research subjects. There are, however, exceptions. The exception is non-invasive viewing of normative practices in educational settings, educational testing, publicly available data and non-identifiable surveys, interviews and observations. This can be summed up as meaning that investigations undertaken to improve government agencies or programs are not considered to be research on human subjects even if interviews or interactions with human subjects occurs. The final exception is DHHS research – which in the opening paragraph of subsection A specifically includes: (emphasis added).

> "*Except as provided in paragraph (b) of this section, this subpart applies to* ***all research involving human subjects conducted by the Department of Health and Human Services or funded in whole or in part by a Department grant, contract, cooperative agreement or fellowship***."

Paragraph (b) part 6, stated that

> "*Unless specifically required by statute (and except to the extent specified in paragraph (i),* ***research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluated or otherwise examine: (i) programs under***

the Social security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs."

This statement appears to preclude most DHHS research from undergoing ethical consideration if taken literally. It is interesting to note that within this there is provision for vulnerable populations to be covered by a certificate of confidentiality. This certificate protects vulnerable participants in studies by preventing compelled disclosure of identifying information [284].

Separate to this Federal Regulation, but related, are Institutional Review Boards. These were established by National Institute of Health (NIH) policies in 1966 and 1977. They were included in the considerations by the committee which produced the Belmont Report. This same committee also made recommendations for the improvement of the process of ethical review. Institutional Review Board review is legally required for any research which is conducted with Federal Funds [285]. However McNeill [30] does note that Curran mentioned "*the American System is far, far more elaborate, far more sophisticated, much more detailed than any other system around the world*".

The process of applying for ethical approval for research in the United States is similar in many ways to both the United Kingdom and Australia, however as with these countries, while the law/regulations may guide the researcher, the implementation between and within states and counties, and even between different institutions is varied. This is particularly true with non-funded research. As the law stands, in all three countries if the researcher can fund his or her own research, and if it takes place at a non-academic institution, they are not legally obligated to present to an ethics committee.

Perceptions of Ethics Committees

Research Ethics Committees are needed to fulfil the requirements of funding bodies such as the NHMRC and its international equivalents. Many bodies require research to undergo ethical approval before they will fund the research. They provide a gateway to research, and committees act as "gatekeepers" for what is perceived to be ethical research. While Australia has not had the documented problems that many other countries have had with regards to dubious research - for example, the Tuskegee Syphilis study in America - research ethics

committees are still required. It is generally accepted that to obtain funding from governmental and private bodies the proposed research plan must be presented to an ethics committee for scrutiny [286, 287].

The Role of Committees

The NERE is one of changing perceptions. These changing perceptions can potentially be seen in the reactions of ethics committees to the types of proposals with which they are presented. Also, within committees, the differing perceptions of the role of members of the committee have influenced the NERE. The papers of McNeill [28, 32, 33] and Wood *et al* [288] explore the makeup and intent of ethics committees within Australia. Authors such as Foster [222, 289] and Hendrick [290] in the UK have highlighted similar problems to Australia, although the UK appears to be further ahead in addressing highlighted problems and discrepancies. Boyce [291] examined the working of a multi-centre committee and found similar problems were encountered with regards to why studies were not approved. From the American stand-point, there do not appear to be many authors who have critically looked at the issues surrounding research ethics committees in an American-only context. From an epidemiological point of view, Rothman's personal account of trying to get IRB approval for an interview study with women whose children suffered birth defects is a story which is still repeated today, over 20 years later [292]. A search on Web of Knowledge using the key terms ethics, committee and American and limited to medical ethics and English returned 82 results, none of which critically examined researchers' perceptions on ethics committees in the United States of America. The closest paper in concept to these search words examines how IRBs and inappropriate restrictions can hamper epidemiological studies [293].

Benefits and Disadvantages

The ethics systems employed in the three countries under consideration, Australia, the United Kingdom and the United States of America have varied benefits and disadvantages. While the United States has advantages in that the ethics committees are mandated and required by law, this can make implementation and monitoring of the ethics committees more difficult. This is due in part to the fact that there are so many exceptions to the rules that determining if a particular research idea is exempt or not can be difficult. Additionally, there is the complication of the extra layer of anonymity that is found in some research with vulnerable populations due to applying a certificate of confidentiality. However, compared to the United

Kingdom and Australia, the American system of being federally mandated in law also has key advantages.

These advantages include greater consistency of ethics committees' practice across sites and states. Even though each state may have more than one ethics committee or IRB, their composition and ethical framework will likely be familiar. Australia and the United Kingdom, while having directives and statements outlining what is considered best practice and/or advisable, do not have any of these directives or statements mandated in law. This can cause confusion and inconsistency between counties, and/or states, especially where multi-centre research is being carried out. The United Kingdom has addressed this by establishing the national ethics research service, and Australia is heading towards commonality between states in the use of the national ethics application form and the HoMER initiative.

Multi-centre studies still appear to cause problems. The United Kingdom is addressing this by having a central body determining the overall ethics approval with representatives from all areas involved in the study highlighting any problems for their area only. This is complemented by a one stop booking system which is essentially country wide, thus allowing research to continue at many levels without the impediment of many committees or administrative bureaucracy [263]. This system is being implemented by the successor of COREC. Australia on the other hand, while making a good start by use of the NEAF form still requires individual approval from each committee. This has been highlighted as a problem by the NHMRC and processes are in place to streamline multi-centre trials through HoMER, which was launched in 2009 and is currently being rolled out through all the states and territories for multi-centre trials [243, 244].

While America has its ethics committees mandated by law, this same fact can restrain them from fully participating in ethical debate about research. As legally constituted bodies, it could be assumed that ensuring that the letter of the law is upheld, as opposed to debating what is good in furthering research, would be their primary concern. This may or not may be the case, as research on research ethics committees in America is limited. However, the number of committees which are constituted in America to advise ethics committees suggests that debate on various areas of research is a structured construct as opposed to developing out of research proposals and the results of research [294]. While Australia and the United Kingdom do not have that legal basis in law, they are slowly heading towards a more legalistic view towards ethics. In both Australia and the United Kingdom, the need for

legally-mandated committees to oversee all research – not just those receiving government funding or being carried out in universities – is imperative.

The influences of the ethics committee is in some ways an unknown quantity, and thus needs to be considered further with regards to the types of studies which are under consideration. McNeill [2, 8, 28] has shown that in Australia at least, committees are sometimes seen as unavoidable. Both the United Kingdom and the United States of America have similar sentiments expressed by other researchers [10, 27, 34-37, 115, 225, 289, 295-299].

Ethics committees can be seen to fit into both the clinical and public policy ethics branches of Thomasma's tree concept. Public policy ethics encompasses the legislation, regulations and institutional policies generated by ethics committees. Clinical ethics is what would guide the thinking of the ethics committees. Applications of various schemas as outlined in

Figure **1** would allow for guided thinking by the committees. While ethics committees could be seen as an applied ethical endeavour (application of ethical thought to a research proposal), in the interpretation of the tree model undertaken in this thesis, applied ethics is seen as almost as an individualist endeavour.

Tissue and Anatomy Acts

While much of the ethical research environment is shaped by the requirements for committees and their decisions, the tissue and anatomy acts have also influenced research is a very significant way. It was the tissue and anatomy acts that first outlined exactly how tissues could be obtained for both learning and research purposes. In both Australia and the United States of America the acts are state based, with each state outlining what they believe to be best practice for obtaining, storing and using samples. The United Kingdom has a national act that encompasses England, Ireland and Wales, with the Scottish national parliament simultaneously passing a very similar act.

These acts need to be considered in conjunction with the ethical environment surrounding research, as well as the relevant legislation and regulations guiding research.

All of these constructs of ethics committees have the underlying foundation of the principles of beneficence, non-maleficence, justice and autonomy. These principles are expressed within the Declaration of Helsinki, which forms the basis of two of the three ethics committee structures examined above. While benefice may not be as explicitly expressed as the other principles the point of most research is to benefit some subset of the community, thus RECs could be considered arbitrators of this potential benefit. Ethics committees are in place to ensure that the principle of non-maleficence, or "do no harm", is upheld. Justice and autonomy are included in the remit of an ethics committee with regards to ensuring that the research participant is allowed to assert these virtues as they participate. In the context of the NERE, these virtues are considered to be the equivalent of the Thomasma ethical tree concept roots –providing a base for an extension of the virtues that they embody.

The NERE is shaped by the evolution of these committees and processes being embodied. This ever-changing environment is the lens through which the following case studies are examined.

Chapter Seven - International Case Studies

This chapter will explain why various international case studies were chosen based on the criteria outlined in Chapter One. It will also undertake the analysis of these case studies response rates and demonstrate whether methodological changes (if warranted) have changed response rates in these longitudinal cohort studies. These changes will be examined in the context of the changing New Ethics Research Environment (NERE). These case studies aim to investigate hypotheses three to six as outlined in the introduction and re-iterated here.

The hypothesis under investigation in the following two chapters is:

> Do changing ethical environments in longitudinal cohort studies have long-term ethical considerations with regard to various factors within the study?

Doll and Hill Smoking Studies

Background

The premise for the GP Smoking study was based on an earlier matched case control retrospective study carried out by Doll and Hill [164, 170] and supported by previous and subsequent investigations such as Hammond and Horn [300, 301], Pearl [302] and Wynder and Graham [303]. The Doll and Hill study showed, through retrospective analysis, that there was a high probability that smokers were more likely to develop lung carcinoma [164]. Based on this premise, Doll and Hill developed the GP Smoking study to investigate the link between smoking and lung cancer prospectively. As they noted in the introduction to their 1954 paper: "*Further retrospective studies of that kind would seem unlikely to advance our knowledge...*" [167].

What sets this study apart from other longitudinal studies, and thus makes it a landmark type study, is the consistency of follow up of the original cohort. All cohort members where possible were followed until death and causes of death recorded. This is primarily due to all doctors being registered on the GP database, so their movements over time were easily followed. Also remarkable in this study is its size and approach to recruitment. The Doll and Hill investigation is seen as one of the seminal works with regards to what are now

considered known risk factors with regards to lung cancer. This investigation was designed as a prospective longitudinal cohort study. The initial potential study group were members of the medical profession in the United Kingdom as at October 31 1951. This group was approached via letter and asked to fill out a simple survey that included name, age, and address. It alsoasked the participant to classify themselves into one of three groups – "smoker", "ex-smoker" or "never smoked". The first two groups were investigated further with respect to length of time smoking, type of smoking and quantity of tobacco smoked [164].

There were significant changes to the ethical environment during the time of this study. Numerous documents on ethical practice on both a world and national level were published. These included:

- World Medical Association Principles in Research and Experimentation (1962);
- Declaration of Helsinki (1964);
- Ethics committees begin to be established in the UK (1966);
- Pappworth [261] published his monograph of questionable medicine (1966);
- Belmont Report published in the USA (1979);
- International Council of Medical Scientists published their guidelines for ethical review of epidemiological Studies (1991);
- World Medical Association reviewed the Medical Ethics Code (1994);
- Research Ethics Committees in the UK gain guidelines (1991);
- Data Privacy Act (1998);
- Central Office of Research Ethics Committees (COREC) established (2000),
- EU Directive 2001/20/EC (2001);
- Governance arrangements are changed for Research Ethics Committees (COREC) (2001) and
- The Regulations on Use of Humans in Trials (2004).

Of these, only the Pappworth Report, the establishment of guidelines for Research Ethics Committees in the UK, the Data Privacy Act and the establishment of COREC could have directly influenced any changes in the methodology of the Doll and Hill studies. These events potentially changed the ethical landscape in research in the United Kingdom by introducing greater accountability of researchers to their potential research participants. In the case of the Pappworth publication, it was through the highlighting of bad practices in

research using humans and a call for reform. The establishment of COREC was the first time centralised ethics came to the National Health Service. However, neither COREC nor the application of Research Ethics guidelines would have had any influence over the study design, as both were established in what could be considered the "twilight years" of the GP study. These events, while affecting surveys which came after the Doll and Hill studies, start to show that ethics in one-off recruitment studies may only exist in the time period and ethical environment and structure in which they were first conceived and first carried out.

Cohort Selection and Recruitment

A blanket approach to recruitment was applied for the GP Smoking studies, with anyone on the Medical Register as of 31 October 1951 receiving an invitation to participate. From the replies and based on their previous study, the investigators extracted the known risk groups (males and aged 35+) to follow up. There was no recruitment after this initial drive, but attrition rates were documented, with numbers' lost as a result of not residing in the UK, of being struck off and of requesting to leave the study detailed in the final paper [173]. The investigators noted that, in many ways, their choice of sample group was done for convenience [173]. While this may be the case, the output of this study (eight papers in high-impact journals such as the British Medical Journal over 50 years), suggested that high quality data was obtained and analysed [166, 167, 169, 171-175].

Response Rates

In the first paper in this study, it is noted that there were replies from 6,158 women and 10,017 men under the age of 35. It was decided that useful results from these groups would not be obtained for a long time; hence, the initial paper concentrated on known at-risk groups. Studies were eventually carried out on female physicians, with similar findings [169].

Over the first three published papers (a period of approximately 30 years) there was an average loss of respondents of 2.44% per survey [172]. This decrease in response rate was, therefore, quite small (see Table 1 and

Table 2) and was largely accounted for by death. These tables utilised male GPs as the majority of the analysis was concerned with this group due to the numbers and age distribution of the original cohort. Only one paper concentrated solely on female GPs and their response rates [169]. The female GP cohort are considered in the final paper, however, the progressive loss of females is not as well recorded as it was for males, and, thus the statistical analysis is not as rigorous [173]. As can be seen from Table 1 and

Table 2 response rates for this survey were very high (average response of 96.8%). This high response rate, as well as the detailed knowledge of why responses were not obtained, allows for investigators to ensure that they still have a representative population for analysis.

Table 1: Initial Response Rate Based on Results as Published by Doll and Hill [167]

	Female	Male	Total
Total Population			59600
Responded	6158	34866	41024 (68.83%)

Table 2: Loss to Follow-up for Doll and Hill Studies – Male only. Modified from Doll and Peto [172] (first three columns), Doll, Peto et al [173, 174] (fourth and fifth columns).

	Second questionnaire *	Third questionnaire	Fourth questionnaire	Fifth Questionnaire [174]	Sixth Questionnaire [173]
Survey period	November 1957- 31 October 1958	March-31 October 1966	July-31 October 1972	1st November 1990 - 1st November 1991	1st November 2000 – 1st November 2001
Known to have died before end of survey period	3122	7301	10634	10449	25346 [1]
Presumably alive at end of survey period	31318	27139	23806	11121	6150 [2]
Replied by end of survey period	30810 (98.4%)	26163 (96.4%)	23299 (97.9%)	10615 (95.5%)	5902 (95.96%)
Reasons for non-response:					
Too ill	31	65	21	**	**
Refused	36	63 ***	102 ***	467	467
Address not found	72	403	22	47	248 [3]
Unknown and other reasons	369	445	362	577	2459

*The first questionnaire was not covered, and the response rates for this paper are seen in Table 1.

**Data for illness not recorded in these two surveys.

***Total includes previous.

[1] Total deaths over 50 years

[2] Total initial replies (34439) minus those who were struck off (17), asked to be removed (467), those Overseas (2459) and known deaths (25346)

[3] Total over whole survey.

Analysis and Discussion

Research Ethics Approvals

The study investigators acknowledge that the fact that this investigation started before the implementation of ethics and the ethics review process. They agree this has probably affected how the study was designed and carried out [173]. This lack of ethical process was primarily due to no new members of the defined community being added, and the methods for contacting the defined community members not being subject to change. In addition, the data being collected did not vary enough for significantly different data collection forms to be needed and, thus, no ethical approval was required.

Major changes to the research protocol would have required ethical clearance which potentially would have affected the comparability of results pre- and post-ethical clearance. Due to not undergoing any ethical or methodological changes, an evolution of the NERE for this study does not exist. The level of risk in the Doll and Hill studies was minimal so even if the proposal had to be presented to an ethics committee within the time frame of the study, the likelihood of permission being granted would have been high.

Due to the non-existence of an evolution of the NERE, this study can be considered to be a "baseline" study. It establishes the fact that a study, with no major methodological changes over a long period of time, does not have to resubmit itself to ethical scrutiny. The initial design of the study provided the information which was required to answer the question being posed. The changes to the study which were undertaken (additional questions, removal due to various circumstances) were either not significant enough to warrant the need for ethics approval, or were instituted before ethical approval became the accepted norm.

If the study under discussion had to be approved through contemporary research ethics requirements, it would be questionable that the data obtained would be as comprehensive. Access to records such as coroners' reports and death certificates would have proved problematic. While access would still have been available, the data linkage that Doll and Hill obtained was comprehensive and did not have any privacy structures in place. Access to the GP database may also have been more restricted. It was the comprehensiveness of this data that allowed for the conclusions with regards to the causes of lung cancer to be clearly elucidated. While others such as Hammond and Horn [300, 301] were carrying out studies at the same time, the length of the studies was not as long, although the sample size was much

larger. Other studies carry out concurrently with the Doll and Hill studies suggests that the effect of smoking would have been elucidated within the same time frame. By the late 1950's, the studies were gaining notice and their methodology was being discussed in the literature [304, 305]. It was not the actual mechanics of the study being discussed, but more if the methodology employed was reasonable to draw the conclusions that were reached. This study starts to show that ethics within a longitudinal cohort construct may actually exist only in the time frame in which the study was conceived and/or recruited. This concept will be examined further in the remaining studies.

Recruitment

If this study were carried out today, based on current ethical requirements, justification for using the sample group would have to be provided, along with samples of the questions the researchers intended to ask. Access to the GP database would most probably be restricted due to privacy concerns. If access were granted, it would have to be negotiated between a number of different stakeholders. The questionnaire could be distributed at the same time that the potential participants were approached. Return of the questionnaire implied consent to participate in the project. If this study were initially to be undertaken today, permission to participate would have to be obtained individually from each GP before any surveys were distributed, and follow up and follow through the databases would have required extra permissions. This defined community of research participants (adults with a high health literacy and awareness) probably made recruitment easier. This would have been due to them being aware of what was required, and thus having the tacit acknowledgement that the data being sought were essentially non-invasive and adding to the body of knowledge.

Consent

Implied participation by returning of the survey would not be acceptable in contemporary British ethical environments - a separate consent form would be required to be returned along with the survey. Alternatively, a request to send out the survey to a participant would have first been undertaken; dependent on the response, the survey would then be sent. This latter approach has been shown to reduce response rates [306]. Furthermore, implied consent does not necessarily equal informed consent. Informed consent would suggest that the participant had been fully informed with regards to potential problems as well as potential benefits to participating in a study. Data gathering by non-invasive procedures such as surveys and questionnaires do not have to undergo as rigorous ethical scrutiny as studies that may require

either discomfort or danger to the participant. This partially explains why, even though the study under examination had more than one survey undertaken, ethics permissions were never required. Studies which may involve trigger scenarios such as remembering traumatic events may potentially cause harm to a participant, but in the case of the Doll and Hill studies actions and habit were being recorded not reactions to past events. The evolution of the NERE would have affected this study, in that implied consent may not have been deemed appropriate, and formal written consent may have been needed. This may have potentially affected the response rate by adding additional paperwork and follow up procedures, thus impacting into both the researchers and the participant's time.

Response Rates

The response rates for this study are very high. Throughout the study the response rates were within the 90% range, and so this response rate could be considered to be unusual. This could be due to the original study group being more socially aware with regards to the contribution this study could make to health outcomes. It could also be due to the non-invasive nature of the study. A response rate in the 90% range is not usual for studies instituted today, although Cummings *et al* note that there is no gold standard for response rates [307]. They also note anecdotally that response rates have been decreasing over time [307]. Average response rates varied between 54% [308] and 86% [309] for physicians dependent on other factors such as method of follow up, and type of survey. While this series of studies has high response rates even for physicians, a typical response rate for a mail out survey is approximately 60% [308].

Conclusions

The NERE does not appear to have impinged this long-term longitudinal cohort study. This could be attributed to the fact that no recruitment or methodological changes were undertaken once the study had started. A sense of community may have contributed to the high response rates, as well as a social awareness of the impact that the study may have. Similar results to this study were obtained in a shorter period by other authors such as Hammond and Horn [300, 301] and Hammond [310], however, the length and ability to follow-up on the total population makes this research unique. It is this follow-up that allowed for the conclusions to be reached with a high degree of certainty and comparability with other studies.

Framingham Heart Studies

Background

This study is a long-term investigation that looks at identifying the common factors or characteristics that contribute to cardiovascular disease (CVD). This long term study is seen as an example of how large scale research (4494 participants in the original cohort) can be carried out sustainably with very little attrition of participants [150]. This community could be assumed to be pre-primed for participation in this type of investigation, having participated previously in Influenza and Tuberculosis studies [311-313].

The Framingham study is differentiated from others which have been carried out over this time, potentially making this a "landmark" study for longitudinal epidemiological studies; this status is due to the length of time that it has been ongoing, the large scale size of the recruited cohorts and the consistency of recruitment to make it a comprehensive study and the low dropout rates. While these individually may not appear to be important, combined, they show a well-developed, long-term investigation with results that have made an impact on the study and knowledge of CVD at an international and national level. It is also an excellent example of research that utilises the population to its maximum.

The Framingham Heart Study was the combination of the Heart Disease Epidemiology Study, begun in 1947, and the Cardiovascular Hygiene Demonstration also instituted in 1947. While initially having separate study sites (the former in Newton, Massachusetts, and the latter in Framingham), when the Framingham study came under the auspices of the National Heart Institute in December 1949, the programs were combined [148]. Oppenheimer noted that the Framingham study was added to a raft of control programmes designed to look at chronic non-infectious diseases utilizing community-based screening and diagnostic interventions [162]. Dawber *et al* [142] observed that many epidemiological studies have lead to findings relevant to cardiovascular health. The quality and number of papers which have come out of the Framingham study has steadily increased as more data has become available – growing from 15 in the first nine years (1950-59) to just over 900 in the last nine (2000-2009). This could be attributed to more data being obtained over time, but also the fact that data linkage between cohorts and generations within the Framingham study is now available. This is an emerging area of epidemiological study and it stands to reason that a large data source such as this would be utilised by both the Framingham researchers and

others. Raw data is available to any researcher on request and submission of relevant ethical approvals.

The Framingham heart study also had a prospective longitudinal cohort study design [151]. The initial aims of the study were to secure epidemiologic data on various features of CVD [142]. Securing this data relied on what has been termed "Macroscopic Epidemiology" – looking at prevalence and incidence of disease through gross observation [138, 141]. As a by-product of this approach, the aim was to obtain data on the prevalence of all forms of CVD in a representative population group and to test the efficiency of various diagnostic procedures [143].

Major ethical events which have taken place during the Framingham study include

- The World Medical Association International Code of Medical Ethics (1949);
- The Wilson Memo (1953) – although this was top secret until the 1970's;
- World Medical Association Principles for Those in Research and Experimentation (1954);
- AMA Revision of Code of Medical Ethics (1957);
- Revision of the Declaration of Helsinki (1964);
- National Research Act passed (1974);
- Belmont Report (1979);
- WMA Revision of Code of Medical Ethics (1994);
- AMA Revision of Code of Medical Ethics (1980 & 2001).

Within these constructs, the two events that would have the highest impact on the Framingham study are the Wilson Memo and Belmont reports. Both reports examined the government's reaction and implementation of policies with regards to human experimentation. The Wilson Memo was a document issued by the United States Department of Defence that enshrined the Nuremburg code as the basis for ethical thought within the military. It highlighted the need for informed consent as a written document, as opposed to recorded verbal consent. As it remained classified until 1975, the wider dissemination of the

need for informed consent was limited until this time [314]. While this may not have necessarily influenced the application of ethics within the non-military environment, it does show how, even though the American Medical Association was one of the first Medical organisations with a written code of ethics, legislation and thinking about ethics has taken time to catch up.

The Belmont report had a large influence on medical research. While it was never fully adopted by the United States Government, it still provided a framework for researchers with regards to ethical conduct and thinking [315]. Cassell [316] highlighted that the principles of the Belmont report still reflected the Hippocratic values of respect, beneficence and justice, albeit in a modern setting. They also note that the rise of the bioethics movement in the 1960's became an influential voice with regards to research and how it was carried out.

Cohort Selection and Recruitment

To increase the likelihood of success and good will of the community, the Framingham study design and cohort selection was developed with assistance of the local hospital and medical fraternity [161]. Gordon and Kannel [148] acknowledged that a study such as Framingham was a learning process; consequently, while approaches such as sampling frames and analysis may be decided before the study is undertaken, refinement will inevitably take place in a study of this kind. Over time, more hypotheses have been developed, as the results have raised further sets of questions. Dawber and Kannel in 1966 note that one of the greatest findings in the Framingham study is that it has shown the value of prospective epidemiological approach in chronic disease [139].

Framingham as a study site was chosen on the advice of Dr. Vlado A. Getting and Dr. David D. Rutstein. It fulfilled both the requirements for the proposed population and the logistical requirements [143, 161]. Framingham had previously successfully been used in a Community Health Study on Tuberculosis, which may have also played a part in the decision making process [158, 311, 313]. Kannel noted that, in 1948 (when the study planning commenced), the Framingham study was placed on a new frontier of epidemiology – being one of the first large scale, planned long-term studies for a specific disease [156]. Castelli [132] noted that the only other heart study with larger numbers than Framingham was a blind case control study on the use of streptokinase carried out in hospitals in Italy and mandated by the Italian government. However, in this Italian study, participation was not voluntary – if

you presented at a participating hospital and matchedthe profile, you were enrolled into the study as a participant [132].

1st Generation Cohort

The initial cohort for the Framingham study was planned to be approximately 5,000 disease free individuals within 30-59 years of age. This number of participants was chosen to yield sufficient numbers for subsequent statistical analysis to be statistically robust and valid [137]. The original assumption was that a sample size of 5000 would show about 400 cardiovascular events within five years and approximately 900 events in 10 years. To obtain this 5000-person sample, it was initially planned to approach approximately 6000 people [151]. The follow-up period was originally planned to be 20 years [136]. However, currently, the original cohort is coming to the end of their 30th examination [180]. Framingham investigators have always acknowledged that while Framingham is a large study, it may not be representative of the United States of America as a whole. Thus there have been, and continue to be, constant comparisons with similar investigation in other areas [135]. It was due to this concern that the Omni cohorts were originally added [317, 318]. The Omni cohorts were recruited to enable the changing diversity of Framingham to be considered as part of the ongoing study. These cohorts are once again generational and made up of what were once considered to be minority groups within the Framingham area. They will be described in a later section of this chapter.

A random sampling frame was generated from the annual town census and was used to select potential participants for the study. This sampling frame yielded a response rate of 69% leading to approximately 4469 people being initially examined [144, 149, 159]. Care was taken to try to keep households together – that is, if one member of the household was selected, all eligible members of the household were invited to participate [148]. While the initial response rate was good, numbers were not as large as expected, thus 740 volunteers who had initially participated in the study before it was transferred to the National Heart Institute were added into the cohort by invitation. For the most part, this latter group were considered as part of the complete cohort – however some analyses have kept them separate to allow for potential volunteer bias [155].

2nd Generation Cohort

It was recognized that the second generation should be recruited to allow for examination of coronary heart disease within families [157]. This would allow one of the later aims of the

study *"to examine the presence of familial and genetic effects in determining the levels of risk factors for CHD*" to be accomplished [145]. Feinleib [145] mentioned the deliberate timing of the recruitment of the offspring study to allow for examination at approximately the same age as their parents. This was thought to be advantageous for increasing the knowledge of Coronary Heart Disease (CHD) risk within families [157].

The offspring of the original participants were recruited via information supplied by their parents at one of their regular biennial exams [145, 157]. This "cascading recruitment strategy" utilised those already in the study to recruit the next cohort. It could potentially influence the study by introduction of bias, as those who were recruited were already aware of the study and what it involved, as well as the related aims. This prior knowledge could potentially affect the attitude that the offspring took to being recruited and therefore potential outcomes. The ethical issues raised by contact details for the offspring being supplied by those already participating in the study are interesting: how does the right to privacy fit into a recruitment strategy that involves other family members who may not be living in the same household? This, and similar issues, will be discussed later.

3rd Generation Cohort

The third generation cohort began in 2002 and aimed to increase the knowledge of phenotypic and genotypic factors to CHD. This cohort comprised of 4095 adults who had at least one parent in the Offspring study and were aged 20 years or older, as well as 103 parents who were not originally enrolled in the offspring study. The aim was to complete family groups to enable familial analysis of genetic factors [163].

Recruitment of the third generation was identical to that used for establishment of the offspring cohort. That is, parents were asked at a regular examination for contact details of their families by completing a family descriptor form. If the parents had not presented for the sixth or seventh examination, or had died before the examination could take place, follow-up through mail, phone and archival research enabled eligible participants to be identified[163]. The primary focus for recruitment in the third generation cohort was to complete large related family groups. This was primarily to enhance the genetic research activity of the study, as large multi generational extended family groups are preferred for this type of investigation, as they allow traditional hereditary trees to be combined with more sophisticated genetic trees and thus allow for potential risk factors to be identified [163].

Omni Cohorts

The final two cohorts who were recruited into the Framingham study are what are colloquially known as the "Omni" cohorts. Officially known as 'minority over sampling' these cohorts were instigated to take into account the changing ethnic demographic within Framingham. This ensures that the results obtained were seen to be inclusive of all different ethnic demographics within the town [319]. The original Omni cohort was part of the Sleep Health Study carried out by O'Connor and reported in Quan *et al* [317]. The Omni cohorts have also provided information in various other studies that have run in parallel to the original Framingham cohort studies such as the Quan Sleep Study [317, 320]. From 2010, both Omni cohorts will be considered under the same auspices as the original three cohorts of the Framingham study, this will allow for comparisons between different ethnic groups within a similar socio economic and geographic area [318].

The Omni cohort were described by Quan *et al* [317] as residents aged 40-74 years who self identify as a member of a minority group. A minority group in this study is considered one that is racially distinct from the original cohort, which was defined as white. A multi-modal recruitment strategy – that is, a strategy that utilised more than one method of recruitment – was employed to enable the largest potential recruitment population to be reached. Precise details of the recruitment strategy were not documented clearly in any of the papers examined. The second Omni cohort was instituted to allow an ethnically diverse comparable cohort to the Generation III cohort [320]. The difference to the third generation cohort was that no relationship to someone in the first generation had to be claimed to be able to participate.

Response Rates

1st Generation Cohort

Good response data is available up until the 7th biennial examination (approximately 14 years into the study). However, after this period, reporting of exact response rates appears to not be as important as analysis of the findings. While this has not been referenced anywhere, many of the papers examined refer back to the papers of the 1950's and 1960's to establish response rates. This lack of reporting of exact response rates could also potentially be caused by a change in what publishers were looking for in their peer-reviewed papers. The study has a very low overall loss of participants to follow-up with only 15% of the population under study (806 people) being lost through death in the first 20 years [149]. Freidman [146] noted

that, after 10 years, the methods of follow-up appear to be catching most cases of Chronic Heart Disease within the study population. At the 16th cycle of examinations, the number of participants available for examination had decreased from 5209 to 2351 (54.87%) [151].

Table 3 and Table 4 show a break down for the first seven examinations in the initial cohort as to the numbers of people lost to follow-up as well as those examined [140, 144, 146, 149, 150, 153, 155].

Table 3: Initial Recruitment and Response to the Invitation to Participate in the Framingham Study [143, 149]

	Drawn Sample	Volunteer Sample	Total Sample [1]
Number Approached	6532	740	
Participating	4494 (68.80%)	740 (100%)	5234

[1] Includes those who had Cardiovascular Disease.

Table 4: Loss to Follow-up Over the First Seven Biennial Examinations (approximately the first 14 years of the study) [155].

Examination Number	Number Examined	Outside examination[1]	Deceased	Lost to Follow-up
1	5127			
2	4717	410		
3	4578	507	41	
4	4470	563	92	
5	4348	605	154	21
6	3984	877	230	35
7	4240	410	415	61

[1] This is taken to mean information was obtained about the participant through sources other than examination at the Framingham examination centre.

Response and follow-up rates within the Framingham study allowed for statistically significant results for the diseases under study. This is due to a few factors – primarily, that the population was centred on one geographic area, and thus participants were followed up rigorously through different methods and over investigations. This included presenting alternative methods of participation with different approaches if participants were unable to attend an examination appointment at the clinic due to distance or illness [144].

2nd Generation Cohort

Using family members already involved in the study gave the researchers 1644 spousal pairs for potential recruitment. A secondary group was also recruited which comprised of offspring who had one parent in the study who had cardiovascular heart disease and/or a lipid abnormality [145]. The initial sampling frame for this study was 4190 participants from a population totalling 5135. The total population who ended up participating totalled 5135. This comprised 3555 offspring with at least one parent enrolled in the original study, and 1580 participants who were spouses of the offspring. Recruitment was vigorous, with potential participants who were no longer resident in the Framingham area being given the opportunity to participate on visits home, or through satellite clinics established in other large population areas [157]. This latter measure enabled an additional 122 participants who otherwise would not have been included in the Offspring study to be included. Table 5 shows the division of the study population.

Table 5: Make-up of the Offspring Cohort – Framingham Study – Higgins [151] and Kanel et al [157]

	Number
Parent/s enrolled in original study	2656
Spouses of above	1212
Parent with CHD or abnormal lipid protein profile	899
Spouses of above	368
Total Population	5135

The spouses of participating offspring were included to enable evaluation of non-genetic factors in the risk of coronary heart disease. The first two examinations for this group were

undertaken eight years apart. At the second examination the response rate was approximately 76% [147]. This response rate was based on 20-49 year olds who presented for the second examination. This response rate may not be totally accurate, as some younger and some older members of the cohort were excluded from the analysis. At the first examination, the age distribution included 166 persons under the age of 20 and 168 persons over the age of 49 [145]. The Offspring cohort has undergone eight examinations, with their ninth scheduled to begin in 2011 [181].

3rd Generation Cohort

A total of 6553 children of the third generation expressed an interest in participating [163]. The loss at each stage is documented in Table 6.

Table 6: Response Rates to Original Contact for Third Generation Cohort – based on Splansky [163]

	Number Responded (% from eligible)
Known Eligible	6553 (100%)
Enrolment Form Sent	6138 (93.7%)
Form not returned	1411 (21.5%)
Form Returned	4727 (72.1%)
Examination complete	4095 (62.5%)
Refused	688 (10.4%)

This is the cohort where ethics committee approval is first mentioned as being obtained, and the option to "opt out" or "opt in" to various parts of the study was presented [163]. The implications for this do not appear to be discussed in the literature - however, the impact of choice within the study cannot be underestimated. The differences in response rates with regards to opt in versus opt out will be discussed in the following chapter.

Omni Cohorts

Recruitment and loss to follow-up for both Omni Cohorts is described in Table 7.

Table 7: Response Rates and Loss to Follow-up for Omni Cohorts. Based on Numbers supplied by Abel [320].

	Omni I	Omni II
Original Number in Study	507	410
Death	30 (5.9%)	1
Loss to follow-up	34 (6.7%)	3
Presented for last examination	298 (62.5%) [1]	406 [2]

[1] Percentage based on known living participants (507 – 30)

[2] Number based on known loss to follow-up, taking into account death and loss.

[3] For Omni I, this is examination cycle three. For Omni II, this is the original examination, as the second examination cycle is currently in progress.

Follow-up rates for the Omni cohorts are still very tentative. These cohorts have not been in progress for as long as the original three groups, and thus the corresponding body of knowledge is not as complete.

If the comprehensive follow-up procedures utilised for the original cohorts are also utilised for the Omni cohorts, it can be assumed that response rates over time will be similar. This should also be true if the same options for examination are offered (i.e. when in town visiting family, at satellite clinics).

Analysis and Discussion

Research Ethics Approvals

The original research study was conceived before formal research ethics approvals were required, but the researchers worked with the community to design and implement the study. As subsequent cohorts have been added, the study has been subjected to ethical scrutiny. As mentioned previously, this was during the recruitment of the offspring cohort, which is when consent forms are first mentioned as being required and utilised. As the Framingham study

holds such a wide variety of information, other researchers may wish to use either previously collected information or the well-defined cohorts for auxiliary studies. These studies, as well as having to undergo ethics approvals at their home institution, also have to undergo an approval process within the Framingham study group itself. This "guardianship" of the data, ties into the sense of community that the Framingham study has fostered since its inception [140, 148, 313]. Even though research ethics approval was not needed, the utilisation of the community to help design and carry out the original study acted as a pseudo committee overseeing the project. The use of the community in a consultative manner continues to this day, with the community being represented on the Framingham Ethics Advisory Board, which provides advice to the Executive Committee.

Recruitment

The initial recruitment in the Framingham study utilised a methodology that is still used today. The use of electoral or census rolls to recruit participants in potentially invasive surveys is not as common as using the rolls to mass-mail potential survey participants. As mentioned previously, the second and third cohorts were recruited through the participation of the previous cohort. The recruitment strategies were not written into the original proposal. The cascading recruitment strategy would have had a higher success rate due to awareness of the study within familial groups.

These changes of recruitment strategies between the original cohorts and the Omni cohorts can potentially be tied into the NERE. The Omni cohorts and the analyses they would be included in were subject to ethical approval. Multi modal recruitment allows for a wider variety of potential participants to be informed of the study and to potentially become involved. While the original recruitment could have been considered multimodal – with the use of town data as well as a call for volunteers - the fact the majority of the original participants the primary mode of recruitment was from town survey data.

In this respect, the NERE can be seen to have greatly influenced the recruitment of the Omni cohorts. If this environment had not existed, the recruitment strategies for the Omni cohorts would have most likely followed those of the first generation cohort.

Consent

It is noted in the Framingham study web pages [177] that documentation of informed consent began in 1971 with the first examination of the Offspring cohort and the 12th examination of the original cohort. This first documented informed consent read:

"*I have been fully informed of the nature of this study which includes a medical history, physical examination, blood tests and electrocardiogram and give my consent to be examined. I also authorize the Framingham study staff to secure pertinent medical information from my family, physician, and/or hospital records for the purposes of this study*."[177]

While simple, the consent form clearly spells out exactly what is required by participation, who may be approached to gather information and who is authorised to gather it. At the time it was used, this type of consent form would have been considered to be thorough and informative. It is not known if a patient information sheet would have been provided with this consent form.

As the NERE evolved, so did the Framingham study. The current consent form for the original cohort is a six page document outlining the procedures, the risks, the participant's ability to withdraw, the study's ability to access medical records as well as alternative examinations which may be undertaken if the participant has had a stroke. It also includes the ability to opt out of certain parts of the study, as well as information on how to remove yourself from the study fully and have your samples destroyed. This current consent form thus illustrates an evolution from an initial all-encompassing simple statement to one which takes into account every possibility and option that a participant may be faced with. The consent form for the current offspring study is even more involved: it is an eight-page document which, while including everything that is in the document for the original cohort, also outlines some further tests and sampling which will take place. These samples were introduced during the offspring cohort recruitment and thus are included in their ethics approval processes. There are nine "opt-in", "opt-out" options on the offspring consent form. It is the evolution of this type of precise controlled environment that is making long-term studies much more complicated to carry out. While choice is an important part of participation – the ability to pick and choose which parts of a study you participate in can cause problems for the investigators.

The NERE has influenced the way that informed consent has evolved in this study. The first 11 examinations of the original cohort had no consent forms. The first examination of the offspring cohort and the 12th examination of the original cohort had simple consent forms. Around the time that these examinations were undertaken, the Wilson memo was being disseminated to the general research community, although it is not known if this had an influence with regards to the initial use of consent forms. It can be seen as an example of how the evolving research environment impacted on studies already in progress.

Response Rates

Sample sizes may have been derived from an assumption that everyone who was selected and agreed to participate would participate in all of the sections of the study. Refusal to participate in some sections may not allow for valid comparisons to be made due to missing data. While this may not be a problem if only one or two people refuse to participate in certain areas, larger lack of participation may change to outcome and the significance of the results.

Conclusions

As can be seen from these case studies, the recruitment strategies for both the Framingham and GP studies have varied over the duration of the life of the cohort investigations. Some have changed over time to potentially take into account changing ethical frameworks and demographics, while others have remained static due to the nature and design of the original study. The methodologies in the Framingham study have evolved as the scientific environment enabled more precise and varying information to be obtained. This evolution of methodologies is independent of the ethical frameworks in place, though they would have to conform to the ethical norms of the time. As mentioned earlier, the GP studies did not show any evolution of recruitment or methodology – thus, the NERE does not apply to that study. However, the Framingham study shows how the NERE changed the way in which participants were approached recruited and retained.

Chapter Eight – Tasmanian Iodine Surveys

Introduction

Many parts of the world have recorded iodine deficiency, both historically and currently. Historically, iodine deficiency has been well-documented in Tasmania [321]. Iodine deficiency in Tasmania is thought to be related to glaciations in the last Ice Age that caused leaching of nutrients from the soil, thus leading to a deficiency of iodine in both the soil and water [182] .

More recently, mainland Australia and areas of New Zealand have also been found to be iodine deficient [199, 322-324]. The reasons for these changes are unknown, but it has been suggested that changes in dietary patterns of the population under examination may be a contributing factor[323] .

Recommended Daily Intake – Past and Present

The World Health Organisation (WHO) currently suggests that the recommended dietary intake should be between 90-150 micrograms of Urinary Iodine (UI), with pregnant women's intake being marginally higher at 200 micrograms [325-327]. Tasmania has historically been close to being sufficient; however, when compared with the WHO recommended intakes, the trend over time has been for mild deficiency [117, 118, 122, 199, 203, 328]. Table 8 shows the accepted levels for urinary iodine analysis.

Table 8: Iodine Nutrition Levels According to the WHO [327]

Median UI (µ g/l)	Iodine intake	Iodine nutrition
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimal iodine nutrition
200–299	More than adequate	Risk of iodine-induced hyperthyroidism within 5–10 years following introduction of iodized salt in susceptible groups
>=300	Excessive	Risk of adverse health consequences (iodine induced hyperthyroidism, auto-immune thyroid diseases)

Prior to UI being the accepted method for measuring iodine status within a community, a staging system based on goitre sized was utilised [329]. Within the Tasmanian Iodine Surveys, a grading system was originally developed in-house and then modified at a later date to be similar to Perez *et al* [198]. This modified system and the Perez *et al* classifications can be seen in Table 9. It should be noted that while Gibson *et al* [198] refer to a category 1a/1b in the Perez *et al* paper when citing equivalence, category one is not split in the Perez *et al* [329] paper referenced by Gibson *et al* [198].

Table 9: Previous Goitre Palpation Categories as Defined by Perez et al [329] and as Developed and Modified by Gibson et al [198]

Category	Category Description	
	Perez *et al* [329]	Gibson *et al* [198]
0	Persons without Goitre By definition these are taken to be persons whose thyroid glands are not 4 -5 times enlarged.	Normal thyroid – no enlargement of the gland, taking into account that the normal thyroid in adolescent girls can often be palpated relatively easily
1	Persons with Palpable Goitres The thyroid is considered to be more than 4 to 5 times enlarged although not visible with the head in the normal position. Most of these will be fully visible with the head thrown back and the next fully extended.	Equivalent to Perez 1a – a mild diffuse swelling, easily palpable and sometimes just visible particularly in a child with a thin neck. Enlargements assessed as 1 comprise the group designated palpable goitre. Enlargements of greater degree are visible in inspection with the head in normal position and comprise the group visible goitre. (i.e. Categories 1+, 2 and 3)
1+	No equivalent category	Equivalent to Perez 1b category – an enlargement discernible as a swelling between the anterior borders of the sternomastoid muscles, with an isthmus of between one and two finger breadths [1].
2	Persons with Visible Goitres Persons with goitres which are easily visible with the head in normal position but which are smaller than those in Group 3. Palpitation may be helpful in determining the mass of the gland but is not needed for diagnosis.	A clearly visible enlargement with isthmus about 2 fingers breadths and lobes bulging at the sternomastoids.
3	Persons with Very Large Goitres The goitres of persons in this category can be recognised at a considerable distance. They are grossly disfiguring and may be of such size as to cause mechanical difficulties with respiration and the wearing of clothes.	A marked enlargement, clearly visible at a distance, producing disfigurement and easily recognized by a lay observer.

[1] From 1965, the majority of visible goitres were of this size.

Terminology

Within the Tasmanian Iodine Surveys, there were three distinct time periods where surveys were undertaken. While the different surveys were undertaken by a variety of people, a naming convention was developed for this thesis to enable different time periods to be easily differentiated. The surveys which were carried out between 1949 and 1984 have been designated the "Gibson studies" as the primary reference source for these studies is Gibson's 1995 book [118]. The surveys carried out between 1996 and 2000 have been designated the "Menzies studies" after the Menzies Centre for Population Health, which carried out the studies during this time. The surveys undertaken between 2003 and 2007 were designated the "Broadstreet studies" as this was the name of the company involved in the set up and execution of these surveys. All of the surveys were undertaken under the auspices of the Department of Health and Human Services Tasmania with co-operation from the Department of Education Tasmania. In this section, study and survey are used interchangeably. In the context of this chapter the broader dictionary definition of a cohort as group or company will be used.

Background

Historical

The first noted case of goitre in Tasmania is recorded as occurring in the 1830's and was noted in a generalised paper on diseases present in Tasmania [330]. Tasmania has normally being considered as an endemic goitrous area – that is an area where goitre is present in the population without any external inputs. Letters in various publications note that the occurrence of goitre – particularly in women – was common during the 1800's and 1900's.

The Tasmanian Iodine Monitoring Programme can be considered as the umbrella under which many different studies of iodine in Tasmania can be grouped. The three major studies on school children are the focus of this chapter with regards to changing methodologies and recruitment strategies. The effect of the ethics environment on these areas will also be examined. Although differing in methodology and scope, the aim of all the studies was the same – to investigate, using population measures, the status of iodine within the Tasmanian community. Hence, the studies can provide an interesting methodological comparison over time to see if changing ethical perceptions have affected long-term study methodologies.

The New Ethics Research Environment (NERE) will be investigated to see if the evolution of this paradigm has been mirrored in the way that studies have changed.

Table 10 provides an overview of the undertaken studies and the methodologies used to recruit participants. These will be explored further later in the chapter.

Table 10: Comparisons of the School Children Iodine Studies with Regards to Recruitment and Participation.

	Gibson Studies[1] [117, 118, 196, 198]	Menzies Studies			Broadstreet Studies [120, 121, 203, 328]
		1996 Pilot Study [120, 200-202]	1998-99 Phase I Study [120, 200-202]	2000 – 2001 Phase II Study [120, 200-202]	
Participated / Eligible	variable	93/100	241/322	215/324	347/781
Follow-up to initial approach			2 week follow-up	2 week follow-up	Follow-up at school level with school initiation
Age Range	4-18 years	8 years old	4 – 14 years	1996: 12-13 years 1998: 5-14 years	Approx 9 years old
Method of determining Iodine Status	palpitation of thyroid	Aquilot of urine from timed overnight sample	Spot morning urine sample	Spot morning urine sample	Random urine sample
Selection Methodology	Whole school participation for schools chosen to participate	Selection of 100 participants from a separate study [331]	2 stage stratified sampling from schools with > 15 primary aged students	Participants of Pilot and Phase I studies, excluding those who are no longer resident in Tasmania	1 stage cluster sampling from all Grade 4 classes within Tasmania.
Length Of Study	1949 - 1984	1996	1998 - 1999	2000 - 2001	2003 - 2007

[1] Process of school selection unknown.

Pre 1940's, there is evidence of Goitre within the school system, as is shown by the Medical Officer reports of the time [120]. These reports highlighted many cases of goitre within the school community up until the early 1920's. Most of the examinations at this time were undertaken under the auspices of the Department of Education. The studies were considered as being part of public health surveillance [332]. In 1923, for a year, goitre was made a disease that required reporting to the health department to gather a clearer picture of overall prevalence of goitre throughout the state [120].

There are no reliable reports of goitre incidence rates between approximately 1932 and the early 1940's. The school medical service was disbanded in 1930, and this may have contributed to the lack of information during this time [120]. The re-establishment in the 1940's of the school medical service highlighted again the large amount of goitre within the school communities [120, 333, 334].

Thyroid Advisory Committee

In Tasmania, the Thyroid Advisory Committee was first convened in 1967. They have guided and instigated many of the studies mentioned here, along with carrying out their own studies as independent researchers into increasing incidences of thyrotoxicosis and other Iodine Deficiency Disorders (IDD) [335]. The formation of the committee was precipitated by the thyrotoxicosis epidemic in the late 1960's and the subsequently disjointed response to it [118, 198]. Over the years, the committee has being primarily composed of representatives of the Departments of Health and Agriculture, members of the clinical professions and endocrinologists from the major hospitals in Tasmania. The committee still has an advisory role in iodine nutrition within the State and its membership composition is similar to that of the original committee.

Supplementation

Prior to the 1940's, there was no documented or organised iodine supplementation procedures applied to the population. Supplementation was, however, proposed by Morris in the early 1920's [336] but never acted upon.

As can be seen from Figure 11, the supplementation landscape changed greatly during the time of the Gibson studies. Notification from endocrinologists in the North of Tasmania highlighted the over-supply of iodine during the cross over period between bread being used

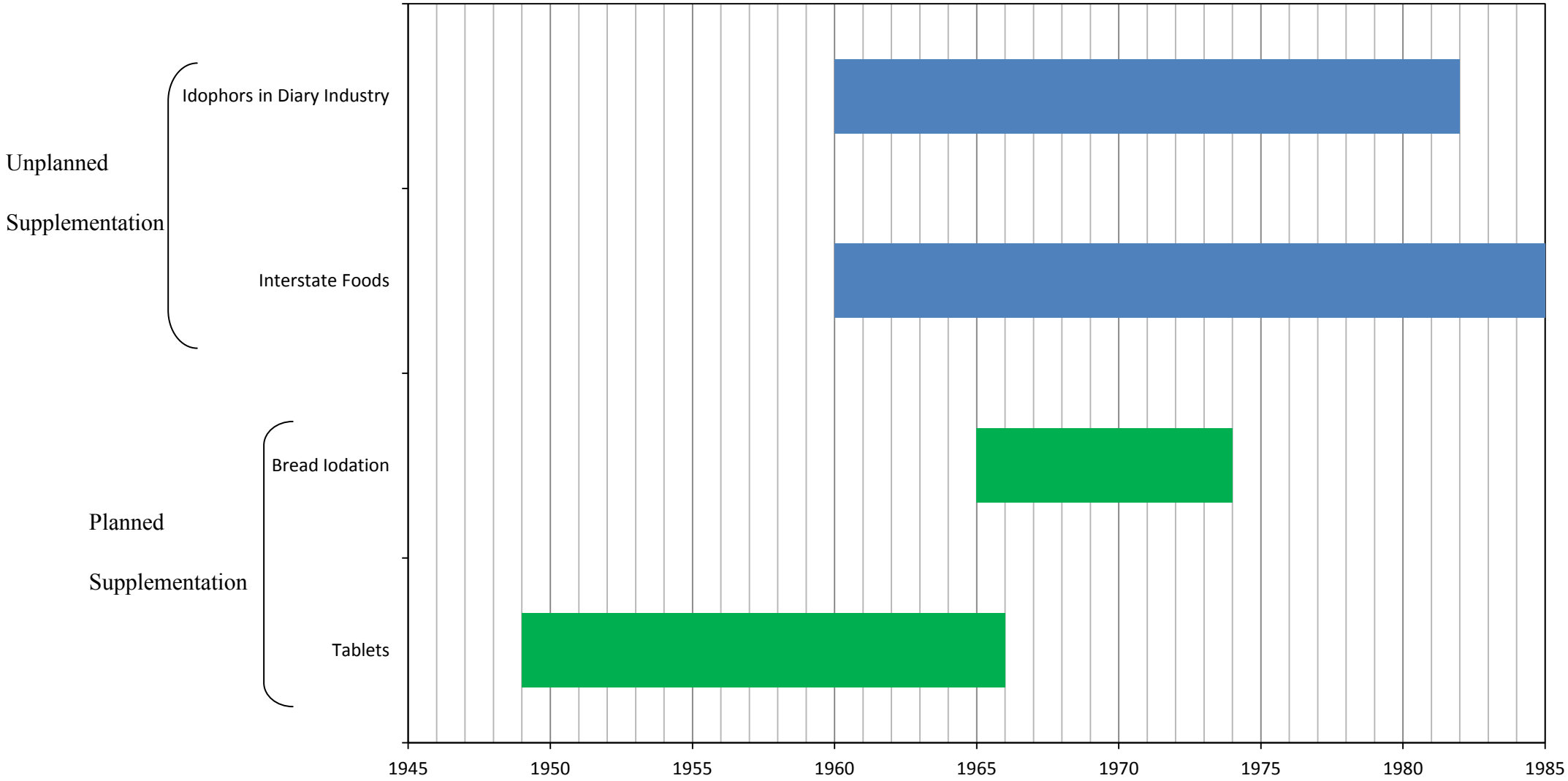
as a vehicle for iodine supplementation and the increasing use of idophors in the dairy industry.

Iodine supplementation of children in the late 1940's to the early 1960's was via school administered iodised salt tablets. Tablets were given out via the school nurse or medical officer system to all children within the school. The supply of tablets was managed federally, but distribution to the children was undertaken on a local basis. It was later found that distribution was inconsistent in some areas [120, 198]. There is evidence of permission being sought from parents and guardians for students to participate in the supplementation program [321]. There does not appear to be any evidence of permission being sought from parents/guardians for the participation of the students in the monitoring process.

Once the distribution problems of the iodine tablets were recognised, and it was determined that food from the mainland was supplementing the iodine sources within the state, tablets were withdrawn [198]. The increasing prevalence of food from the mainland came about with the advent of the roll-on/roll-off ferries around 1960, which provided a continuous and accessible link to the mainland. The total withdrawal of iodine tablets was not carried out in a systematic way. Information about the discontinuation of the program did not necessarily reach all relevant parties. This is evidenced by correspondence at the School of Distance about iodine tablets and how to obtain them after the program had been discontinued [337].

Once the tablet distribution was discontinued, it was decided by the State Department of Health and Human Services that the use of potassium iodate as a bread improver would allow for more comprehensive coverage to ensure that the population was receiving its required iodine intake [196]. Ongoing monitoring took place during this time with studies being undertaken utilizing the same methodologies as were implemented earlier to monitor the iodine status of the community. While goitre palpitation is not the most accurate method currently available, at the time it was the recommended method for determining goitre status.

Figure 11: Methods of Supplementation with Iodine during the Gibson Studies. Adapted from Gibson [198].



The 1970's saw supplementation with iodised salt tablets and bread improvers being discontinued. Idophors in the dairy industry became the only known iodine supplementation in the state. While maximum levels of idophors were legislated for, there was no minimum level, thus the population's intake would vary dependent on factors such as relative food type intake. An increasingly varied diet with food being imported from the mainland and thus from iodine replete areas were also considered to have influenced the overall iodine situation. Decreases in the usage of idophors in the diary industry in the early to mid eighties were reflected in an increase in goitrous individuals being reported within the community. This was confirmed by final survey of the Gibson studies in 1984, which showed an overall increase of palatable goitre within the school populations [118]. This was complimented by a re-appearance of visible goitre [118]. These changes, as mentioned earlier, were significant and although the schools surveys were being discontinued, the Thyroid Advisory Committee was aware that Tasmania was still considered to be iodine deficient.

During the 1980's and 1990's, there was no recognised or formal supplementation program in place within Tasmania. Iodine was still being supplied in the 1980's by idophors in the diary industry; however, changes in dairy practices remove this as a reliable source of iodine for the population by the 1990's.

In the early 1990's, it was found that iodine levels in Tasmania were once again insufficient [199, 200]. The Menzies Centre for Population Health Research (as it was then known) was commissioned by the Department of Health and Human Services to undertake a study to determine the extent of the reported low levels of iodine. The Menzies studies identified mild iodine deficiency within the target population [199]. This led to a voluntary memorandum of understanding being developed between the Department of Health and Human Services and the bakery industry. Voluntary fortification of bread with iodised salt was the supplementation method employed. This method is still being used currently. Initial uptake was very good with six of eight major bakeries and approximately 70% of smaller bakeries signing [121, 203].

Ethical Environment

Within the context of ethical events of the time the following world and national events took place:

- Federal Health Council (1927);
- National Health and Medical Research Council formed (1936);
- Medical Endowment Act (1937);
- World Medical Association Principles in Research and Experimentation (1964);
- Declaration of Helsinki (1964);
- National Statement on Human experimentation (1966);
- Supplementary Note No.1 to National Statement (1976);
- Medical Research Ethics Council established (1980's);
- International Council of Medical Scientists published their guidelines for ethical review of epidemiological Studies (1991);
- National Health and Medical Research Council Act (1992);
- World Medical Association reviews the Medical Ethics Code (1994);
- National Ethics Application Form launched (2006);
- Harmonisation of Multi-Centre Ethical Review (2010).

Many of these events have had an impact on the iodine surveys in Tasmania. Changing perceptions of privacy have also had an impact with regards to subject selection. Of the events outlined above, the national statement would have impacted on later iodine surveys, as would have the National Health and Medical Research Council (NHMRC) Act. Both of these events clarified and expanded the use of ethics committees and their position when it came to research. As will be seen later in this chapter, influences with regards to public health in Tasmania have changed how a certain series of surveys was carried out.

Cohort Selection and Recruitment

All these studies were instigated by the Department of Health and Human Services in response to concerns about goitre or iodine levels within the community either via medical notification or school health inputs. The cohorts for all of the following surveys were generally drawn from the school population of Tasmania at the time that the survey was undertaken. The exception to this is the pilot stage of the Menzies studies. Anecdotal

evidence was also been utilised by the Department to determine if another survey was needed.

Gibson Studies

The 1949 study was undertaken to determine the extent of goitre within the school community acting on concerns from school based medical officers [118, 198]. It was used to determine if Tasmania was an endemic goitre area, or if it was just harbouring small "pockets" of goitre [118]. The study was undertaken State-wide but known goitrous areas such as the Huon and Derwent Valleys were not tested in the initial survey [118]. Excluding known outliers allowed an accurate picture of the extent of goitre within the community to be established. The later Gibson studies [117, 118] originated from a need to see if the endemic goitre noted in the 1949 study was being combated by the supplementation measures implemented after the first study.

Between 1950-59, there was one survey of school children undertaken in 1954. It was a large scale survey encompassing approximately 20,000 children as the study was extended to include the known goitrous areas of the Huon and Derwent Valleys, which had been excluded from the initial survey in 1949. The incidence of goitre enlargement had increased slightly in males but decreased in females [117].

Between 1960 and 1969, four surveys were undertaken: two in 1960, one in 1965 and one in 1969. A twenty percent sample of the total school population was used to conduct the 1965 survey, while a ten percent sample (approximately 9,000 children) was used in the 1960 and 69 surveys.

Two surveys were undertaken in 1960 in an attempt to determine if there was seasonal variation as had been noted in the Hobart and Channel areas. Children were tested in spring and autumn as opposed to autumn only with the previous surveys. The cohorts for these surveys were, once again, ten percent samples of the total eligible school population.

In 1976, another survey was undertaken. It followed the format of the previous surveys and the number of students tested was similar to the 1969 survey (10% sample). This sample size was less than surveys carried out previous to that.

In 1983, there was anecdotal evidence from experienced school medical officers that cases of enlarged thyroid were increasing [118, 198]. This was confirmed in the final survey in 1984,

which showed an increase over all ages and sex groups in the percentage of palatable goitre. Visible goitre also started making a re-appearance.

All of the Gibson surveys were of the opt-out model. That is, if you were present on the day the study took place, you participated unless the school had been notified prior by a parent/guardian or caregiver. Whole of school testing was generally employed.

Menzies Studies

The Menzies studies were undertaken as a series of three surveys, with the final phase combining the participants of the pilot and Phase I surveys. While the methodologies were similar for the Phase I and II surveys, the recruitment methods differed for each part of the study as is seen in Table 10.

The Menzies Centre for Population Health was contracted to conduct an investigative survey on the current state of iodine levels in Tasmanian School Children from 1996-2000. The Pilot study took place in 1996, with Phases I and II taking place during 1998-99 and 2000-2001 respectively. These studies were carried out utilising a differing methodology in recruitment and analysis to the Gibson studies. The sample size was smaller and the recruitment methods differed.

For the Pilot study children were randomly selected from participants in the Menzies Centre Study of Blood Pressure and Bone Density [200]. To determine the urinary iodine levels of the selected study participants, an aliquot from a timed overnight urine sample was collected. As the study was considered a Public Health Project, it did not require clearance from an ethics committee. The Public Health Project moniker was also applied to the Phase I study, but ethical permission was obtained as it was considered to be best practise.

The Phase I survey selected students using a two stage stratified sampling procedure. Schools were selected using a proportional probability based on the number of students and fifteen children within those schools from grade K-6 were selected and their details were passed onto the Menzies Centre for contact and follow-up. Thirty schools were originally selected of which 28 agreed to participate. Randomly selected students from the school population were approached via letter to participate. Samples were spot morning urine samples, and were returned to the Menzies centre via post [200].

A combined sample of participants of the pilot study, along with those who were invited to participate in the Phase I study were used as the sample frame for the Phase II study of the Menzies studies. Participants were deemed ineligible if they no longer lived in Tasmania.

Broadstreet Studies

The last series of studies undertaken for the Tasmanian Iodine Program were instituted as part of a monitoring of the voluntary bakery supplementation initiative [203] . These studies were a one stage random cluster sample utilising both public and private schools in Tasmania [203]. The study was carried out over five years (2002-2007) with spot urinary iodine sampling occurring in four of the five years (2003-2005, and 2007). A listing of state schools containing grade four students and approximate numbers in each class was obtained from the Department of Education. Similar lists were obtained from the Catholic Education Office and Christian Schools Tasmania. Independent schools not included on these lists were contacted individually. Each eligible class was entered into a database and the list sorted alphabetically. Classes were assigned a number and then numbers were randomly drawn using a random number generator until the desired sample size was reached. Schools were approached with an invitation to participate. If the school agreed, consent forms were distributed to the class to be signed by the parent or caregiver and collected by the teacher in charge. If a school refused, another was randomly drawn from the remaining schools to replace it.

Schools had the option of two testing arrangements: Either the field officer collected samples supplied by the participants at the school, or testing kits were sent home the day before and collected by the field officer the next morning. Many schools opted for the latter form of collection to minimise disruption to the school day.

Response Rates and Results

Gibson Studies

Exact response rates are not available for the Gibson studies due to the inclusive nature of the original selection procedure. However, estimated response rates from total potential populations can be derived from data supplied in Gibson and Clements [117, 118]. These response rates presented in Table 11 are only available for the first six surveys, but provide an indication of the coverage of the studies. These can be used as a pseudo response rate, as it is documented that 100% examination was taken for smaller schools, and an arbitrary

grouping for larger areas, which are mentioned in historical documentation from Archives. This includes archive references of the Thyroid Advisory Committee which includes meeting notes and correspondence [338]. This correspondence give numbers which were tested in the larger centres for the period from 1968 onwards [339]. The correspondence from the 18/10/1973 and other dates noted the Iodine/Creatine ratios from school student testing with school, full name, date of birth, weight, height and results.

In 1949, it was found that there were higher incidences of goitre in girls over the age of twelve; however, overall it was established that with the exception of a small area centred on the town of Burnie in the North West, the whole state of Tasmania was in fact a goitrous area.

Results of the 1960 surveys showed that goitre rates were still high in both sexes (average of 43.82% in females and 28.41% in males). These results improved in both 1965 and 1969 with noticeable decreases in palatable goitre (down from 25.85% in October 1960 to 16.52% in 1965 and 13.79% in 1969).

The results from the 1976 survey showed that visible goitre had essentially disappeared in the sample group, being recorded at less than 1% of the total population examined. Palpable goitre also decreased from previous surveys decreasing from 13.79% in 1969 to 3.64% in 1976.

Less than a decade later in 1983, there was anecdotal evidence from experienced school medical officers that cases of enlarged thyroid were increasing [118, 198]. This was confirmed in the final survey in 1984, which showed an increase over all ages and sex groups in the percentage of palatable goitre. Visible goitre also started making a re-appearance. The increase in total goitre was statistically significant ($z=13.067$ at 95% confidence) and suggested that iodine may once again not be replete within the population [118, 198].

Table 11: Potential Population and Participation Rates Based on Gibson [118], Gibson [198] and Clements [117]

	1949	1954	March 1960	October 1960	July 1965	1969	1976	1984
Potential Female	28000	29930	43100	43100	33600			
Potential Male	29040	32370	44910	44910	54800			
Total Potential	57040	62300	88010	88010	88400	81320 [1]		
Participating Females (%)[2]	4747 (16.95%)	10377 (34.67%)	8830 (20.49%)	8830 (20.49%)	11711 (34.85%)	4085	4569	4590
Participating Males (%)	4189 (14.42%)	9898 (30.58%)	10085 (22.46%)	9994 (22.25%)	12446 (22.71%)	4047	4596	4621
Total (%)	8936 (15.67%)	20275 (32.54%)	18915 (21.5%)	18824 (21.39%)	24157 (27.33%)	8132 (10%)	9165	9211

[1] Estimate based on Literature

[2] All percentages are derived from total divided by participation rates or total divided by potential in the case of participation

Menzies Studies

The urinary iodine level varied between a median of 42 micrograms per litre for the pilot study to 77 micrograms per litre for the Phase II studies [200]. Participation rates and median UI levels can be seen in Table 12.

Table 12: Participation Rates and Results for Menzies Studies. Data from Hynes [200]

	No. approached	No. Participated	Median UI (µg/l)
Pilot (1996)	100	93 (93%)	42
Schools (1998-99) [1]	30	28 (93.3%)	
Students (1998-99)	322	241 (74.8%)	75
Phase II (combination Phase I and Pilot)	324	215 (66.3%)	77

[1] Schools are included to allow comparison to the schools recruitment in the Broadstreet Studies.

These surveys showed that UI levels were below the level that the WHO would consider for a population to be considered replete. As shown earlier, the WHO considers a population to be replete in iodine at over 100 micrograms per litre of iodine in the urine. The results from this phase of the Menzies studies showed a median urinary iodine level of 42 micrograms per litre, which according to the WHO is in the moderate deficiency range [325].

Broadstreet Studies

Testing was conducted either at home with school pick up or during school hours using a field officer to organise and collect the samples. Table 13 shows the loss to sample from class level downwards. In the later years, only classes that had previously participated were invited, hence the higher response rates at the class level.

Table 13: Participation rates – Modified from Seal et al [121] and Unpublished Data

	2003	2004	2005	2007
Number of classes invited to participate	52	60	47	44
Classes agreeing to participate	31 (60%)	43 (72%)	42 (89%)	43 (97.7%)
Total number of children in classes	781	968	1075	1036
Consent forms returned	535 (69%)	663 (68%)	619 (58%)	596 (57.5%)
Positive consent*	391 (50%)	466 (48%)	415 (39%)	384 (37%)
Samples collected*	347 (44%)	430 (44%)	401 (37%)	331 (31.9%)

*Percentages are of total number of children in participating classes.

Throughout this final series of studies, the median iodine level remained at the low end of replete according to WHO standards. This is presented in Table 14, which demonstrates the median iodine level along with the sample size tested for each of the years testing was undertaken.

Table 14: Median Iodine Levels during Broadstreet Studies – Modified from Seal et al [203] and Unpublished Data.

Year	Median UI (µg/l)	Sample Size
2003	105	347
2004	109	430
2005	105	401
2007	115	331

Analysis and Discussion

Research Ethics Approvals

Similar to the two previous case studies, the process of ethical clearances has changed over time period of the iodine surveys. Research ethics approvals were not undertaken for the original Gibson studies. The pilot phase of the Menzies studies did not undergo traditional research ethics approval. The study the samples were obtained from did undergo research ethics approval, but the use of the urine samples for the Iodine survey would not have been explicitly included in that approval. The Public Health Act of 1962 included a provision for epidemiological studies to be carried out at the direction of the Director of Public Health. It is assumed it was this provision that was utilised in the pilot phase of the Menzies studies. The provision suggests that the Director of Public Health can, at their discretion, instigate epidemiological studies or research that may benefit the population without undergoing normal ethical approvals.

The first and second phases of the Menzies studies went through normal ethical approval processes as did the Broadstreet studies. These processes as outlined earlier changed over time with regards to the requirements to gain ethical approval, particularly with regards to the methods of recruitment and follow-up.

Recruitment

The initial iodine studies undertaken by Gibson *et al* [118] can be considered the base point for investigation of the NERE. As the NERE evolved, the recruitment strategies changed to incorporate that new environment. This is notably demonstrated by the change between the pilot and the Phase I studies in the Menzies studies. The pilot study utilised an already

recruited cohort, while the Phase I study recruited a totally new cohort. The Phase II study combined the two cohorts. While the Gibson studies did not recruit participants individually, there is evidence that selected children were chosen to provide urine samples outside the goitre studies in the 1970's [339, 340]. These students appear to be randomly selected from a group of schools and the students within those schools. Other smaller studies were carried out during the Gibson studies. These studies also show how the NERE has evolved since the hypothetical line in the sand was drawn.

Recruitment procedures, which were utilised during Phases I and II of the Menzies studies, were similar to those applied to the Broadstreet studies in later years. Differences can be seen which are related to the ethics of contacting participants at an individual level. The major exemplar of this was the Menzies studies were able to follow-up individual potential participants, while the Broadstreet studies did not have this ability.

This ability to target a small selected group enabled a more targeted sampling frame, in which individuals could be followed-up in the case of no response. While the Menzies studies allowed for follow-up of non responsive participants at an individual level, the Broadstreet studies only allowed for secondary follow-up through the schools and classroom teachers. While this could be taken as resulting from the influence of changing privacy legislation, the effect of the changing privacy legislation on the evolution of the new ethic research environment cannot be discounted.

Consent

There is no evidence in the literature of the Tasmanian Iodine studies carried out by Gibson *et al* [198] of any permission for participation being sought from parents, guardians or care-givers. When the lack of permissions in the Gibson studies were first encountered, ad hoc inquires were made. People who had been involved in either the studies themselves or had extensive knowledge of the studies suggested that the culture of permission was originally very much an explicit opt-out scenario – as contrasted to the more prevalent ideology today of explicitly stating the intention to opt in. This process of opting out would have allowed for a more varied population to be sampled, due to the lack of participant "self selection". There is, however, evidence for seeking of consent for the distribution of the iodine tablets. This juxtaposition between the seeking of permission to supply a tablet to an individual, yet not seeking individual permission to examine a student for goitre, shows how the NERE has developed unevenly with regards to varying research modalities.

The Phase I and II Menzies studies were explicitly opt in with regards to consent. The Pilot study, as discussed earlier, had implied consent as explicit consent for participation in the original study had been given.

The Broadstreet studies once again utilised an explicit opt-in approach to participation. This model is now the prevalent paradigm in the NERE.

Response Rates

The Gibson studies at first glance appear to have very low response rates. However, as their total potential population was much larger to begin with, the numbers of students sampled is actually more substantive and thus potentially gives a better indication into the status of goitre within the Tasmanian community.

The response rates in the Menzies studies were high compared to the Broadstreet studies carried out later. There are many reasons for this, though the primary explanation would be the ability of the Menzies studies to follow-up on non-responders at an individual level.

The Broadstreet studies had the lowest response rates, even though they had the second highest number of individuals approached. This can be seen as a direct result of the NERE. The environment particularly with regards to privacy and follow-up to non-responders has changed significantly since the Menzies studies. Within the Broadstreet studies, continual follow-up and information allowed the study to increase its response rates in the first two years. The reasons for the lower response rate in 2005 are unknown. However, the lower response rates at positive consent and sampling level in 2007 could possibly be attributed to lack of knowledge of the program within the school community as there was a year break in the sampling protocol between 2005 and 2007.

Conclusions

The Tasmanian Iodine surveys show the greatest evolution with regards to the NERE. This is due to the fact that the iodine surveys are a series of studies examining a single outcome, while both the GP smoking studies and the Framingham study are singular studies following a series of outcomes over time. While it may seem that these three case studies are not comparable, the Iodine studies clearly show how research plays catch up with the NERE. Comparison to previous studies, and building on the results they may have obtained is part of research. The NERE, by influencing the changing methodologies as seen in Table 10, does not allow this exact like to like comparison to happen.

The impact of the NERE on public health orientated studies will be explored in the final chapter.

Chapter Nine – Discussion, Conclusions

Introduction

This thesis set out to investigate the effect of changing ethical constructs on long running longitudinal health studies. The questions under investigation were:

> Have legal issues such as privacy impacted epidemiological research with regards to recruitment and follow-up?
> Has research governance affected research ethics?
> Do changing ethical environments in longitudinal cohort studies have long-term ethical considerations with regard to various factors within the study?

All three of these issues potentially impact on various processes within a longitudinal study. These constructs include research ethics approval, recruitment, follow-up, consent and response rates. Each of these has been examined in relation to individual case studies, and the intention in this chapter is to synthesise these findings, and to explore the conclusions reached with regards to each of these studies for the purpose of applying them to a more generalised model on the effect of ethics frameworks on critical elements of longitudinal study design.

Examination of the case studies determined, in general, that while the New Ethics Research Environment (NERE) moved forward as ethical thinking in research evolved, the ethical guidelines for these studies remained rooted in the time period when the first study was undertaken. This was the case unless a major change in the way the studies were carried out forced a catch-up of ethical thinking.

It could be said that it is not the ethical construct that has changed, but rather the measures used to evaluate and consider the ethical elements of research have evolved over time. However, the author believes that the two concepts are inter-related. The ethical construct is built from various ethical elements such as the virtues, best practice, and public perception and is influenced by factors such as legislation and regulation. It is the interaction of these various elements and the varying influences that they have had over time that has changed how the ethical construct as a whole is perceived and interacted with.

Prior to this thesis, there have been no investigations into how ethical frameworks impacted on ongoing, long-term, longitudinal studies. While there was awareness about ethics in epidemiology, and there are guidelines in place to assist researchers, the body of knowledge as to the effect changing ethics has on long term studies has not been explored [48, 51, 341, 342]. While being influenced by ethical events, the NERE still has its basis in the classical context of beneficence, non-maleficence, justice and autonomy.

The countries where these case studies are based all have differing views and interpretation of where epidemiology fits within the research construct. These differing views shape how the NERE influences the studies.

Epidemiological perspectives

One key issue is how best to define the differences between public health surveillance and epidemiological research. All three of the studies presented here can be considered to be epidemiological research.

Public health surveillance can be defined as the ability to monitor the health status of a community, taking into account known risk factors as well as emerging threats to community health. It should be able to facilitate a prompt effective and corrective response. Agencies are generally required by law to conduct health surveillance.

Epidemiological research occurs when medically relevant information about individuals and groups is accumulated, so those features of interest to researchers may be investigated. This is irrespective as to whether or not the information was or was not originally obtained for research purposes.

Australia

There is evidence that epidemiology has been considered in the national ethical code. This is seen in the 1992 version of the National Statement which includes epidemiology in a separate heading [343] . The 2007 version of the national statement does not include this separate section on epidemiology [226]. Australia does not appear to have any process of epidemiology documents such as those found in the United Kingdom [344] or ethical epidemiological guidelines such as those published by the American Epidemiological Association [51] . However, the Australian Epidemiological Association did express concern at the proposed changes to the 1992 National Statement when the changes were put

up for public submissions [345]. These concerns included the retrospective application of ethical constructs to data banks as well as concerns surrounding definitions of consent and participants [345].

The current statement considers epidemiology as a type of data bank [226]. Data banks in the author's opinion are not an appropriate descriptor of epidemiology, as they imply that the data have already been somehow obtained and are being stored for future use. Epidemiology is a dynamic and changing discipline, which uses many different kinds of data.

Data banks according to the current national statement should only be instigated if consent has been sought from those people participating for their data to be stored and used at a later time [346]. The current statement also suggests that if consent is sought for the data to be banked that access permissions be established for future usage [346]. While this is currently articulated in the national statement, previous versions did not explicitly outline what types of consent could be required. While epidemiology utilises databanks, considering epidemiology as being solely concerned with data which has bankable properties does not allow for the full potential of the discipline to be explored. The lack of a distinct epidemiological section within the current statement suggests that epidemiology and its' varied methods are covered elsewhere within the statement. While the potential data collected from epidemiological studies are considered, the methodologies and obtaining of consent can present differing situations to those considered in the national statement.

From this, it can be seen that there is a distinct lack of specific guidance relating to epidemiology at a national level in Australia. While this may not necessarily inhibit the use of epidemiological studies, having to legislate for an individual study, as can be seen with the Australian Epidemiological Act and its associated notes [347, 348] is surely not the most logical nor efficient way to carry out a study. Intuitively, an act called the Australian Epidemiology Act should be a broad ranging document appertaining to the entire discipline, but in practice, the act is specifically geared towards just one study and the potential ethical risks from that one study.

United Kingdom

There are frameworks for epidemiology research in the United Kingdom which come under British Medical Association jurisdiction [344]. Process type documents are common in the United Kingdom, but many of the problems appear to be more with data protection and

privacy laws then the processes involved in the actual act of carrying out the survey [13, 349-354].

These data protection laws set out how data may be obtained, how it should be stored, and who can access it. It also outlines what sort of data may be collected under different types of studies [278, 349, 353, 355, 356].

United States of America

Through its Epidemiological Association, the United States has a code of ethics, but it is not aligned towards large-scale public health. While there is discussion about ethics and public health, only some of these authors examine ethics, public health and epidemiology [51, 127, 351, 357-366].

Allmark [357], Watterson [364] and Weed [365] all take into account the fact that in epidemiology there is an overlap between the working "on" a community and "with" a community, and it is that overlap which can cause an ethical problem. The term "lay epidemiology" has variously been defined by these authors as:

> "*processes by which lay people understand and interpret health risks*"[357]

or

> "*The direct involvement of specific communities in epidemiological research which may affect them should improve communications and understanding between epidemiologists and the public*."[364]

These definitions show that even within the field of epidemiology the understanding of how epidemiologists interact with the general populous and the communities under study varies. Allmark [357] explores the interaction between public health professionals (primarily epidemiologists) and the greater community with regards to communication and understanding when trials are undertaken. They note that taking into account the values of a community when the results are disseminated and interpreted to the community is important.

On the other hand, Watterson [364] looked at how community involvement with a study can enhance the outcomes – as opposed to just using the community as a study population and sharing the results at a later date.

Weed [366] takes yet another approach, examining how the crossover of epidemiology and the humanities can help epidemiologists be aware of some of the ethical and humanitarian dilemmas which they as researchers may face. Weed uses the example of the medical humanities to illustrate the fact that showing how the placement of a group within the context of another group can change the way that the groups perceive each other.

These contexts can be seen to be subtly influence research, from the research ethics approvals given by committees down to the researchers and their approaches to recruitment, consent and follow-up. Carrel and Rennie [367] highlighted that, while the Belmont Report differentiates between medical research and practice, it does not take into account on-going surveillance, which is a critical methodological dimension of all three of the studies examined in this thesis.

Research Ethics Approval

Research ethics committees need to uphold the principles of beneficence, non-maleficence, justice and autonomy when assessing a study for approval. These principles, while classical in origin, still underpin the NERE as it has developed. The NERE and its evolution can also be linked back to Thomasama's tree concept, as described in Chapter Two. The public policy and clinical ethical branches are those that would have influenced research ethics committees by the use of regulation and legislation as well as what is considered best practice in a clinical setting. These influences on the NERE – and thus the research ethics committees – would have a cascading effect through other areas of research such as recruitment. While recruitment is not an ethical construct, the effect of ethical constructs on design and methodology can be seen in the types of recruitment, which can be utilised for different types of studies [368-370]. This cascading effect can change the interpretation of results and the outcomes of studies [371-374].

As all three studies were based in different countries, events that influenced the studies were varied. International codes, while generally providing guidance and suggested actions, are not legislated for in any of the countries under consideration. Even though these codes and events could, and have, influenced ethical thinking, there is no solid evidence that links ethical events to precise changes in methodology and thinking in the case studies described. This aspect of the NERE highlighted that while research ethics approvals can be obtained, those approvals will not evolve with ethical thinking unless a new ethical approval is

required. This is presumably driven by external agencies rather than by decisions by the investigating team.

Related to this, research governance in the form of institutional committees has affected research ethics. This is particularly evident in the Tasmanian Iodine surveys where methodologies for recruitment have changed the ability of researchers to interact with the potential participants. The evolution of the NERE and its ability to remain static can be seen in the comparison of the ethical approvals in the Doll and Hill smoking studies compared with the Framingham studies.

As described earlier, Doll and Hill did not have to undergo any ethical clearances while Framingham study did not require consent forms until the 2nd generation cohort [173, 181]. This difference in research ethics approval shows that the ethical environment in a study remains static until a large-scale event such as recruitment of a new cohort, or large methodological change causes it to catch up to the NERE that is current at the time.

Using this catch up analogy we can see that the Doll and Hill study had no ethical shifts. Framingham has had four ethical shifts – one at each new recruitment event, and the Iodine studies showed the changing methodologies at each new study. These changing methodologies can be attributed to a combination of evolving best practice for determining iodine status and the NERE.

Recruitment

The three examined case studies utilised different methodologies in recruitment and implementation. It could be suggested that the differing methodologies may, therefore, be aligned with differing sets of ethical considerations. However, this was not the case. In all three cases, the major ethical construct that inhibited the studies was recruitment. While all of the case studies showed varying methods of recruitment, if the studies had been instituted today, recruitment approaches would have differed. The ability to recruit a pre-determined sample size is dependent on recruitment methodologies. In this regard, while sample sizes for longitudinal studies are determined by various statistical tests based on factors such as prevalence of the condition, potential relationships among factors in the study and the degree of power (the ability of a study to show an association), the methods for recruiting the determined sample size are varied and change within the ethical constructs.

The Doll and Hill studies utilised the simplest of the recruitment methodologies under examination. This methodology was effective for the type of study undertaken. It would have worked for neither the Framingham nor the Iodine studies due to the limited sampling frame.

The Framingham studies showed a changing ethical construct that affected the methodology of the study. However, in this case, the research design was only affected with regards to consent, and recruitment of later cohorts. The evolution of consent within the study, which is well documented on their web pages [177, 179] mirrors ethical events in the United States of America, such as the Belmont Report being made public. In this regard, the Belmont report released in the 1970's influenced the introduction of consent forms for the first time in the Framingham study.

Conversely, the initial recruitment methods utilised for the Framingham study would, potentially, raise privacy concerns within a contemporary ethics committee. The Framingham studies used a readily accessible sampling frame for their initial recruitment. Follow-up of participants after the first survey was undertaken using various combinations of friends, family and supplied information [135]. While the sampling frame used in the Framingham study could have still being used if the study was instituted today, the frame in question may not exist in an easily assessable and useable form due to privacy legislation. This influence of the NERE on research governance and ethics committees is implied in accessibility of sampling frames.

Recruitment of the second and third generation cohorts within the Framingham study would also have been affected if the study had been initiated more recently. The provision to recruit for 2nd and 3rd generations would have to be incorporated into the initial study plan, as well as details on how the generations would be initially contacted and recruited.

In contrast, the Tasmanian iodine surveys demonstrated substantial changes in recruitment and consent based on the changing ethics research environment. In this regard, issues such as privacy have impacted upon recruitment and follow-up in the Tasmanian iodine investigations. This is not obvious within the Gibson studies, but in the comparison of the Menzies and Broadstreet studies, the effects of the ethics frameworks on the ability to follow-up potential participants were reflected in participation and sampling rates. Other factors, such as time of year and previous knowledge of the program, may have also influenced the recruitment and response rates in the Broadstreet studies.

As has been discussed in a previous chapter, the Gibson studies were the least ethically constrained with regards to recruitment and consent and, thus, had the largest sample sizes and potential response rates. The Broadstreet studies were the most ethically constrained with regards to recruitment and consent and had the lowest participation rates. The Menzies studies showed how changing perceptions and events can change the ethical construct of a series of surveys. This is seen by the fact recruitment changed within the surveys, from sampling using samples from other studies to follow-up of participants by researchers using data supplied by a third party.

Ethically, the Broadstreet studies had to undergo both research ethics and office of equity standards clearances to be allowed into the State school environment. Within the private school environment, the authors experience was that Parents and Friends committees were occasionally used to discuss the study before permission was given. Even after the schools were approached, there were layers of permission. First the principal, then the teachers of the relevant classes, than the parents and finally the students themselves were approached. There was no way that a sample could be forced, so even if a parent had given permission for a child to participate, if that child did not want to, or could not supply a sample during the specified time, a sample could not be collected. This partially explains the differences between the number of positive consent forms and the number of samples eventually collected.

While all of these layers may be considered to be important in protecting the eventual participant (who is an underage minor), the potential loss of samples at each level is a factor that may affect the degree to which the results can be generalised to the greater community.

However, both the Framingham as well as the Doll and Hill studies showed how an ethical environment exists in the time period of the initial study, and if there are no changes to the study over time, the ethical environment doesn't move forward. This static ethical environment is what shapes the methodologies that are utilised in recruitment strategies.

Recruitment can be problematic for researchers. There is a fine line to be walked between persuasion, and what can be seen as coercion. Epstein [371] highlighted this in regards to developing an ethnically and racially diverse group for clinical studies. His concerns are centred around the rise of what he terms "recruitmentology", or the "*scientific evaluation of the efficacy of various social, cultural, psychological, technological, and economic means of convincing people (especially members of 'hard-to-recruit populations') that they want to*

become, and remain, human subjects" [371]. While Epstein was referring to clinical trials, the concerns he raised about ethics committees requiring diverse populations can also be applied to epidemiology. This concept may have come into consideration with the Omni cohorts of the Framingham studies. These cohorts were recruited to be ethnically and racially distinct from the original cohorts, allowing for comparisons to be made.

The changes in recruitment strategies, as influenced by the NERE, are reflected in concerns such as Epstein's and other authors such as Feinlab [368] and Hewison and Haines [369]. Feinlab highlighted the fact that researchers need to be aware of their responsibilities to participants, from study design, through recruitment strategies to participation, follow-up and dissemination of information [368]. Those responsibilities have changed as the NERE has evolved. Initially, it could be hypothesised that the researcher would have been more intent on obtaining useful and relevant data for their study, while participant care and information was a secondary consideration. As the NERE evolved, participant care and information started to become more important, as the research ethics committee became more paternalistic [296]. This paternalism is seen in ethics committees requiring community consultation prior to studies being implemented.

Rogers [363] found that paternalism in public health studies was perceived when although community consultation was carried out, the community in question did not actually posses the power or control to define their needs. He also found that paternalism was perceived in the choice of interventions being limited by professionally imposed parameters, such as a requirement for an evidence base.

Edwards[296] highlights this by arguing that research ethics committees (RECs) should not reject research that poses a risk to people competent to decide for themselves. They acknowledge that REC's do have a role in protecting vulnerable participants who may not act in their own best interest but believe that if potential research participants are informed of the risks and benefits of participating in a study, the REC should not presume to make an assumption as to the risk benefit for participants as a whole if they are deemed to be competent [296].

Hewison and Haines [369] also highlight the paternalistic nature of research ethics committees when it comes to recruitment. They suggest that the preference for ethics committees was for "opt in" studies, which reduced the potential sample size before the study

even started. Their studies however were once again based on medical research and not on long term longitudinal public health studies [369].

The impact of "opt-in" versus "opt-out" methodologies can be tied to the potential introduction of healthy responder bias. This bias is discussed under consent. Researchers have shown that there are also potential differences between participants if recruited via opt in versus opt out methodologies [372].

Consent

The choice to participate is one of the biggest potential biases in a study [373]. The healthy responder may induce a selection bias, which may affect the conclusions of the study [375, 376]. While healthy responder bias may not have been a major methodological limitation in the Smoking studies, it potentially affected both the later Framingham cohorts through prior knowledge of the studies by participants. It could also have affected the Broadstreet studies in the Tasmanian Iodine Surveys. While compelling people to participant may have occurred prior to, and during, the beginning of the NERE, it cannot be undertaken easily today. This is particularly true with regards to research involving minors. In this regard, contemporary ethics frameworks emphasises the rights of the participants within a survey need to be taken into account when designing recruitment strategies. This is supported by Coughlin and Beauchamp [377] who assert that when conflicts in methodology and ethics occur in epidemiological studies, the conflict should be examined with respect to beneficence, non-maleficence, justice and autonomy. They also argue that, as well as these, the scientific validity of a study as well as the health and welfare of the subjects participating in the epidemiological study should be considered at all levels of design and implementation [377]. This paradigm is evident in the layers of permissions required in the Broadstreet studies, as well as the community involvement in the Framingham study initial set up.

Encouraging follow-up to non-response in long term studies is an area which is lacking in literature. While there is a large body of literature for increasing response and follow-up in mail out surveys, general literature in increasing response rates for studies which require interaction between the researcher and respondent is limited. While previously searching of medical records of non-responders could be undertaken, increased privacy concerns are making this much more difficult [18, 355, 378-381]. While researchers such as Boardman *et al* [375] have investigated methods to quantify the differences between responders and non-

responders without the use of medical records, there is no magic formula that allows this to happen.

Part of the strength of the Framingham studies was the use of the community to encourage others to participate. This subtle peer pressure cannot be quantified, and thus the true extent of it cannot be investigated retrospectively.

The exhortation to examine studies using the virtues of benefice, non-maleficence, justice and autonomy is one that links back to the ethical tree. Those virtues are evident throughout the trunk and branches, yet are never explicitly expressed. The responders could be considered to be reacting to the virtues of benefice and justice, while exercising their autonomy to participate. Community and peer pressure/knowledge may also play a part in recruitment and follow-up. While there is a large and diverse literature covering this topic using data from HIV/AIDS advocacy and research, more generalised literature with regards to community and peer involvement is sparse.

The over-emphasis of non-maleficence, and autonomy by research ethics committees in their thinking is highlighted by O'Neill [382]. He noted that while informed consent supports individual autonomy, the point of consent procedures is actually to limit deception and coercion [382].

However, Carrel and Rennie [367] note that:

> "*Stringent requirements for voluntary informed consent have been developed to protect the autonomy of human subjects in research activities*."

They also note that:

> "*... the complications in the consent process specific to surveillance activities – related to conception of autonomy, the position of individuals within households and communities, and the multi-generational nature of longitudinal surveillance – have received only slight attention in the surveillance ethics literature*."

This concept of community affecting individual autonomy is something which Jedge [70] examines in the context of African communities. The concept of community is examined later in this chapter.

Consent is the area where the NERE has had the biggest impact. While there was evidence of consent prior to the line in the sand being drawn at Nuremburg [383], the implicit understanding since then has been that informed consent would be given before participating in a study. However, the NERE does not take into account studies in which a participant begins as a minor, but reaches an age where they can make autonomous decisions during the study. Helgesson [384] examines this in the context of when should a child be allowed to choose to participate. This dilemma is one that the Broadstreet studies also faced, and which the NERE is not evolved enough to consider.

Response Rates and Follow-up

The varying response rates within the case studies show that the NERE has had some effect. However, the factor that influences these comparative rates is how the researchers have defined response rates. This question of definition was highlighted by Kviz [385] over thirty years ago. He noted that this lack of clear definition had frustrated methodological investigations due to a lack of comparative data.

The responses rates in the case studies are generally well defined. In Gibson studies the response rates are estimates based on population totals derived from other data. Due to the differing methodologies in the iodine studies, response rates between the studies cannot be directly compared.

As discussed in recruitment the concerns about data privacy have influenced how response rates and follow-up are managed. Authors such as Davern *et al* [386] have shown that a desired response rate in some cases is better obtained through a larger sample size than through aggressive follow-up tactics to non-responders.

While follow-up in cohort studies is important, the onus is on the researcher to maintain accurate contact details and follow-up. While many layers of permissions are normal for contact with under-age minors, the ability to choose a truly random selection of the population for large-scale studies has been reduced as privacy laws have increased.

Under-age minors present a problematic group for recruitment for a number of reasons. These include understanding of what will be required, parental involvement as well as the inclusion of significant measures to ensure child safety. The current national statement in Australia contains guidelines for dealing with consent from minors, and highlights that the

maturity level of the minor influences their ability to actively participate in the decision making process [346]. This maturity level is something that should be considered when utilising minors as a response group in research. The ability of a participant to understand what is happening, and why, can lead to a much easier experience for both the participant and the researcher.

This is seen particularly in the iodine studies where even if parental permission for participation had been granted, if the minor did not want to, or refused to participate they could not be forced. While the age group targeted for the iodine studies generally did not fall under those considered in cases such as Gillick's competence [387] or Marion's case [388] the effect of these rulings cannot be discounted. While these cases relate to clinical interactions, the need for informed consent from the child has to be considered.

The impact of privacy law on the NERE cannot be discounted. Nor can the principles of benefice, non-maleficence, justice and autonomy be ignored with how follow-up is carried out. The greatest of these is autonomy: the potential participant has to have the autonomy to choose if they should participate.

Odinera and Schmidt [389] show that "*The effects of failure to retain hard-to-reach respondents are not predicable based on respondent characteristics."* They recommend that *"Retention of these respondents should be a priority in public health research*" [389]. These types of recommendations show that both response rates and the conclusions reached are dependent on the generalisability of the population that responded.

The Doll and Hill smoking studies were the least likely to be affected by any legal issues with regards to follow-up, particularly privacy, due to the composition of the initial study group. As the group were all doctors, the ability to follow-up on non-responders due to inaccurate databases was made easier. This is due to the fact that most doctors' surgeries will be listed in the telephone book and non-practising doctors would be listed as such with a governing body.

This study followed the GPs until death. The utilisation of death notices, obituaries and automatic notification by the Office of Population Census and Surveys allowed for comprehensive loss to follow-up by death to be obtained [174]. The Office of Population Census and Surveys notified the researchers when one of the participants' was registered as

having passed away. This close working with that office is something that the NERE would make more difficult due to privacy concerns.

The Framingham studies utilised various follow-up methods, which included use of town surveys, family and friends follow-up as well as contacts through medical practitioners. It is not mentioned if the Framingham researchers had similar confidentiality problems to those that Fenester [390] encountered on doing a 20 year follow-up to a foster care survey. On attempting to locate 40 participants of a survey in child welfare 20 years after the initial survey, Fenester found that if contact had not been maintained, finding and contacting the original participants involved considerable time and expense. They raised the ethical issue of informed consent extending to collateral contacts used to trace the initial respondents to the survey as well as the assumption of confidentiality of participation of the original participants [390]. Framingham differs from the Fenester study in that contact has been maintained with participants over the years, and the nature of the cohort as part of a greater community is emphasised.

The nature of the Gibson studies meant that follow-up of the participants was not necessary either to see if they would participate, or to follow-up on them once they had participated. This was due primarily to the "opt out" approach, which was taken with regards to the initial consent.

The Menzies studies allowed for follow-up of non-responders on an individual level, something which the Broadstreet studies did not allow primarily due to ethical constraints which were developed due to privacy concerns. The smaller response rates within the Broadstreet studies can partially be attributed to this, and could have impacted on the health outcome data derived from those studies. As the primary outcome of these studies was median UI, the smaller response rates may distort the true median level. As discussed later, the concept of healthy responder bias can also influence the median level.

The public policy branch of the ethical tree has as one of its sub branches legislation and regulation. Recruitment and follow-up in the NERE is regulated by Human Research Ethics Committees who enable the implementation of legislation in the United States. In Australian and the United Kingdom while the HREC's provide ethical oversight for studies as outlined in various acts, the do not possess the legislative backing that occurs in the United States of America. It is the regulation of privacy, ethical conduct and methodology within the NERE which has most been effected by this implementation.

Follow-up on non-responders to increase participation rates and sample sizes is an area which can be affected by the NERE. The number recruited for a particular study is determined by the sample size calculation as discussed earlier. However, some authors do not necessarily agree with how a sample size is determined and how it can be related to an ethical study.

Bacchetti [391] argues that study size may not be as ethically important as current thinking suggests; he asserts that the scientific community generally assume that a

> "*[The] projected scientific or clinical value of a study will be unacceptably low if it has low power, that is, it has less than an 80 percent chance of producing $p < 0.05$ under an assumed minimum important effect size."*

He goes on to show that the scientific and clinical value of a study may still be ethical even with a lower power. He does this by examining projected burdens on participants compared to scientific outcomes. The results suggest that while the average projected burden per participant remains constant as the sample size increases, the projected value of the study does not increase as rapidly as the required sample size [391]. Thus a large sample size may not be required to obtain results that ethically do not place too great a burden on the participant.

While he was talking about clinical trials, his argument could be applied equally to epidemiological studies – particularly the conclusion:

> "*In general, ethics committees and others concerned with the protection of research subjects need not consider whether a study is too small... Indeed, a more legitimate ethical issue regarding sample size is whether it is too large*."

Prentice [392] counter acts this with the argument that:

> "*Value to a participant from his or her altruistic contribution to a definitive study of an important clinical or public health question is relatively independent of the number of trial participants*."

Prentice also notes in the commentary on Bacchetti's paper that researchers do not necessarily dismiss the small under powered studies as unethical, as they can contribute to the literature in intervention effect estimation and meta-analyses [392].

It may be that Bacchetti is arguing for a sense of community within a study population and that Prentice prefers a more individualised, altruistic view. Bacchetti, in refuting Prentices views, suggested that participants' altruistic satisfaction is not a relevant consideration at the planning and development stages with regards to sample size [393]. Halpern *et al* [394] supports Prentice's view of the more individualised contribution. They did note in regards to Bacchetti's assertions about ethics committees that:

> "*[it] would not only represent a major step backwards in the protection of human research subjects but also encourage the conduct of studies less likely to improve public health."* [394]

Both of these arguments are valid for clinical trials, and, to a certain extent, longitudinal studies. However, while clinical trials are testing the effect of new drug on a population with a certain disease, epidemiological studies are generally looking at the occurrence of that disease within a defined population. The sentiments expressed by Prentice are also valid in epidemiological studies, but the effects of that sentiment can have larger effects than with a clinical trial construct. This can be attributed to public health surveys tending to be carried out on a more generalised population than is the case with clinical trials.

Coughlin and Beauchamp have also looked at ethical validity with regards to methodology and sample size specifically in epidemiological studies [377]. They have noted that there can be ethical conflicts between moral standards and methodological principles. Beneficence (that is, the potential benefit to subjects and society) is one of the virtue principles which methodological design has to take into account. This factor is something ethics committees take into account when considering research proposals [377].

The decision of an ethics committee to take a teleological or deontological approach to assessing epidemiological research can influence the way the research is perceived. Capron suggests that:

> "*an adequate description of epidemiological research must locate it within moral-not merely factual-terrain because it rests on competing ethical orientations about research involving human beings, roughly involving the competition between deontology and utilitarianism*" [395].

A teleological approach, when applied to the virtue principles mentioned earlier can lead to a need to find balance between benefit at an individual and group level against perceived risks,

and the probability of failure [377]. A deontological approach, as applied to the virtue principles leads to an assessment of the obligations of the researcher to the participant as well as the obligations and freedoms of the participant. Capron suggests that this balance is found in the notion that a researcher's obligation extends beyond non-maleficence towards beneficence, but produces social benefits where possible [395]. How this is communicated to potential research participants is not clear.

Methodology in this context walks a fine line between not being rigorous enough to obtain the results needed, and being overly rigorous with the effect of discouraging potential participants [377]. This line has been walked since before the advent of the NERE with the likes of George Mitchell in the 1860's, where epidemiological methodology was used to examine the success of a boarding-out scheme for the lunatic asylums in Scotland [396].

Other Influences

One long-term ethical consideration that is evident in the Framingham and Iodine studies, but not the Doll and Hill studies, is the consideration of informing the participants about their results. Jeffreys *et al* [397] highlight this dilemma in the context of "do no harm", with potentially abnormal results during a longitudinal study of diabetes.

Jeffreys *et al* [397] noted that just because a study has ethical approval does not necessarily mean that the participant will benefit from taking part. This long-term consideration of the participant and the ethical dilemma potentially associated with informing them of a potentially life changing result is a primary ethical consideration.

In the Framingham studies, this was overcome by involving the participants' GP from an early stage, with results of the testing cycles being forward to them for action as appropriate. The Doll and Hill studies did not have this type of moral dilemma, as it was a prospective study endeavouring to determine a relationship between an action and a disease.

The iodine surveys, especially in the years when goitre was used as an indicator of iodine sufficiency, also dealt with the issue of informing participants of their results. Due to the nature of goitre, participants in the Gibson studies were generally aware that they had goitre before the study commenced. Thus, informing the participants of their result did not occur. The later iodine surveys varied in their approach. The later surveys in the Menzies period did inform participants if they were within the normal range; however none of the Broadstreet

surveys provided individual results, either as a normal range indication or as an exact measure. Both the Menzies and Broadstreet studies stressed to the participants that UI levels were very much a reflection on recent dietary intakes, hence either just informing the participants if they were within normal range or not informing them at all.

The Doll and Hill study could be considered to be the typical long-term study. Once the cohort had been recruited there were no major methodological changes. As there were no major methodological or recruitment changes, there was no need for ethical clearance or consent participation forms. Implied consent could be assumed by the fact the surveys were returned.

The use of guidelines to enable researchers to develop ethical studies is something that did not occur in any of the studies under consideration. Prineas *et al* (1998) [42] found that even though guidelines were available in the United States for epidemiologists to consult, only 54% of them were aware of their existence and only 29% of them were aware of their content.

While Soskolne [398] noted that ethical decision making cannot be short circuited, he suggested that it is a process that has the means to challenge the way a practitioner make both research and epidemiological decisions. Accordingly, Soskolne [398] noted that *"the end lies in making an ethical decision*". This supports the notion that longitudinal cohort studies have long-term ethical considerations.

The Concept of Community

While the intent of this thesis was to investigate the impact of ethical changes on longitudinal health studies, what became apparent during the analysis of the data was the impact that community had on the studies. The concept of community is something that initially was not considered, however it became apparent that in all of the methodologies the utilisation of the community was an influencing factor in recruitment and on-going participation.

The purpose of using the GP and Framingham studies was to provide a varied and broad range of comparative populations and methodologies within the range of 1940 to 2010. This would allow for changes in the ethical framework for longitudinal research to emerge. This allowed for comparisons for the Tasmanian Iodine Studies with regards to ongoing follow-up, loss to follow-up and cohort selection. While the Tasmanian study does not follow a

single cohort over as long a period of time as the two earlier studies do, it retains the concept of examining a community – be it a changing community – to determine outcomes based on behavioural habits.

In the case of the Doll and Hill studies, the behavioural habit in question was smoking and the outcome was to determine the risk factors for lung cancer. In the Framingham study, it was originally designed to determine potential factors for CHD, but has evolved over the years to determine other factors linked to the risk of heart disease. The concept of a community being an epidemiologic laboratory (as put forward by Kessler and Levin [399]) may be dependent on the definition of community and whether an individual is using the scientific or popular definition. The Oxford English Dictionary defines community as "*A body of people or things viewed collectively.*" However, community and population cannot be used interchangeably. While both the Framingham and Doll and Hill studies can be considered to comprise a community, a community has to be populated. There are two types of population which are considered in these studies: one which can be considered a physical population, the other a conceptual population. The physical population is defined by certain physical boundaries (such as the Framingham Study). The conceptual population is where the population is characterised by something other than residence within a defined boundary.

These definitions are analogous to Lasts population and sampling population definitions respectively [400]. With respect to these case studies: while the physical population could be considered to be the sampling frame, within that physical population a conceptual population has been established. The establishment of the conceptual population in all three of these studies described in this thesis varied from the primary method of population establishment (GP Study) to a secondary population establishment after the physical population had been defined (Framingham and Tasmanian Iodine). However, all three populations became a community by virtue of the fact that certain results with the study are viewed at a collective level – this is particularly true within the Framingham study, which is constructed of many populations as differing cohorts, yet they are viewed collectively within the studies in question.

The GPs are a community by virtue of them all having a particular degree and membership of a certain society, Framingham is a community by virtue of location and the Iodine study is a community as it looked collectively at a group of young people in a defined area. Even though within the Iodine studies the students under study changed each time the study was

undertaken, the concept of looking at changes within a defined community is still valid. This concept, based in ethnographical research, may not seem to be relevant to a science based study but is actually pertinent to the perception of study populations and recruitment [3].

It is the concept of community in the Framingham study that allowed for the 2nd and 3rd generation cohorts to be recruited so successfully. The community contributed to the successful recruitment of the 2nd and 3rd generations, as well as the recruitment of the Omni cohorts by participating in the collection of potential participants' information [145, 163]. This could be interpreted as strategic use of the people already involved in the study, but could also potentially be seen as a case study for the use of a whole community in public health studies. Studies such as the Busselton Health Study [129] have built on the work that Framingham have done with regards to community involvement in the study. They have done this by involving the community. This has given the community a vested interest in the study itself and its ongoing success.

Within the Tasmanian iodine studies, the concept of community as mentioned earlier is evident in the Gibson studies. The whole school testing concept allowed for community engagement and a feeling of doing good for the greater benefit could be assumed to be established. This use of community is something that does not occur in the Menzies studies. This could not only be primarily due to the methodology, but also to the significantly smaller sample sizes than the earlier studies. In the Broadstreet studies, there is an apparent loss of potential sampling through the layers of permissions. Personal experiences of the author suggest that the smaller schools, while having potentially smaller sampling frames, were much more willing to participate and follow through on completing consent forms and missing samples.

This context of community, and the community getting together to help for the greater good, in public health type studies can be perceived as important. As can be seen from a study such as Framingham, community investment through participation and time can allow for a large representative study with minimal community impact with regard to methodologies can lead to significant outcomes for the wider community. This is also the case in the Iodine studies. The result from the sampling undertaken in all the studies has influenced the supplementation process by either changing the type of supplementation or confirming that supplementation was either needed or the current supplementation regime was working.

This concept of doing good for the greater community is summed up very well by Ashcroft [350] who stated:

> "*We want people to act morally, it is not because so acting is in enlightened self interest alone, but because sometimes we need people to make genuine sacrifices of their interests to the benefit of others: to act against their interests, in the certainty or high probability of personal loss*."

However, the sense of community and doing the greater good for the community as a whole is not as prevalent nowadays in Western society as it used to be. This can be seen in the some of the studies undertaken in the mid to late 1900's, such as the Framingham Heart Study, The Tecumseh Michigan Community Health Study, the Health and Ways of Living in Alameda County California Population Laboratory and others [399]. While large-scale community studies such as the Busselton Health Study are still undertaken, there is not the proliferation of studies which existed earlier. It is still evident in other countries, such as, for example, Africa. Jegede [70] noted that a Western bioethical construct of individual autonomy is not necessarily prevalent in Africa; it is more likely to be a communal or social autonomy.

This move from communal or social autonomy to a more individual approach with regards to selection and consent is a concept that can potentially affect human studies in many different ways. While it may seem to be a societal norm to try to protect the individual, this protection appears to be potentially biasing the selection process for many varied longitudinal studies. Various studies have been undertaken to determine if there are differences between known responders and non-responders [372, 375-377, 401-404]. Junghans [372] found that the opt-in arm of their angina study generally had healthier participants and a lower response rate. Kristman [401] noted that a certain type of non-responder in cohort studies can bias the results. They have named this type of non-responder "Missing Not At Random". This type of non-responder generally has a reason for not responding to follow-up after the initial survey, but this reason may be unknown. Kristman [401] has shown that statistically this group can bias the results in a long term study.

This concept of community generally appears to be an underlying theme throughout most of the case studies. To undertake a successful long-term longitudinal study involving surveillance, the support of the community appears to be paramount. While protection of the individual is required, numerous layers of protection can inhibit the true random nature of

selection within a community. A balance between protection of the individual and doing research for the greater good needs to be established. It will probably only be found through communication with the potential research participants, ethics committees and researchers.

This need for balance has already been highlighted by various researchers. Madhavan *et al* [405],while approaching the issue from a demographical point of view, highlighted that "*community involvement*" allows a longitudinal study to be undertaken in a more equitable manner. They found that once lines of communication within the community had been established, information was transmitted between villages within the communities much quicker. The use of locals as field workers also allowed the researchers to gain the trust of the community, as well as an understanding of concepts unique within that community [405].

The NERE, as an entity that has been evolving since the late 1940's, is still in a state of flux even today. While studies ethically are encapsulated within the ethical time frame in which they are originally conceived, the evolving environment will affect them if major changes to their methodologies are proposed. The consequences of changes to methodologies within a study can have an impact on the conclusions drawn and the decisions made within the context of the study and the greater good.

Conclusions

Have legal issues such as privacy impacted on epidemiological research with regards to recruitment and follow-up?

The ability to follow-up on non-responders, recruit participants and develop sampling frames has been affected by legal issues such as privacy. This suggests that legal issues have had an impact on epidemiological research.

The ability of researchers to deal with such ethical dilemmas in a moral way is diminishing due to increasing regulation of the research environment. This is due to the increasingly regulatory needfor privacy and the requirements for data not to be linked to an individual. While this may be societal expectation, data linkage and the thought of Big Brother watching also influences this expectation of privacy. As can be seen specifically in the Broadstreet studies of the iodine surveys, the ability to determine reasons for non-response or to follow-up on non responders individually was not available.

Within Australia the application of the National Privacy Principles in conjunction with the Privacy Act (1998) and the NHMRC guidelines provides participants with the knowledge that data collected by the researcher will be stored in a manner to protect their right to privacy [406]. This however can cause complications with regards to the use of data for ongoing or associated studies. The privacy principles associated with the act suggest that various modes of collection, use and storage need to be adhered to [406].

While these principles are relevant and best practice, in reality they can cause problems. The relevant section of the privacy principles state that data can be disclosed:

> *"(d) if the information is health information and the use or disclosure is necessary for research, or the compilation or analysis of statistics, relevant to public health or public safety:*
>
> *(i) it is impracticable for the organisation to seek the individual's consent before the use or disclosure; and*
>
> *(ii) the use or disclosure is conducted in accordance with guidelines approved by the Commissioner under section 95A for the purposes of this subparagraph; and*
>
> *(iii) in the case of disclosure—the organisation reasonably believes that the recipient of the health information will not disclose the health information, or personal information derived from the health information; or*
>
> *(e) the organisation reasonably believes that the use or disclosure is necessary to lessen or prevent:*
>
> *(i) a serious and imminent threat to an individual's life, health or safety; or*
>
> *(ii) a serious threat to public health or public safety;"* [406].

These restrictions, if applied ethically, could easily restrict contact data being made available for follow-up of study recipients to partake in similar but methodologically different studies.

This construct is not so apparent in either the GP or Framingham studies.

Follow-up methods employed by these studies may not have been permissible under contemporary ethics frameworks. While the initial recruitment may be similar – utilisation of census and electoral enrolment or of professional databases - follow-up methods would

have had to have differed. The GP studies method of follow-up was via reminders and notifications of deaths via the Register General of anyone listed as a medical professional [167]. While reminders could still be utilised today, the notifications by the Register General would be subject to privacy laws. This would not allow for cause of death to be determined, thus one of the main objects of the study would not be able to be achieved.

In the Framingham Study, while recruitment could have taken place utilising freely accessible census and voter databases, follow-up would have also proved problematic. Different data sources have been utilised in this study, from records of hospitalizations, death certificates, medical examiner reports, and information from private physicians [146]. Many of these would now have to be given permission individually by the participant to allow the data to be pooled and analysed.

Has research governance has affected research ethics?

Varied influences, dependent on the country of origin, were seen in the three case studies. International codes, while generally providing guidance and suggested actions are not legislated for in any of the countries under consideration. Thus, even though these codes and events could and have influenced ethical thinking, there is no solid evidence that links ethical events to precise changes in methodology and thinking in the case studies.

Hence, while research governance may have made research ethics more problematic, there is no hard evidence that it has adversely affected the studies under examination. Anecdotal evidence points to instances of change in recruitment methodologies. In particular research governance being seen to have a negative effect with regards to self-selection and response rates [372, 407].

Protection of the individual is part of the remit of an ethics committee. However, ethical requirements are not study dependent. That is, the requirements do not vary depending on how a study is designed, and how its researchers propose to carry it out. Capron [395] confirms this and proposes that non interventional studies may be better managed by the implementation of the ability of a subject to remove themselves post participation after they are made aware of the true nature of the study.

Do changing ethical environments in longitudinal cohort studies have long-term ethical considerations with regard to various factors within the study?

All of these studies if they were to be undertaken under contemporary research ethics environment would be affected. The differences would be dependent on the country of origin. Epidemiologically, the research methodologies would impact on drawn conclusions.

In conclusion, the NERE and the studies it influences can be seen to be a balancing act. For every piece of legislation added to the environment that influences studies, a part of the study may have to be modified to accommodate this. While small adjustments are par for the course with regards to long-term studies, too many may change the results and the comparability of them to earlier results.

Has the New Ethics Research Environment had an Effect on Longitudinal Cohort Studies?

The NERE has evolved since the line in the sand was drawn over 60 years ago. But has that evolution had any impact on how longitudinal cohort studies are designed, implemented and analysed?

The case studies that were examined suggest that the impact of the NERE may not be as comprehensive as was originally suspected. It was thought that the studies would show a changing construct with regards to how researchers interacted with the study and the participants. While this was shown in both the Framingham and Iodine studies, only within the Iodine studies did the ability to compare the results of the studies become impacted. The Framingham studies methodologies remained consistent enough through the impacts of the NERE to allow for comparison with earlier groupings to be undertaken. The impact this may have potentially had with regards to comparative analysis of the iodine studies has not been quantified using the methodologies in this thesis, however, the changing methods of recruitment through the studies does not allow for direct comparative analysis to be made.

While the three studies are superficially different when it comes to methodologies, the underlying idea – that of following a disease or public health concern over a number of years - is valid for all of them. They all conform to the definition of long-term public health studies, utilising known populations and comparing those populations (or results from those populations) over time. Both Framingham and the Doll and Hill studies used a cohort based

study to follow an outcome over time. While Framingham has added in cohorts during the length of the study, the Doll and Hill study has remained constant with one cohort and no methodological changes. As mentioned earlier, Doll and Hill could be considered to be the "baseline" study, from which all other long-term longitudinal studies are compared with regards to changing ethical constructs. Framingham in contrast shows how cohort recruitment can evolve with changing ethical constructs, while maintaining the initial aims and outcomes of the study. The iodine study, with its individual surveys of unique cohorts show how while the initial hypothesis in a study may not change, using distinct time periods means that each new investigation of the initial hypothesis has to conform to the ethical expectation of the time.

The Iodine studies showed the greatest changes, but this can be attributed more to the fact that the studies were a series of individual surveys. This independent study design over the three different time periods allows the NERE to fully catch up and influence the next design. The changes within the iodine studies also reflect changing best practice. This changing best practice would be influenced by the NERE, but also by changing attitudes to participation in research.

The types of conclusions drawn from the three studies have all impacted on various communities. Both the Doll and Hill and the Framingham studies have helped to draw very significant conclusions with regards to influences on health. As has been discussed all the way through this thesis, if these studies were instituted today under the current NERE, the methodologies would not necessarily be comparable to what was instituted when the studies began. Various factors would influence the achieving of results with similar impact. These factors would include the ability to actively follow-up participants through various means at a minimal cost. As noted earlier, Fester [390] found that follow-up if not undertaken regularly posed problems with regards to tracking, confidentiality and cost.

It could be suggested that the conclusions drawn from both the Framingham and the Doll and Hill studies demonstrate robust initial study design and not an initial lax ethical environment. With the Doll and Hill studies, it was the more relaxed ethical environment that allowed for access to the GP database, as well as the unfettered access to data such as coroners reports and death certificates. Doll et al even noted this in their final paper stating that

> "*principally because their subsequent mortality would be relatively easy to follow, as they had to keep their names on the medical register if they were to continue to*

practise. Moreover, as most doctors would themselves have access to good medical care, the medical causes of any deaths among them should be reasonably accurately certified." [173]

So the choice of subject, and the study design could have been done for convenience rather than the ability to obtain robust and accurate results. This convenience sample produced robust and accurate results due to the initial ethical environment.

The NERE while allowing access to the database utilised by this study, would have required the researchers to justify their choices. The reasons presented by Doll et al in their final study, could have been considered justification under the NERE, thus suggesting it was initially a robust design. However, the ongoing access to the database may have been restricted, thus not allowing the researchers timely access to death certificates and corners reports.

Oppenheimer [162] of the Framingham studies notes that in the early years competing interests left the study objectives open to contestation and negotiation. These changing of objectives and goal-posts, could not have happened under the NERE, and thus the original studies were constituted under what could be considered a lax ethical environment.

The use of stakeholders however strengthens the initial ethical environment. The initial recruitment, through both town census and volunteers could have happened under the NERE, however, the free flow of other data sources such as hospitalizations, death certificates, medical examiner reports, and information from private physicians would have all had to have been agreed to by the participant during the initial consultation and examination [146].

It could be contended that as the end events within both these studies were so dramatic (Lung Cancer and CVD) that the NERE would not have affected the study aims. It may have affected the methodologies, but in both cases it would have been a matter of obtaining informed consent from the patient to access the required records as and when needed.

So does the NERE stand up to epidemiological studies that may be looking for smaller effects? The author believes it does. Susser proposes that modern epidemiology – which provides the framework for long-term longitudinal studies, has had three eras and we are

moving into the fourth. These eras are Sanitary Statistics, Infectious Disease Epidemiology and Chronic Disease Epidemiology [408]. All three case studies can be considered under the Chronic Disease Epidemiology era. Susser proposes that the era we are entering into is the Societal and Molecular Epidemiology one. Societal epidemiology will hold up well to the NERE, as it moves away from examining people as individuals and moves back to examining people as part of a society or community. The smaller, more subtle effects which Molecular Epidemiology looks for within a population would hold up to the NERE by starting to explore the use of databanks, as shown earlier in the Australian national statement [226].

Overall the NERE did not have the effect on the case studies that was expected. However, it did show that as long as the ethical environment continues to evolve and be influenced by factors outside the virtues of beneficence, justice, non-maleficence and autonomy. This context allows a researcher to develop longitudinal studies that are flexible enough to enable change as the NERE changes.

Further Work

As noted at the beginning of this thesis, there were limitations to this work. To extend the concept of the NERE further to investigate whether the NERE potentially exists in studies other than longitudinal studies should be carried out.

Further examination of the effect of the NERE with regards to how it is perceived by researchers involved in longitudinal cohort studies may allow for interviews and a discourse analysis to be undertaken. While research on ethics committees has been carried out previously by authors such as McNeill [2, 8], this did not quantify the effect of changing ethical constructs on ongoing studies from a researcher's point of view.

Finally, an examination of time lag between documented ethical changes at an international and national level is needed. Other aspects that should be included is when they were integrated into national codes/statements, and the effect on previously instituted studies which had an ethical change. The time lag between the evolution of an ethical change and implementation of an ethical construct should also be examined.

These three sections of further work will not only help develop the NERE, but also examine how it is perceived by researchers.

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Appendices

Appendix A: Sample of Data Extraction Document

Year:

Study:

Paper Title:

Paper No in Series:

Relationship of Paper to others in Study:

Initial Type of Recruitment:

Initial Type of Study:

Has any of the Methodology Changed?

If so how?

Is there any indication WHY the methodology changed?

If so What?

RESPONSE RATES:

Total Potential Population:	
Approached:	
Responded:	
Participated:	
Percentage Responded:	
Percentage of total Approached that Participated:	
Loss since Last Paper:	

How long is this into the Follow-up from the Initial Study?

What World events happened ethically around this time?

Was an Ethics committee/approval process required FOR THIS REITERATION of the study?

Why?

Where any Ethical Problems noted in the document?

If so What?

Pertinent Info:

Appendix B: Peer Reviewed Oral Conference Abstracts Resulting From This Work

Australian Bioethics Association Conference June 2006

Brisbane Queensland

Ethics and Empirical Evidence - Finding the Balance

Zelda Doyle - University of Tasmania

The need for empirical evidence to support hypotheses walks a fine line with the need to undertake ethically viable research. To stray too far in one direction or the other may compromise either the results obtained or the integrity of the research.

Epidemiology, like many sciences, relies on empirical evidence to draw conclusions about populations. However, ethical considerations can impact on how a study is designed and carried out. In surveillance, this may impact on the amount of data from which conclusions can be reached.

Researchers historically were responsible for determining their own ethical standards. Thus making their own conscious decisions with regard to what they considered to be ethically carried out research. This responsibility in the last decade or so has been transferred to institutional ethics committees, which, while relieving the researcher of supposed responsibility, has potentially affected the quest for reasonable empirical data.

So who is responsible for finding the balance between the need for well thought out and obtained empirical evidence and ethically sound research? Should researchers rely on ethics committees to guide them, and thus potentially lose some of the power of their study due to decreased sample sizes? Or should the researcher proactively design their study taking into account the requirements to receive ethical approval?

The responsibility of finding the balance lies both with the researcher and the institutional ethics committee. The researchers' responsibility is to empirical research with considerations for the ethical implications of that research. The institutional ethics committee's responsibility is to the participants who may potentially partake in the research. Between the two, it is to be hoped that research which is ethically sound and empirically viable can be carried out in a responsible manner.

Goodenough College Unhealthy Professional Boundaries Conference December 2007

London, United Kingdom

Title: Jumping Through the Hoops? Towards an Ethical Code for Epidemiological Research.

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Background: CP Snow in his book "The Two Cultures" identified the importance for greater communication between science and the humanities. Historically, the subject of 'ethics' has been the province of philosophy and law. However, in the advent of new technologies, medicine and science have a growing need to understand and incorporate ethical considerations. Where, we now wonder, is this communication, between disciplines of science, as well as the accounts of being and doing ethics and that which is regarded as science and medicine. Interdisciplinary subjects such as epidemiology require greater attention as science develops. This is partly due to the fact that epidemiology has a wide remit, from analysing minute genetic differences between population groups to broad scale public health surveillance; it is this broadness of scope which can, potentially, lead to miscommunication when shaping ethical research that spans different disciplines. Currently, many professional epidemiological societies have ethical guidelines which they suggest their members subscribe to, and which operate at a personal and moral level. On a larger scale, guidelines for the design of research– particularly those issued by the Councils for International Organisation of Medical Sciences and the World Health Organisation- may not be appropriate for epidemiological research. For example, some guidelines assume, often erroneously, that the individuals or the populations which are being studied can provide informed consent, even if the study's remit is technically complex. Furthermore, these guidelines are biased toward the reviewer on an ethics committee examining an epidemiological proposal, not towards the researcher developing the study which is being reviewed. While studies in genetics and of individuals are regulated by ethical principles

such as those embodied in the Helsinki Declaration, the ethical requirements for long term monitoring of disease through subject participation as opposed to compulsory notification remains a grey area, and an area in which interdisciplinary research groups as well as stakeholder groups are struggling to find clarity.

Aim: To present a way in which epidemiology and ethics can work together with other disciplines, and to shape a discourse that can form an ethically viable series of guidelines for interdisciplinary epidemiological researchers to follow. Health surveillance and genetic epidemiology, while superficially different, both face similar problems when it comes to designing ethically sound epidemiological studies. This project aims to carry out an initial survey on what guidelines are available for researchers developing projects and reviewers on ethics committees. This review can then be used as a basis to develop guidelines for 'best practice' on a large, interdisciplinary project.

Methods: A database search (including Medline, Google Scholar, Google, Web of Knowledge and Scopus) on "ethics of epidemiology" and "epidemiological ethics" showed that while there were various statements, there were no substantial, coherent documents addressing this topic of research. Various professional informants and researchers were also asked to contribute knowledge of relevant literature. Professional informants' prior experiences of researchers who have been involved in epidemiological research in the areas of public health were also obtained, and the type of ethical problems they encountered while submitting their research to ethics committees was analysed. This information was then collated and compared.

Conclusion: Our survey identified a clear need for guidelines addressing the situation of researchers involved in public health interdisciplinary research with an epidemiological content. Current practice for ethics did not reflect the complexity that epidemiological studies encompass. Development of future guidelines should enable both researchers and ethics committee members to present and evaluate studies from an ethical and scientific point of view. Ideas for the specific content of such guiding principles are currently being elucidated.